Dysostoses vertébrales
Aspects diagnostiques

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Journées de Foetopathologie Osseuse

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RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Nosology and Classification of Genetic Skeletal Disorders: 2015 Revision

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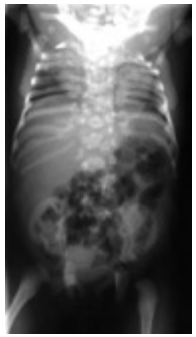
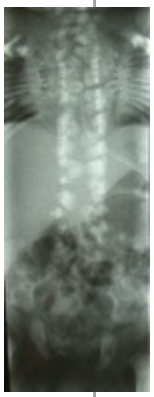
Am J Med Genet Part A 9999A:1–24.

35. Dysostoses with predominant vertebral with and without costal involvement					
Currarino triad	AD	176450	*HLXB9*	Homeobox gene HB9	
Spondylocostal dysostosis type 1 (SCD01), type 2 (SCD02), type 3(SCD03), type 4 (SCD04),	AR	277300	*DLL3*	Delta-like 3	
		608681	*MESP2*	Mesoderm posterior 2	
		609813	*LFNG*	Lunatic fringe	
		613686	*HES7*	Hairy-and-enhancer-of-split-7	
type 5 (SCD05)	AD	122600	*TBX6*	T box 6	
Spondylothoracic Dysostosis (STD)	AR		*MESP2*	Mesoderm posterior 2	
Vertebral segmentation defect (congenital scoliosis) with variable penetrance	AD		*MESP2*	Mesoderm posterior 2	
			HES7	Hairy-and-enhancer-of-split-7	
Klippel–Feil anomaly with laryngeal malformation	AD	148900	*GDF6*	Growth and differentiation factor 6 and 3	Role of *GDF6* mutations in dominant spondylothoracic dysostosis unclear
		613702	*GDF3*		
	AR	214300	*MEOX1*	Mesenchyme homeobox 1	
Cerebro-costo-mandibular syndrome (rib gap syndrome)	AD	117650	*SNRPB*	Small Nuclear Ribonucleoprotein polypeptide B and B-prime	
Cerebro-costo-mandibular-like syndrome with vertebral defects	AR	611209	*COG1*	Component of oligomeric Golgi complex 1	Also classified as CDG type IIg
Diaphanospondylodysostosis	AR	608022	*BMPER*	Bone morphogenetic protein-binding endothelial cell precursor-derived regulator	Possibly overlaps with ischiospinal dysostosis
Spondylo-megaepiphyseal-metaphyseal dysplasia (SMMD)	AR	613330	*NKX3-2*	NK3 Homeobox 2	
See also Spondylocarpotarsal dysplasia in group 7					

Incidence : 0.5 - 1 p. 1000

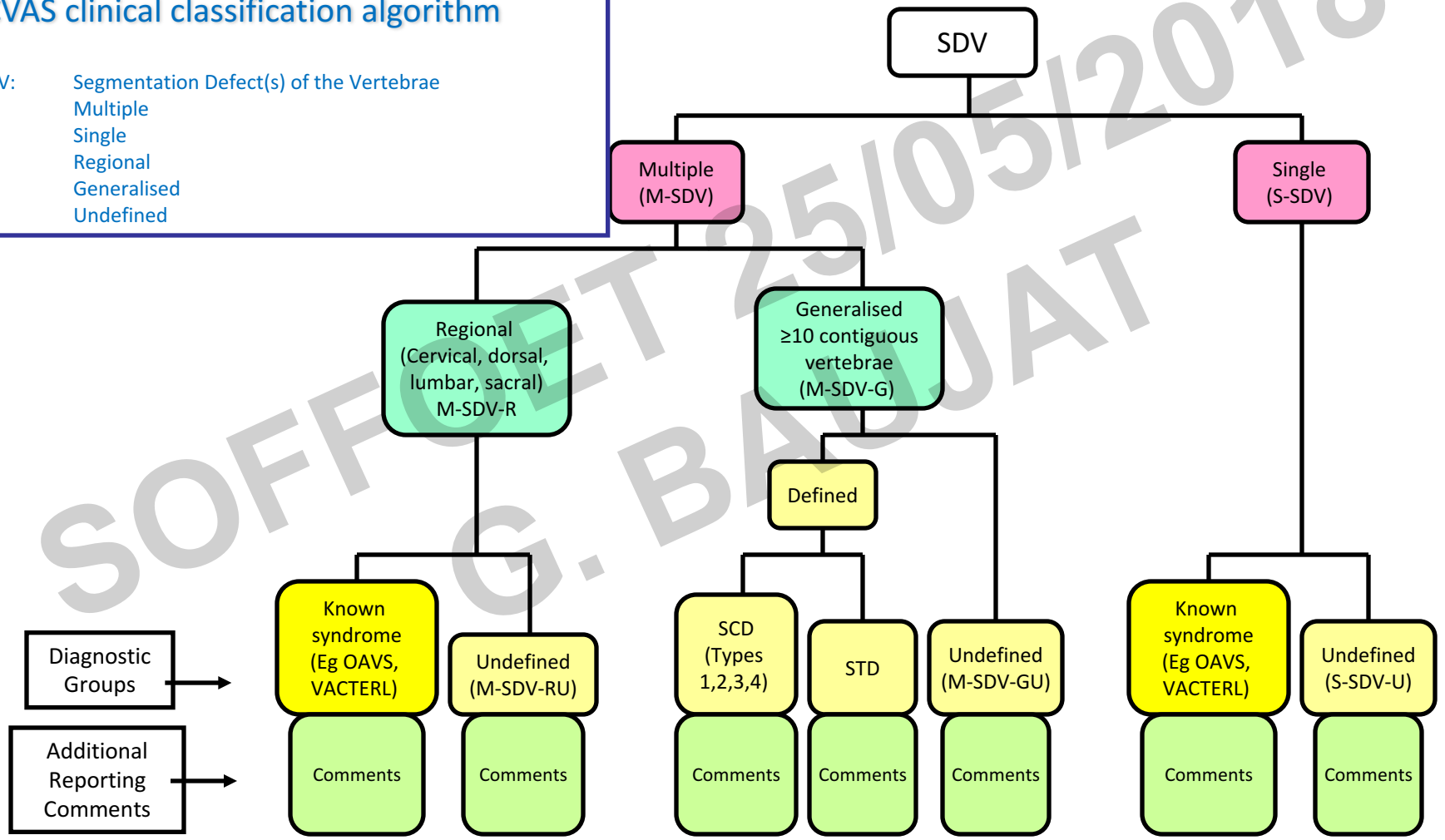
Proposed definitions:
Spondylocostal Dysostosis (SCDO) & Spondylothoracic Dysostosis (STD)

	Spondylocostal Dysostosis (SCD0)	Spondylothoracic Dysostosis (STD)
General features	possible asymmetry of the chest shape Mild, non-progressive scoliosis M-SDV >10 contiguous segments Mal-aligned ribs with intercostal points of fusion	Chest shape symmetrical, with ribs fanning out in a 'crab-like' appearance Mild, non-progressive scoliosis, or no scoliosis Generalised SDV Regularly aligned ribs, fused posteriorly at the costovertebral origins, but no points of intercostal fusion
Specific descriptive feature(s)	'Pebble beach' appearance of vertebrae in early childhood radiographs 	'Tramline' appearance of prominent vertebral pedicles in early childhood radiographs, not seen in SCD 'Sickle cell' appearance of vertebrae on transverse CT imaging (Cornier et al, 2004) 

Une classification des anomalies de segmentation vertébrale ?

ICVAS clinical classification algorithm

SDV:	Segmentation Defect(s) of the Vertebrae
M:	Multiple
S:	Single
R:	Regional
G:	Generalised
U:	Undefined



Classification International consortium for vertebral anomalies and scoliosis ICVAS; http://www.icvas.org

Turnpenny 2008

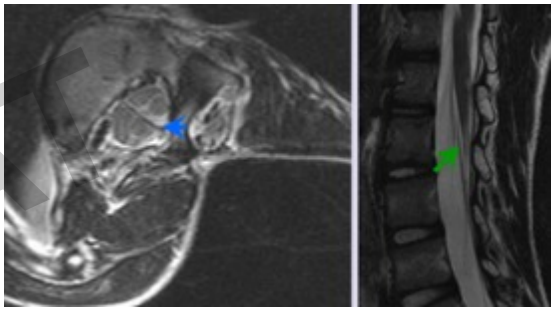
Malformations et déficits associées

- Anomalies des somites, anomalies de champ embryonnaire (?)
- Anomalies viscérales, cœur, rein , digestif
- Malformations cranio-faciales et extrémités : membres, face et crâne, audition
- Osteo-chondrodysplasies et malformations vertébrales (ciliopathies, chondrodysplasies ponctuées, campomélique)
- déficience intellectuelle associé (syndromes polymalformatifs, microremaniements chromosomiques)

Troubles de la segmentation rachidienne **généralisé**

I/ Dysostoses spondylo-costales (SCDO)

- Anomalie de segmentation vertébrale touchant l'ensemble de l'axe rachidien
- Anomalie de l'alignement des côtes, avec anomalie de nombre, fusion et asymétrie
- Malformations associées
  - Anomalie du tube neural, diastématomyélie
  - Hernies multiples
- Malf. anale et urogenitale, malformation cardiaque : en théorie absence



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Spondylocostal Dysostosis, Autosomal Reces

Synonyms: Costovertebral Dysplasia, Spondylocostal Dysplasia

Peter D Turnpenny, BSc, MB, ChB, FRCP, FRCPCH, FRCPath, Melissa Slo
Consortium for Vertebral Anomalies and Scoliosis).

- **Multiple segmentation defects of the vertebrae (M-SDV).** Abnormal segmentation of virtually all vertebrae, with at least ten contiguous segments affected; the strict diagnosis excludes most cases of congenital scoliosis in which segmentation anomalies affect very few vertebrae (or a single vertebra). The radiologic presentation is therefore crucial and most easily assessed from an anteroposterior radiograph of the whole spine.
- A mild degree of scoliosis, which is usually non-progressive
- **Rib abnormalities.** Malalignment of at least some ribs with a variable number of intercostal rib fusions, and sometimes a reduction in rib number
- Overall, a general symmetry to the shape of the thorax (at least, no major asymmetry)
- Absence (usually) of other congenital anomalies (e.g., renal and cardiac) (see Differential Diagnosis)

Dysplasie spondylocostale - conseil génétique

- Cas sporadiques les plus nombreux

- Formes récessives +++
  - Familles avec consanguinité
  - Lésions vertébrales étendues
  - Peu de problèmes respiratoires initiaux
  - Pronostic fonction des fusions costales
  - Prise en charge orthopédique spécialisée

- Formes dominantes rares
  - Phénotype plus modéré
  - Expressivité variable

European Journal of Endocrinology (2013) **168** R95–R103 ISSN 0804-4643

REVIEW
MECHANISMS IN ENDOCRINOLOGY

Notch signaling in skeletal health and disease

Stefano Zanotti and Ernesto Canalis

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Table 1 Skeletal diseases associated with *Notch* mutations.

Disease	Mutated gene	Major manifestations	Possibly impaired Notch function
Spondylocostal dysostoses	*DLL3*, *MESP2*, *HES7*, *LFNG*	Dwarfism Vertebral developmental defects	Regulation of the segmentation clock during somitogenesis
Spondylothoracic dysostoses	*MESP2*	Dwarfism Vertebral developmental defects	
Brachydactyly	*CHYS1*	Short digits Stunted growth	Patterning of the digits during development
Alagille syndrome[a]	*JAG1*, *NOTCH2*	Facial dysmorphism Vertebral abnormalities Bile duct atresia Cardiovascular defects	Craniofacial development; regulation of the segmentation clock during somitogenesis; vascular development
Hajdu–Cheney syndrome[a]	*NOTCH2*	Acro-osteolysis Osteoporosis Fibular deformities Polycystic kidneys	Unknown

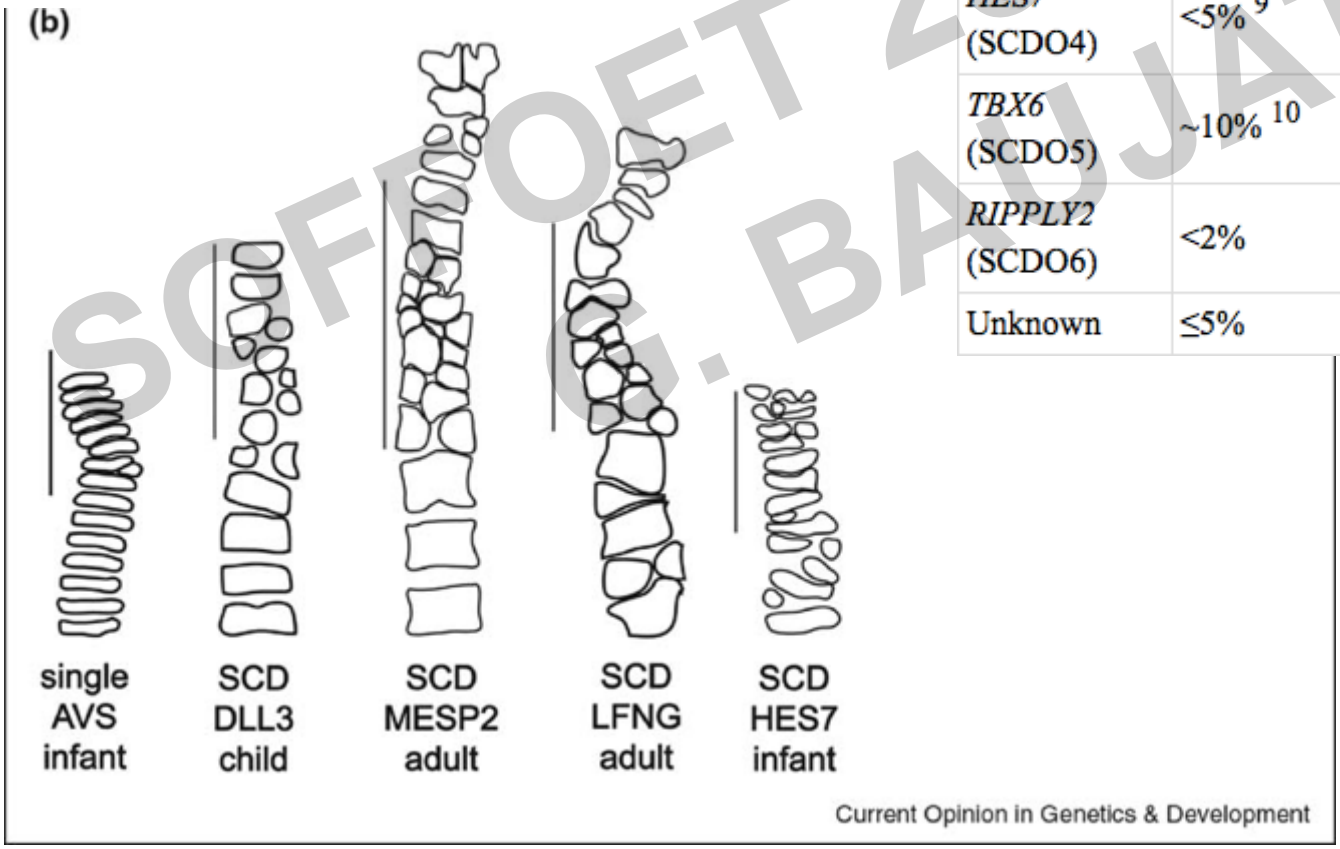
DLL3, delta-like 3; MESP2, mesoderm posterior 2; HES7, Hairy and enhancer of split 7; LFNG, lunatic fringe; CHSY1, chondroitin sulfate synthase 1; JAG1, Jagged 1.

Spondylocostal Dysostosis à ce jour

Gene	Inheritance	Vertebral pattern
DLL3 (SCDO1)	AR	Whole spine Thoracic > Lumbar ? Some variability
MESP2 (SCDO2)	AR	Mainly thoracic Less severe lumbar region STD phenotype
LNFG (SCDO3)	AR	Whole spine Marked trunkal shortening
HES7 (SCDO 4)	AR	Whole spine Marked trunkal shortening
TBX6 (SCDO5)	AD/ AR	localized or multi level
RYPPL2 (SCDO6)	AR	Variable Cervical involvement

aspect radiologique

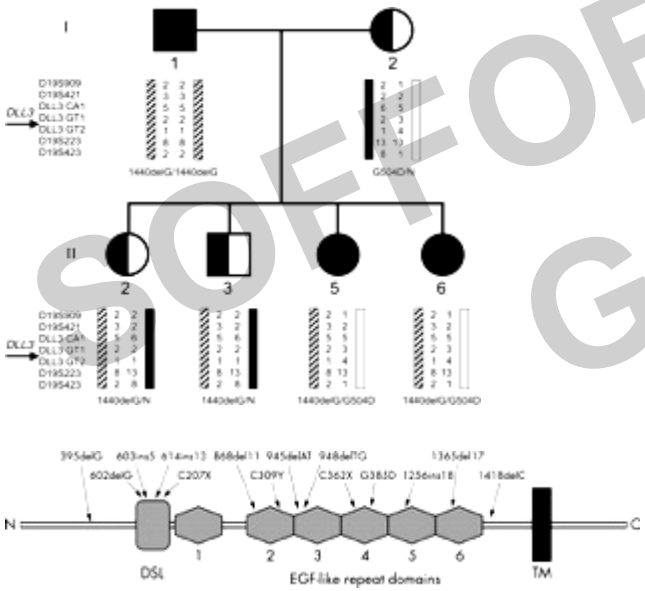
Gene [1] (AR SCDO subtype)	Proportion of AR SCDO Attributed to Pathogenic Variants in This Gene
DLL3 (SCDO1)	~60% [5]
MESP2 (SCDO2)	~20% [7]
LFNG (SCDO3)	<2%
HES7 (SCDO4)	<5% [9]
TBX6 (SCDO5)	~10% [10]
RIPPLY2 (SCDO6)	<2%
Unknown	≤5%

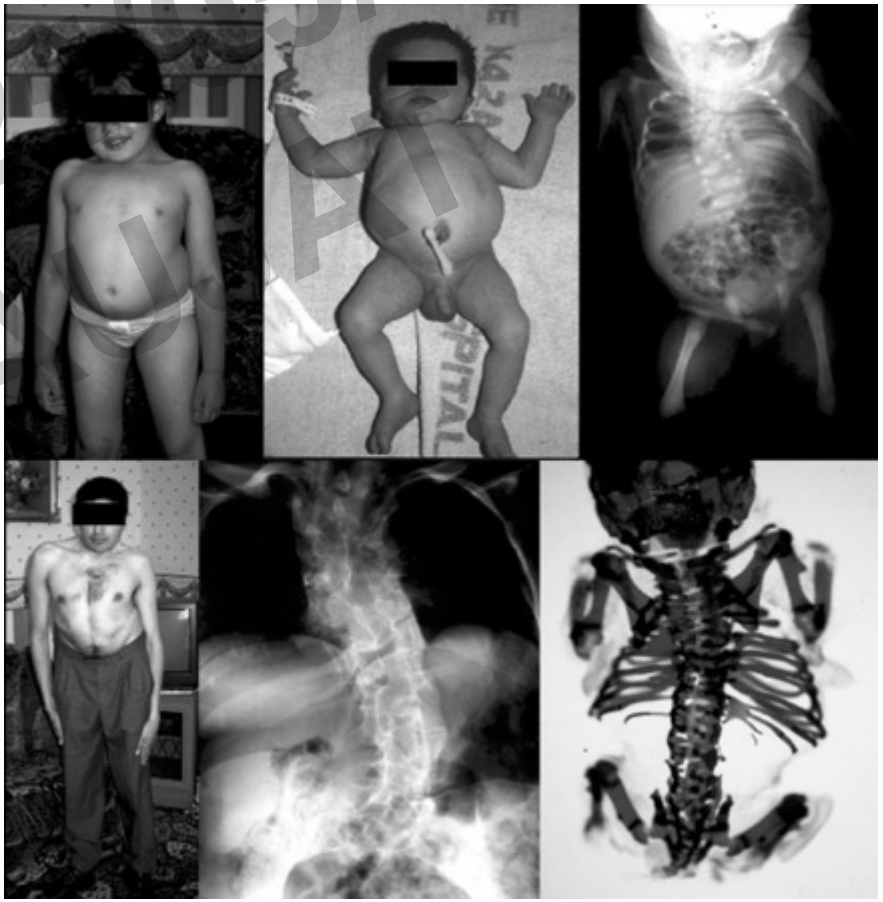


fréquence relative ?

1/ Dysplasie spondylocostale 1 (SCDO1) et *DLL3*

- Grande famille consanguine (TURNPENNY, 1999)
  - Cartographie par » homozygosity mapping »
  - 19q31.1-q13.3
- Identification *DLL3* (delta-like3)

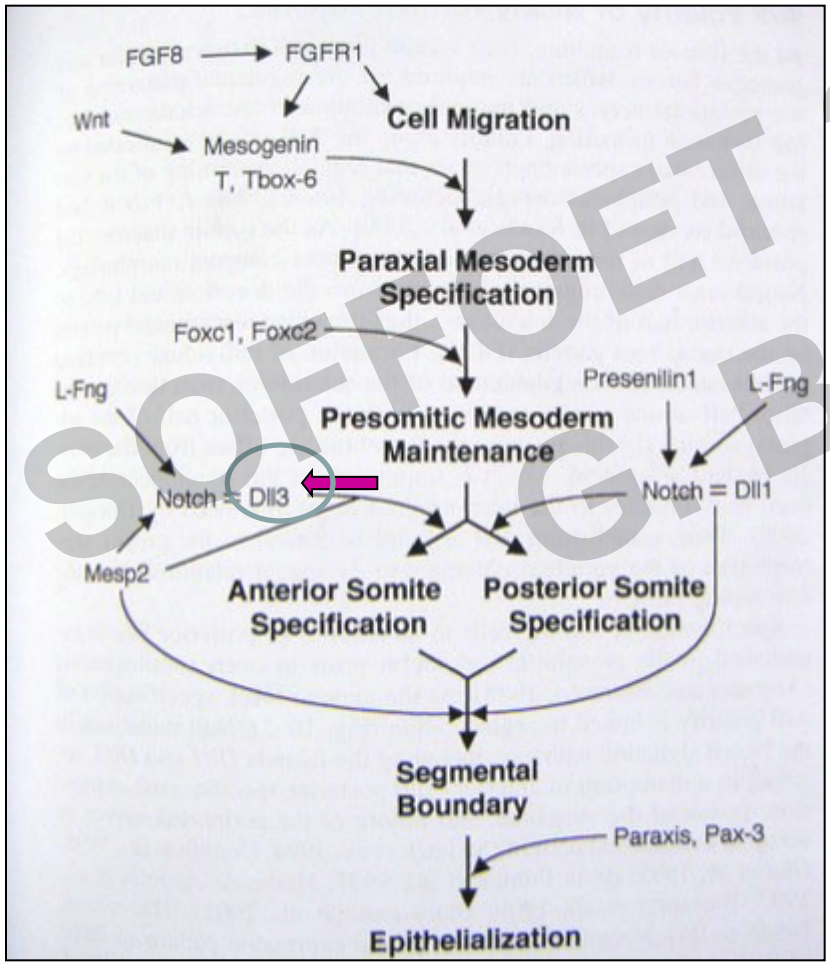


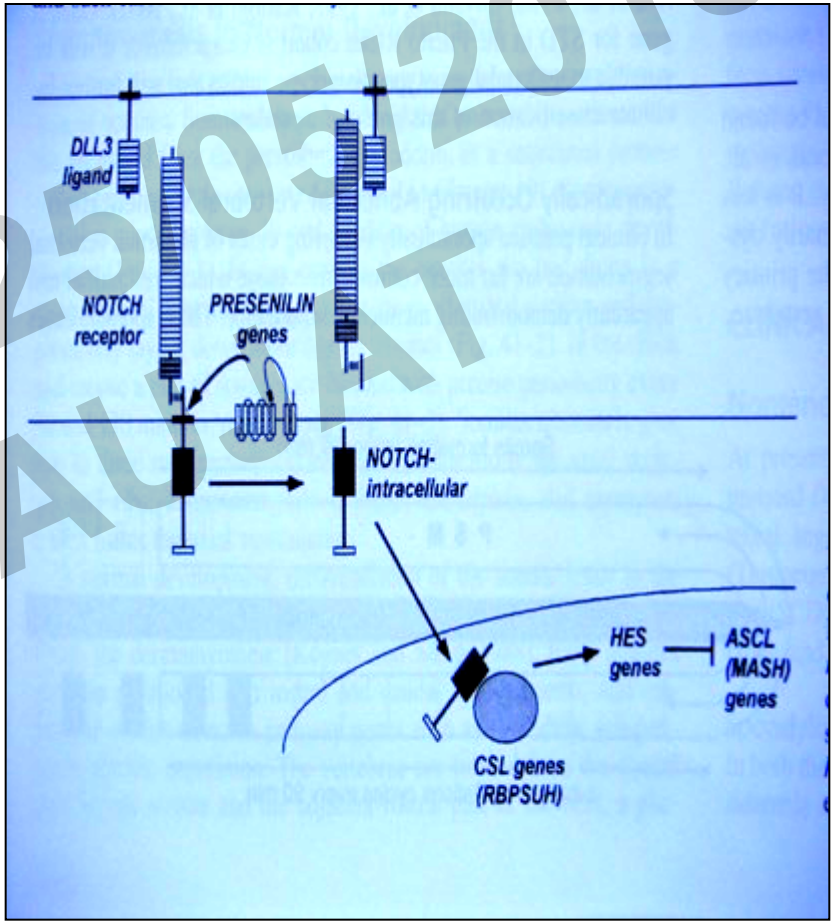


Giampietro et al. 1151: 38–67 (2009).

DLL3 : ligand de Notch, impliquée dans la segmentation vertébrale

DLL3 nécessaire à la formation initiale des somites

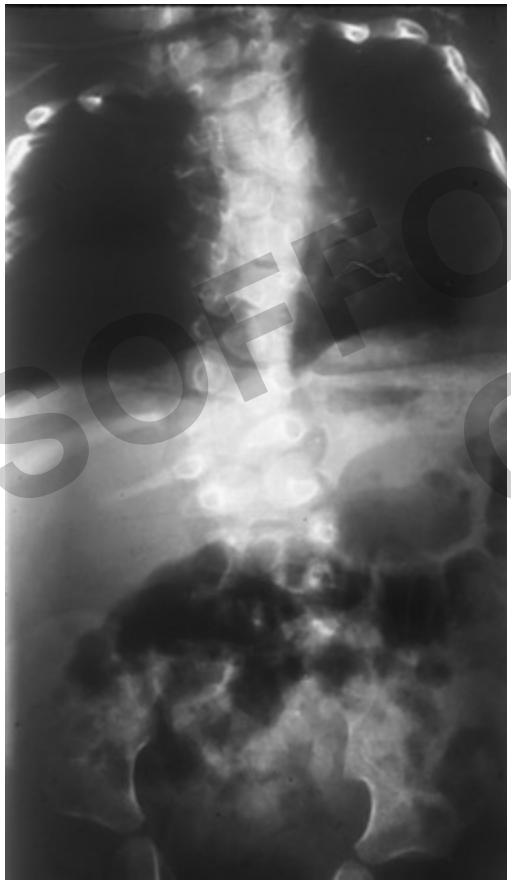


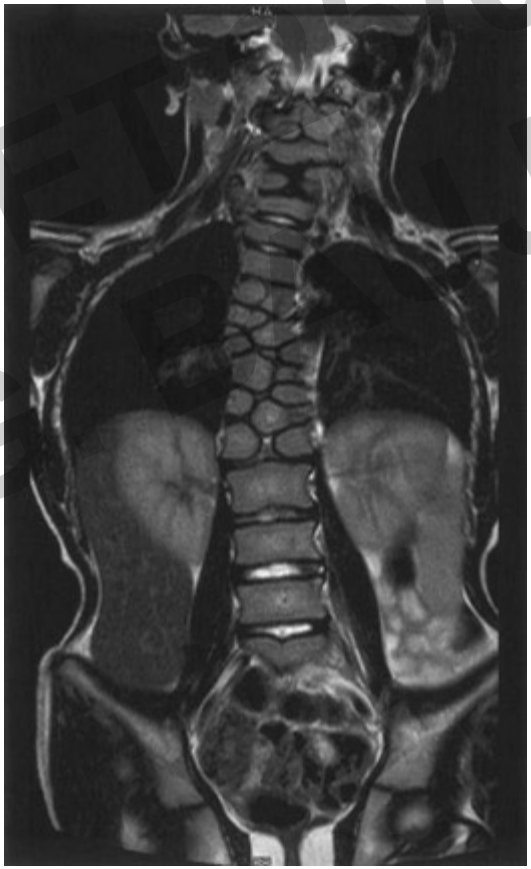


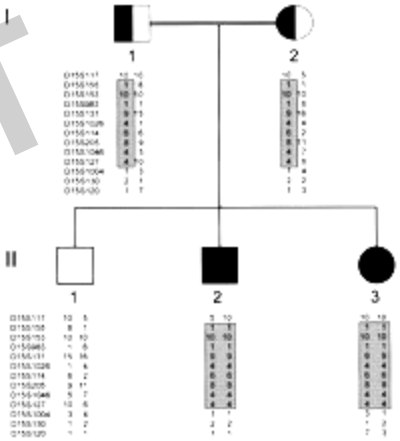
- Mutations homozygotes, mutations troncantes, stop, mutations ponctuelles
- Rares mutations hétérozygotes, phénotype semblable

2/ Dysplasie spondylocostale 2 (SCDO2) et *MSP2*

- Famille libanaise, homozygotie mapping, 2004
- Localisation en 15q21.3- 15q26.1
- Modèle murin Msp2 : anomalies de la segmentation vertébrale



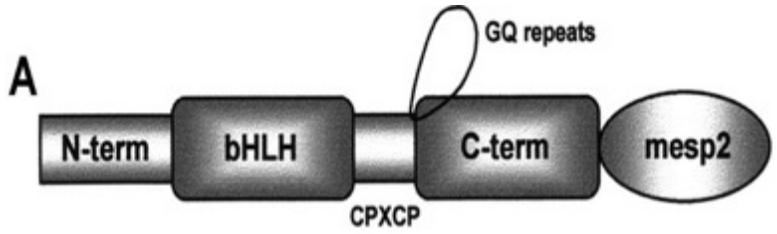


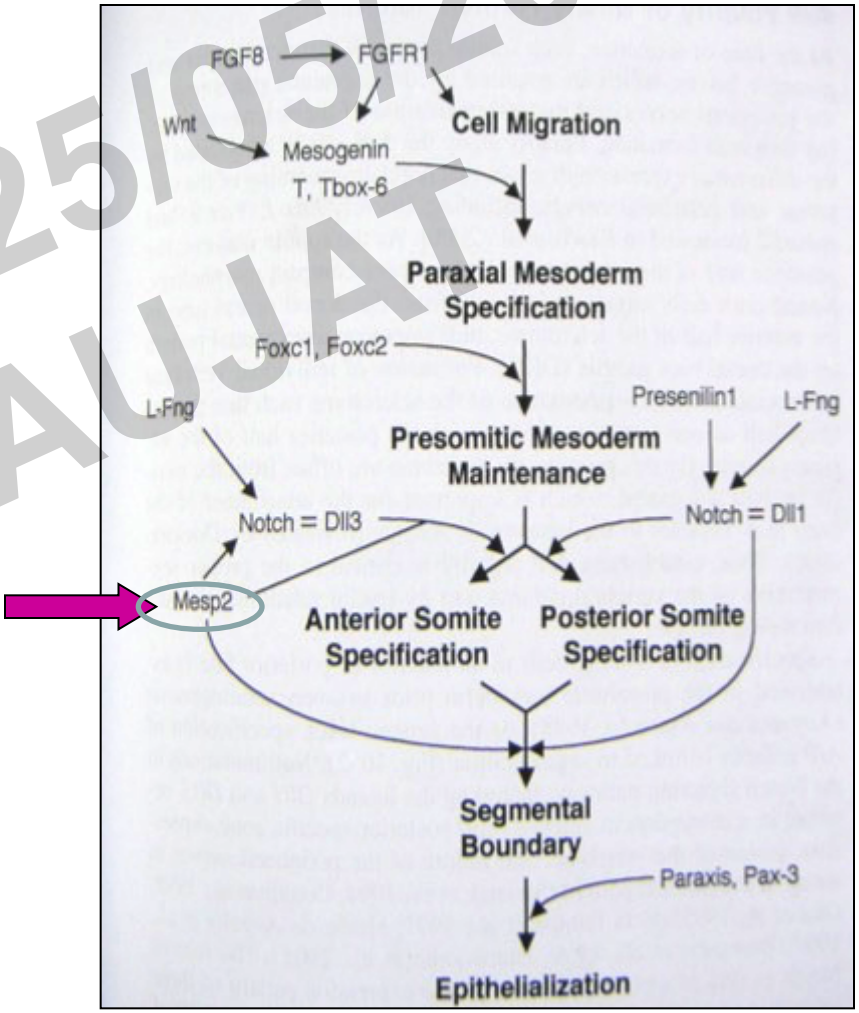


M.A. Wouters, et al. 2004. Mutated MESP2 causes spondylocostal dysostosis in humans. Am. J.Hum. Genet. **74: 1249–54.)**

MSP2

- Protéine de 397 AA
- Facteur de transcripton avec domaine bHLH
- Exprimé des la gastrulation et la somatogenese

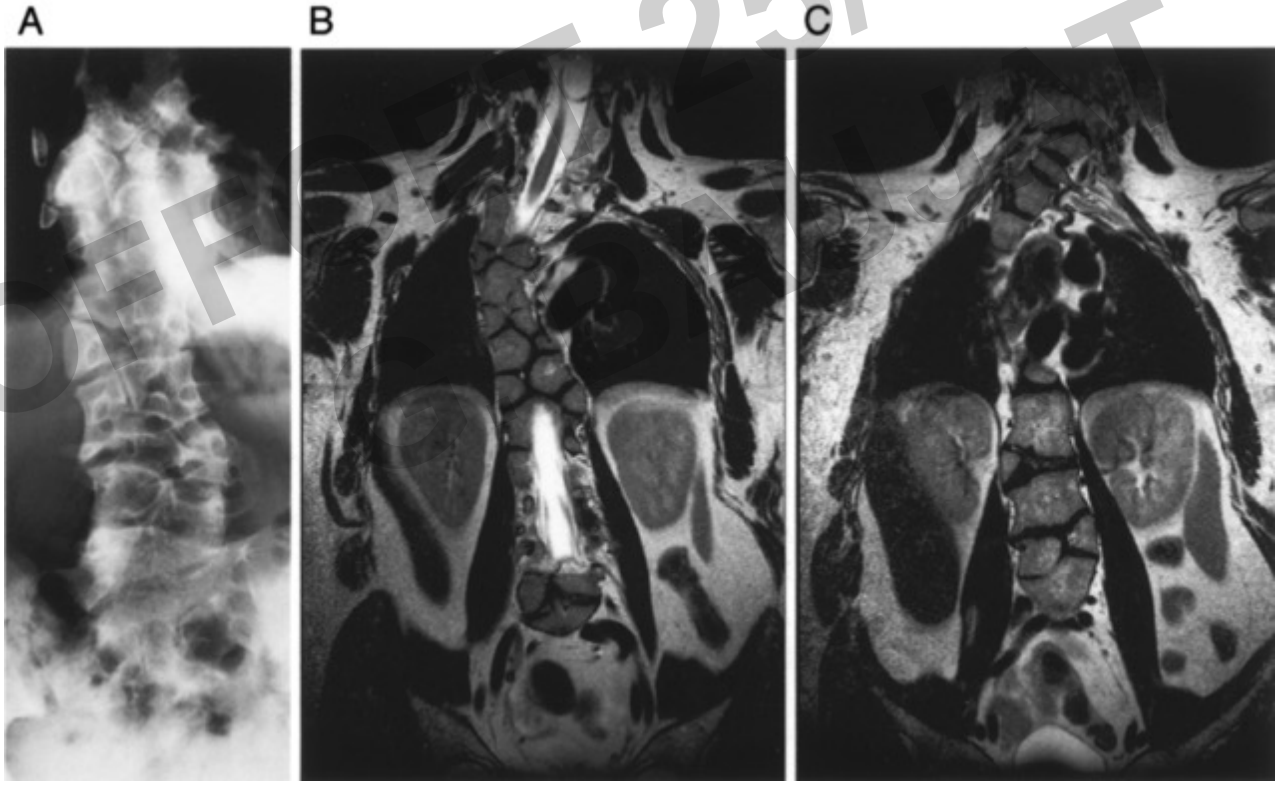




3/ SCD03 - *LFNG*

Mutation of the *LUNATIC FRINGE* Gene in Humans Causes Spondylocostal Dysostosis with a Severe Vertebral Phenotype

D. B. Sparrow,[1,*] G. Chapman,[1,*] M. A. Wouters,[2] N. V. Whittock,[8] S. Ellard,[8] D. Fatkin,[3,4,5,6] P. D. Turnpenny,[8,9] K. Kusumi,[10,11] D. Sillence,[7] and S. L. Dunwoodie[1,5,6]



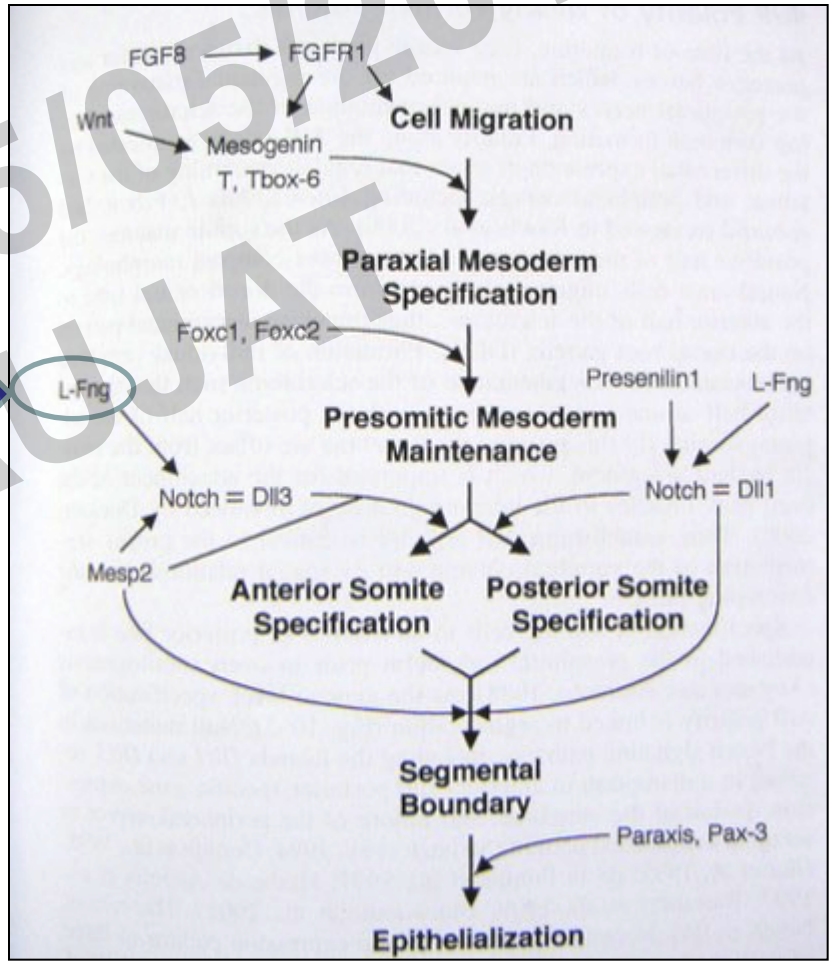
Sparrow et al ; The American Journal of Human Genetics Volume 78 January 2006

SCDO3 et *LFNG*

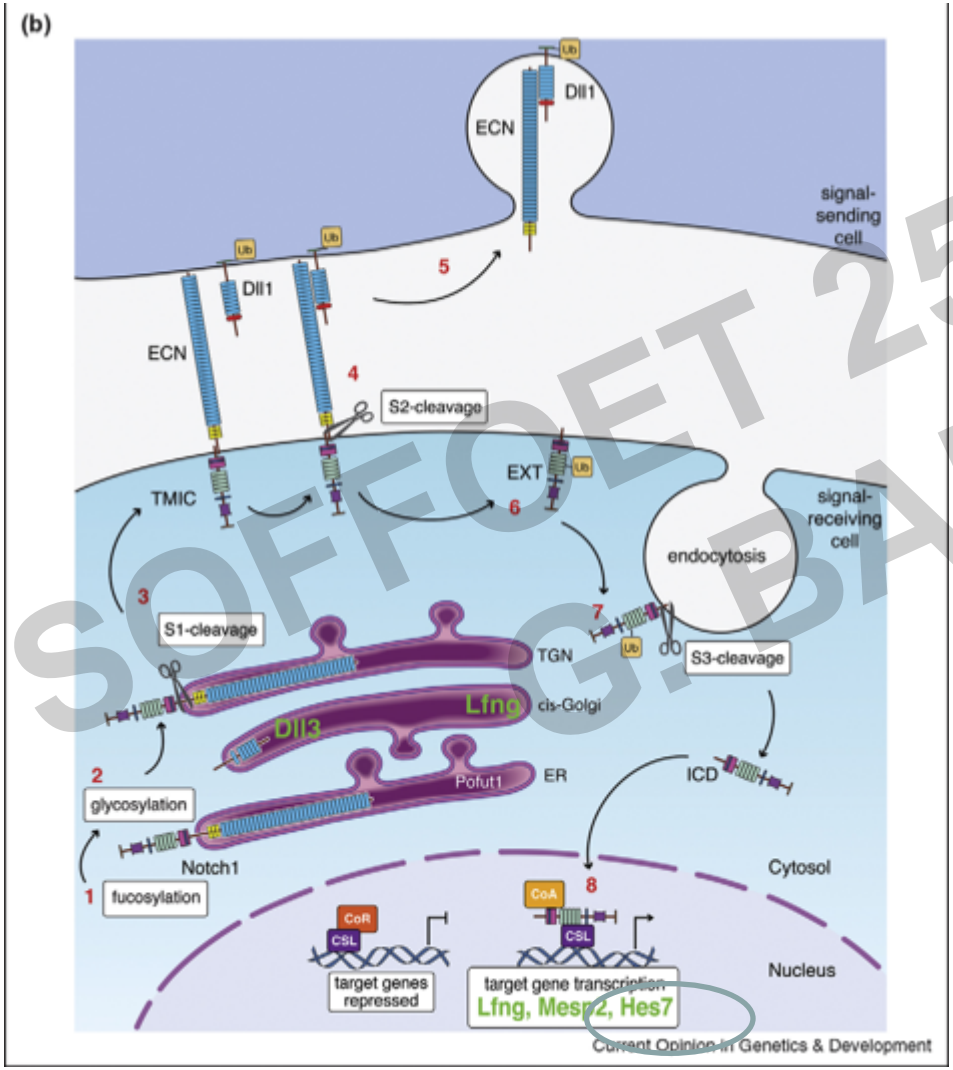
- SDC sévère touchant les vertèbres cervicales, thoraciques et lombaires avec hémivertèbres et anomalies costales

- Mutation Homozygote de exon 3 de LFNG

- Glycosyl transferase



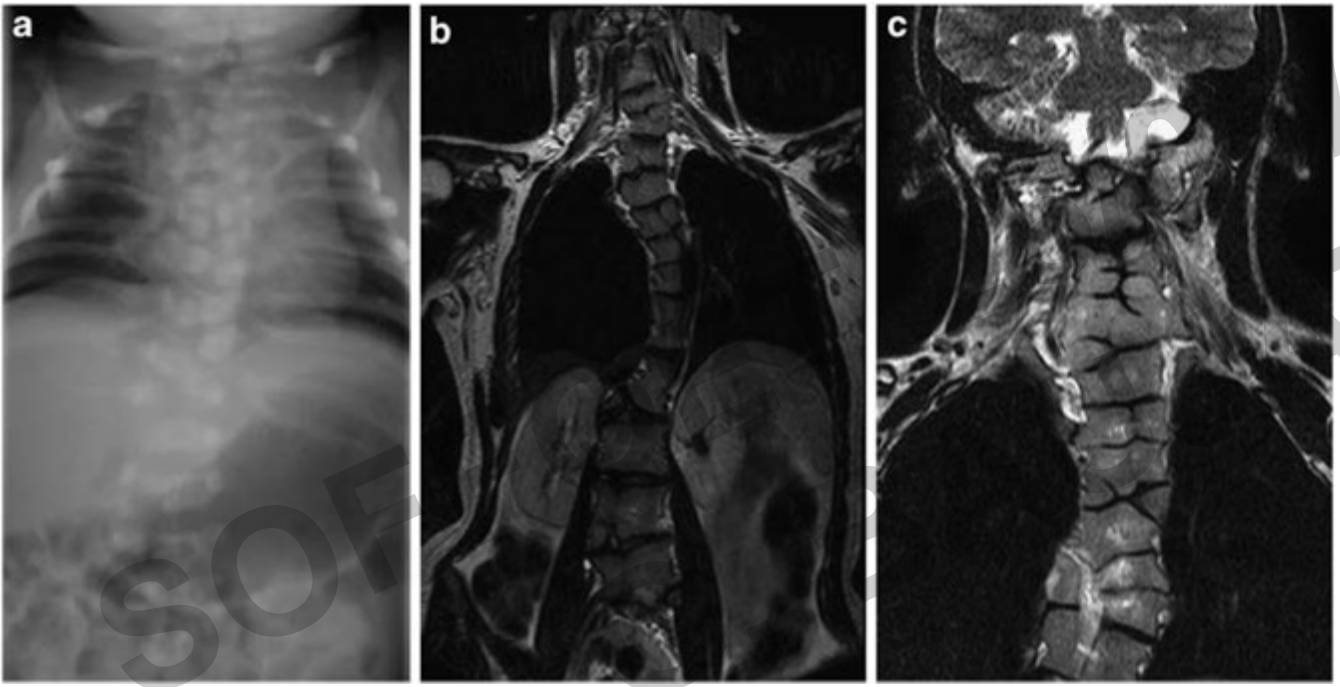
4/ SCDO4 - *HES7*

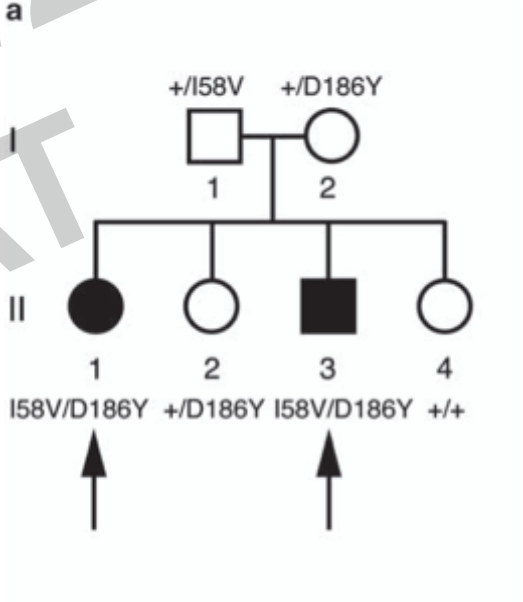


Sparrow et al; Hum Mol Genet 17(23):3761-6

- Hairy and enhancer of split 7 (HES7)
- facteur de transcription bHLH
- impliqué dans le retrocontrole de Notch via LNFG

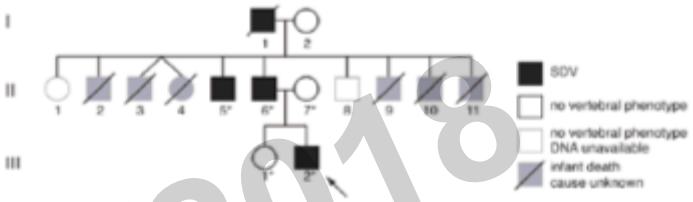
HES7-SCDO4



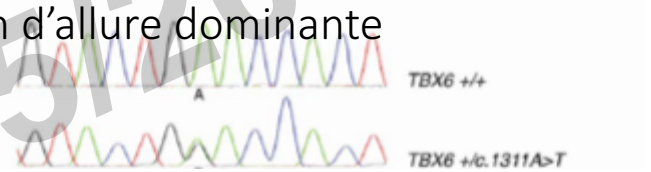


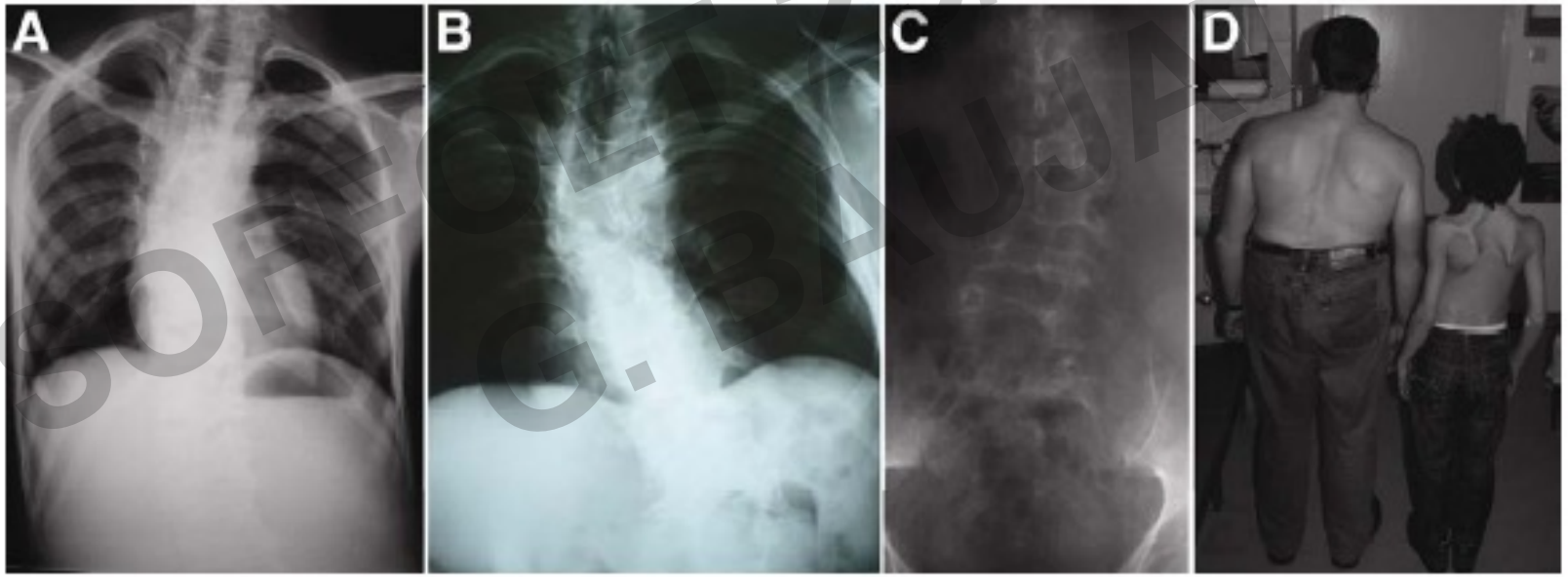
Sparrow et al ; European Journal of Human Genetics (2010) 18, 674–679

5/ *TBX6* –SCDO5



- Décrit initialement dans une grande famille avec ségrégation d'allure dominante
- mutations tronquantes
- en fait formes récessives également décrites



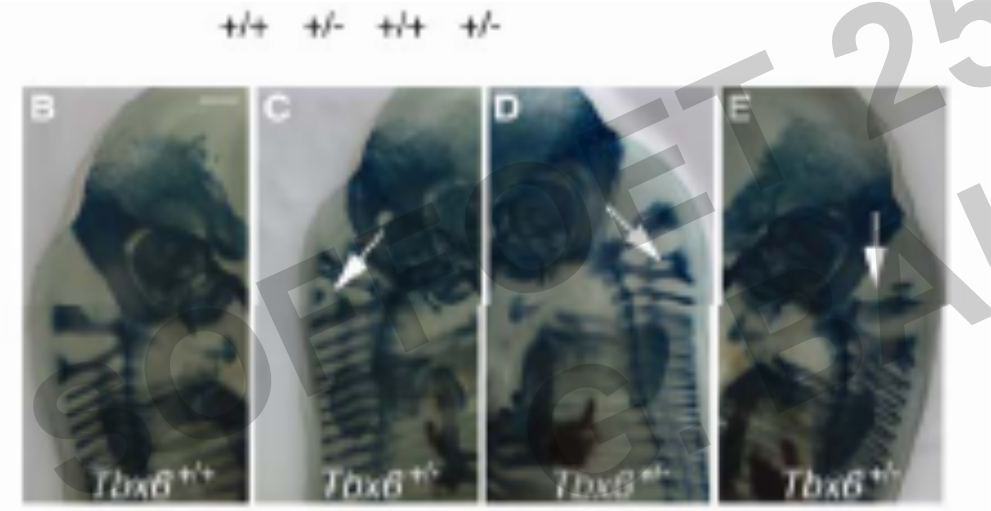


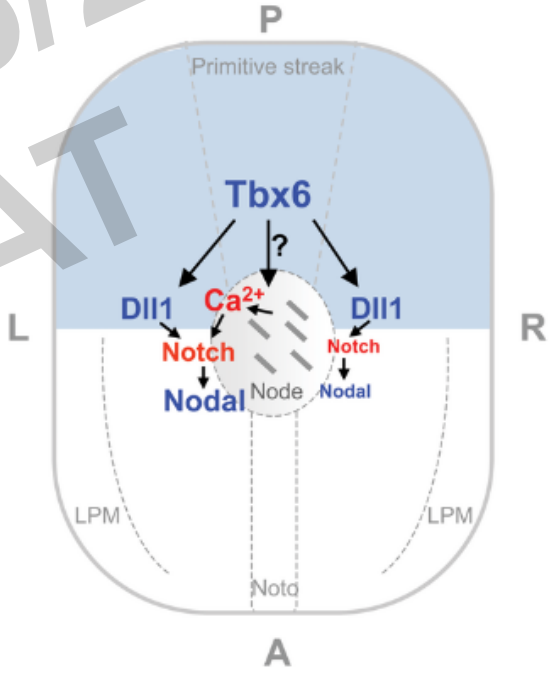
Autosomal Dominant Spondylocostal Dysostosis is Caused by Mutation in TBX6.
Sparrow et al, Hum Mol Genet. 2013 Jan 17.

TBX6 –SCD5

1- Mouse mutant *rib-vertebrae (rv)* is a hypomorphic allele of Tbx6

2-Heterozygous null *Tbx6 mouse embryos have mild vertebral defects with variable* penetrance.





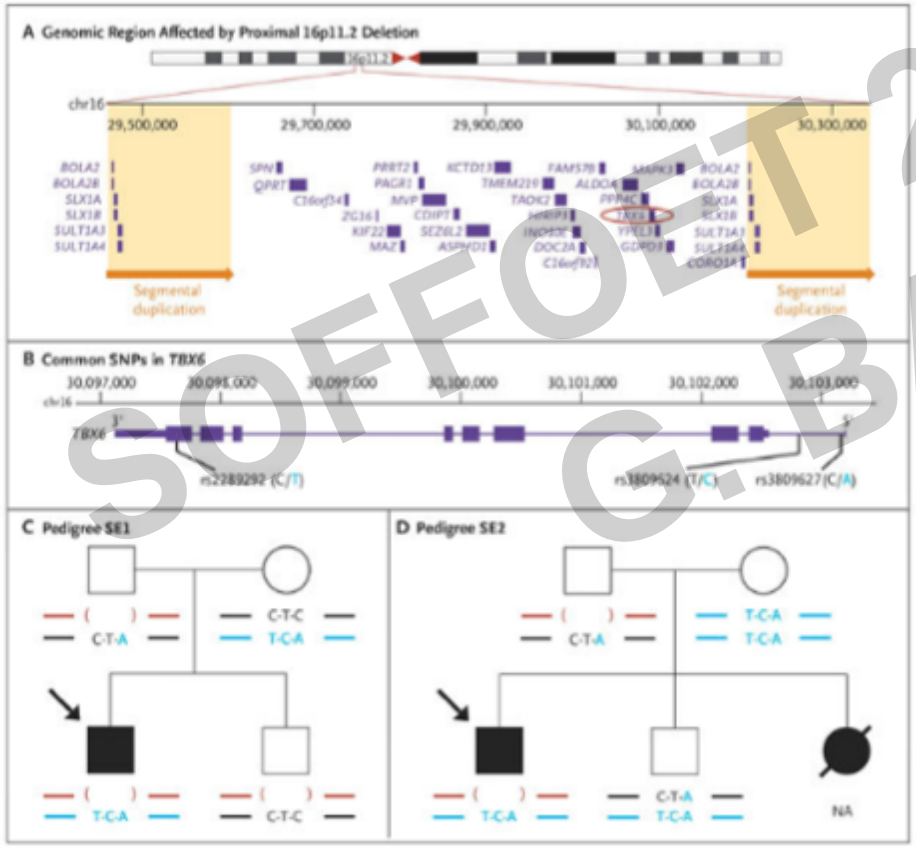
3- TBX6 directly binds to the **promoter of the Notch ligand Dll1**, and in combination with WNT signaling activates the expression of *Dll1*, a key requirement for the cyclical activation of NOTCH signaling. In addition, TBX6 **directly activates the transcription** of *Mesp2 and Ripply2*

Published in final edited form as:
N Engl J Med. 2015 January 22; 372(4): 341–350. doi:10.1056/NEJMoa1406829.

TBX6 Null Variants and a Common Hypomorphic Allele in Congenital Scoliosis

Wu et al

- Wu et al. en 2015 cohorte de 23 scoliose congénitale
- Altération monoallèlique tronquante (délétion 16p11.2 ou mutation ponctuelle)
- et haplotype commun sur l'autre allèle de TBX6



RESEARCH ARTICLE

Human Mutation

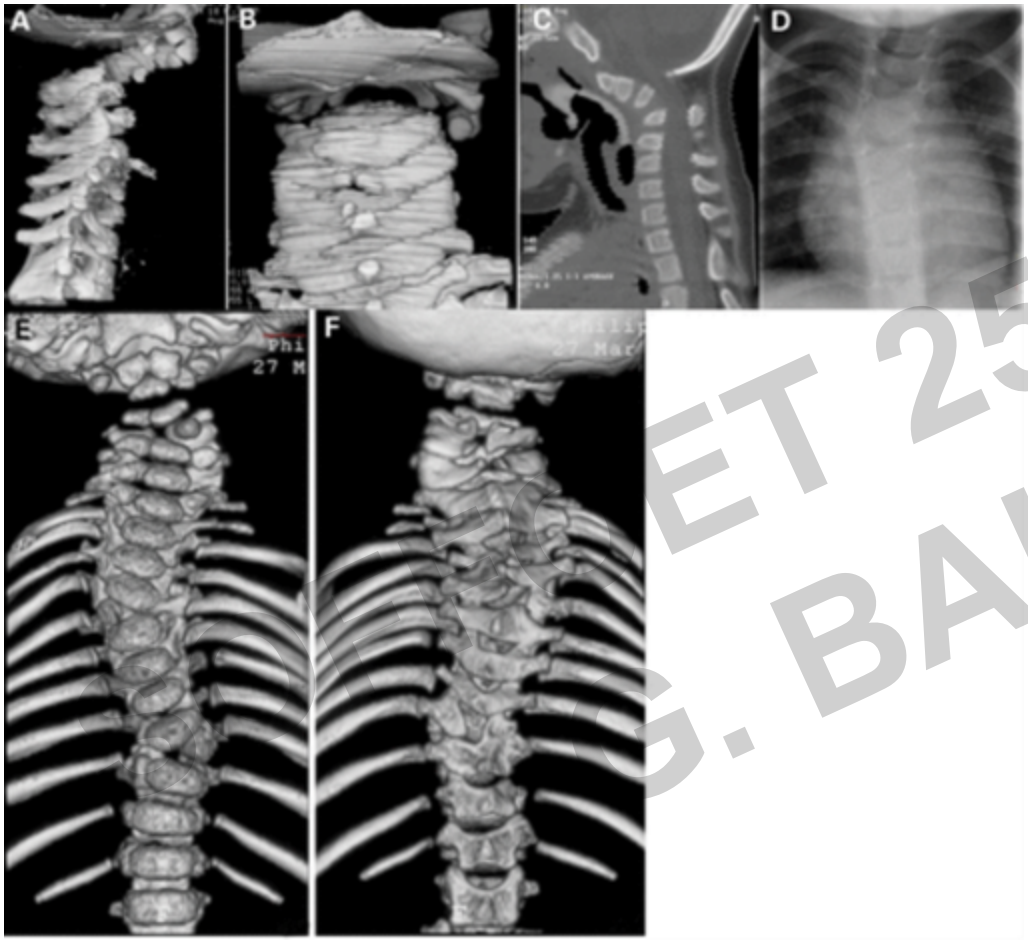
OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

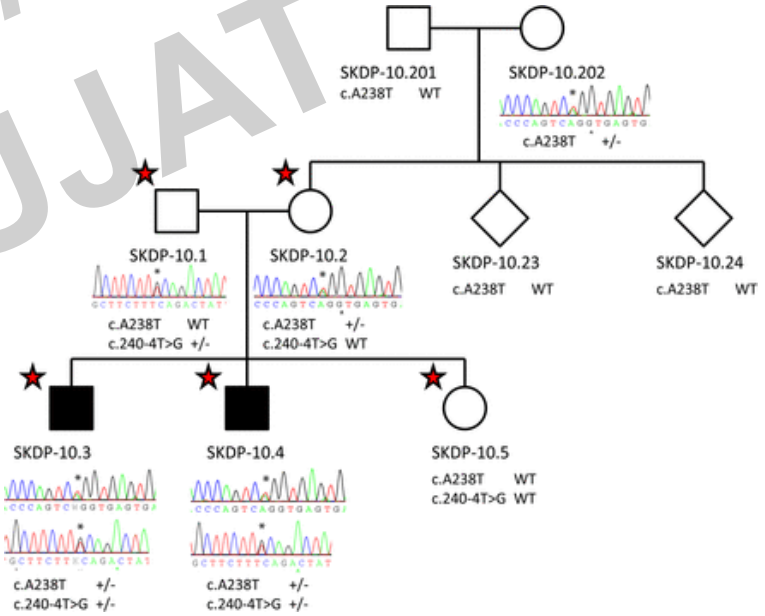
Compound Heterozygosity for Null Mutations and a Common Hypomorphic Risk Haplotype in TBX6 Causes Congenital Scoliosis

Kazuki Takeda,[1,2] Ikuyo Kou,[1] Noriaki Kawakami,[3] Aritoshi Iida,[1] Masahiro Nakajima,[1] Yoji Ogura,[1,2] Eri Imagawa,[4] Noriko Miyake,[4] Naomichi Matsumoto,[4] Yukuto Yasuhiko,[5] Hideki Sudo,[6] Toshiaki Kotani,[7] Japan Early Onset Scoliosis Research Group,[†] Masaya Nakamura,[2] Morio Matsumoto,[2] Kota Watanabe,[2*] and Shiro Ikegawa[†‡]

[†]*Laboratory of Bone and Joint Diseases, Center for Integrative Medical Sciences, RIKEN, Tokyo 160-8582, Japan;* [2]*Department of Orthopaedic Surgery, Keio University School of Medicine, Tokyo 108-8639, Japan;* [3]*Department of Orthopaedic Surgery, Meijo Hospital, Nagoya 460-0001, Japan;* [4]*Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan;* [5]*Division of Cellular and Molecular Toxicology, National Institute of Health Sciences, Tokyo 158-8501, Japan;* [6]*Department of Advanced Medicine for Spine and Spinal Cord Disorders, Hokkaido University Graduate School of Medicine, Sapporo 060-8648, Japan;* [7]*Department of Orthopaedic Surgery, Seirei Sakura Citizen Hospital, Sakura 285-0825, Japan*

5/SCDO6 – *RIPPLY2*





From: Compound heterozygous mutations in RIPPLY2 associated with vertebral segmentation defects
Hum Mol Genet. 2014;24(5):1234-1242.

RESEARCH ARTICLE

Ripply2 recruits proteasome complex for Tbx6 degradation to define segment border during murine somitogenesis

Wei Zhao[1,2†‡], Masayuki Oginuma[1†§], Rieko Ajima[1,3,4†], Makoto Kiso[1,3], Akemi Okubo[1], Yumiko Saga[1,2,3,4*]

[1]Division of Mammalian Development, National Institute of Genetics, Mishima, Japan; [2]Department of Biological Sciences, Graduate School of Science, The University of Tokyo, Tokyo, Japan; [3]Mouse Research Supporting Unit, National Institute of Genetics, Mishima, Japan; [4]Department of Genetics, SOKENDAI, Mishima, Japan

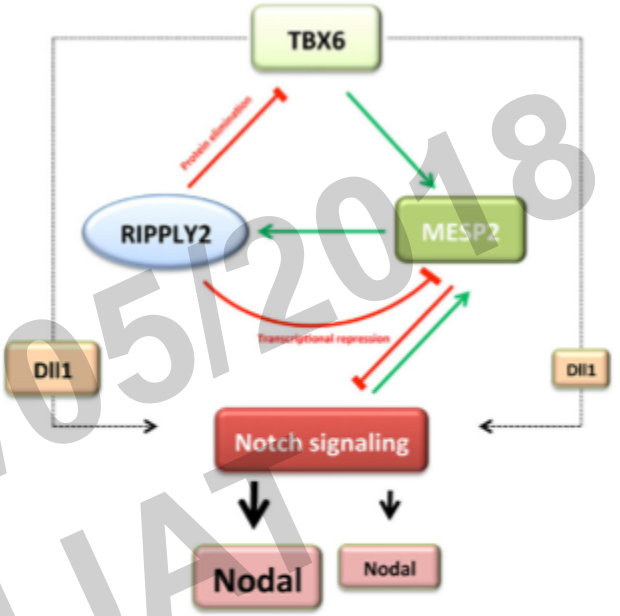
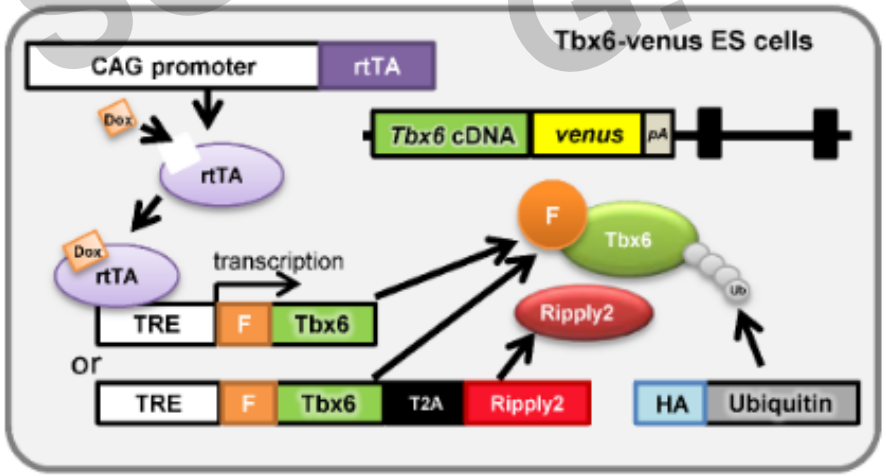


FIG. 2.
Characteristics of the interplay among *RIPPLY2*, *TBX6*, and *MESP2* and their relation in the notch signaling pathway and L/R axis determination. *RIPPLY2* is negatively regulating *TBX6* via transcriptional repression and protein elimination. *TBX6* is proposed to regulate asymmetric nodal expression through Dll1 expression and notch signaling. This scheme was prepared based on the functional data provided by Hadjantonakis et al. [2008] and Takahashi et al. [2013]. Green arrows represent activation and red lines represent inhibition.

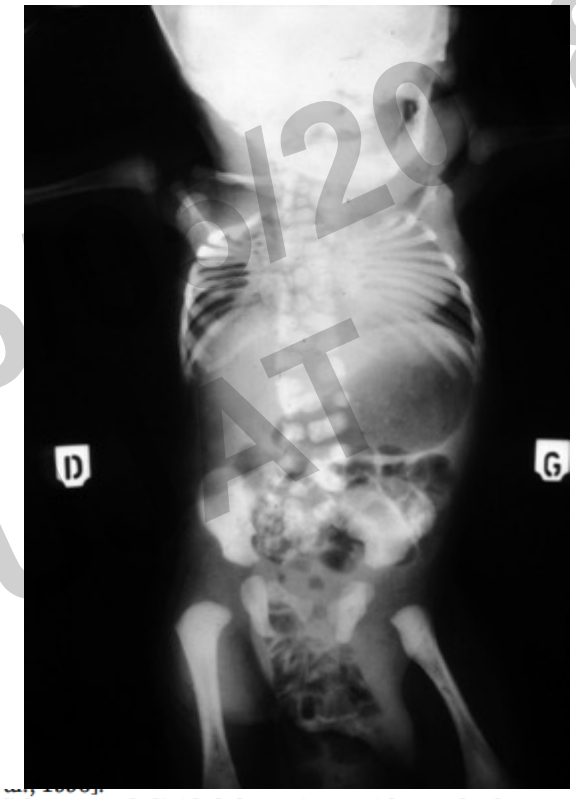
T

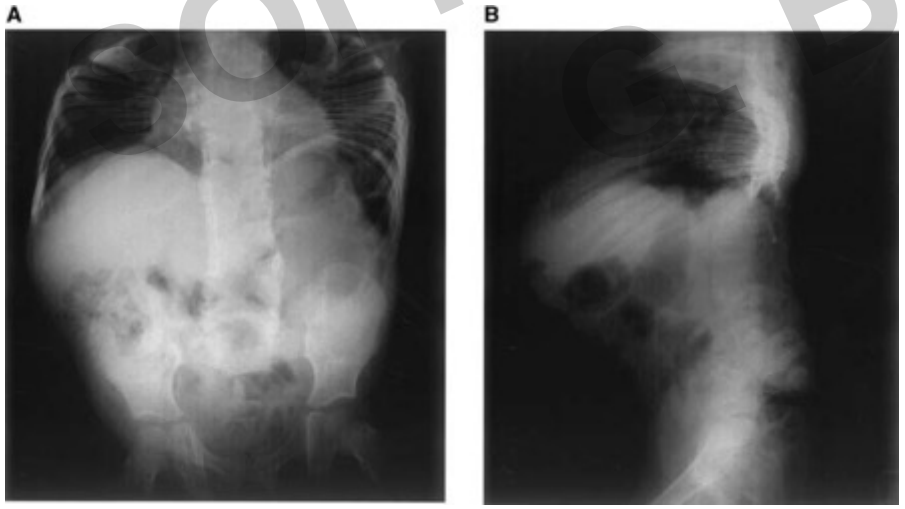


Karaca 2015

II/ Dysostose spondylo-thoracique / Jarcho-Levin

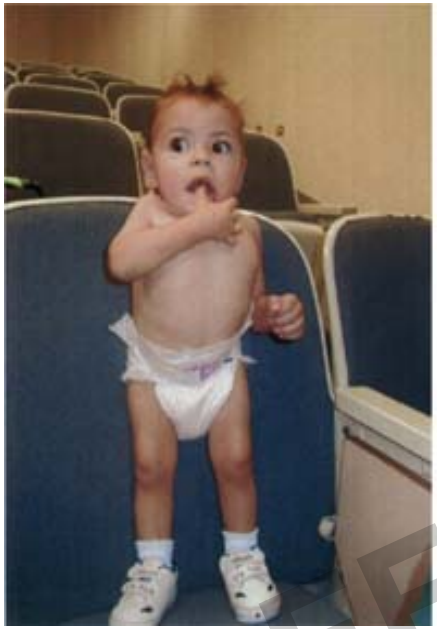
- Jarcho et Levin, 1938
  - Déformation des cotes en crabe
  - nombreuses fusions vertébrales
- Dysostose spondylo-thoracique
  - Désorganisation des noyau vertébraux
  - Fusion de l'extrémité postérieure des cotes responsable de l'éventail
  - Hernies
  - Décès par insuffisance respiratoire

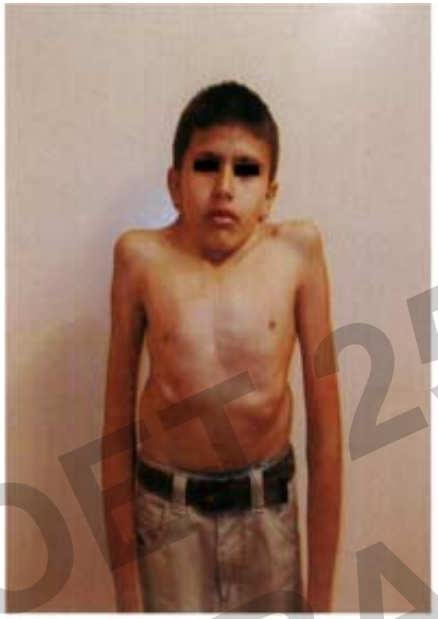


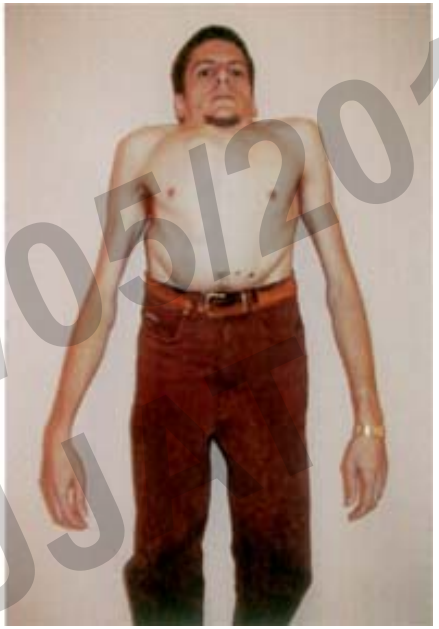


Solomon et al. divided the patients with vertebral anomalies and thoracic cage deformities in two groups: spondylothoracic and spondylocostal dysostosis, based on the extent of the skeletal anomalies, mode of inheritance and survival. The term "spondylocostal dysostosis" was suggested for patients with associated intrinsic changes of the ribs such as broadening, bifurcation and fusion without the fan-like configuration of the thorax. Both autosomal dominant and recessive modes of inheritance have been described and associated with good prognosis. The term STD was restricted to patients with an apparent autosomal recessive pattern of transmission and a fan-like configuration of the ribs (crab-like chest) due to fusion of the ribs at the costo-vertebral junctions without intrinsic costal anomalies. All of the patients described in their paper died early in life due to pulmonary complications.

Dysostose spondylo-thoracique







- Port Rico (Cornier et al 2004)
  - côtes en éventail avec fusion posterieure, par anomalie de la jonction chondro-costale
  - vertèbres en puzzle dorsales et lombosacrées en nombre diminué
  - pronostic sévère
  - mortalité 50%,
  - RA

number of vertebral bodies. Characteristic vertebral shape consisted of a decrease in antero-posterior diameter and an increase in lateral length, giving the vertebra a sickle shape. Eight out of 18 prospectively follow patients died within the first 6 months of life, a 44% mortality rate. Cause of death was respiratory insufficiency secondary to pneumonia and pulmonary restriction. This is an important finding since the vast majority of STD syndrome patients cited in the medical literature have died in the newborn and early childhood periods. Age of the remaining patients ranged from 4 months to 47 years. This represents the largest collection of patients with STD reported and it has allowed us to determine a detailed phenotype

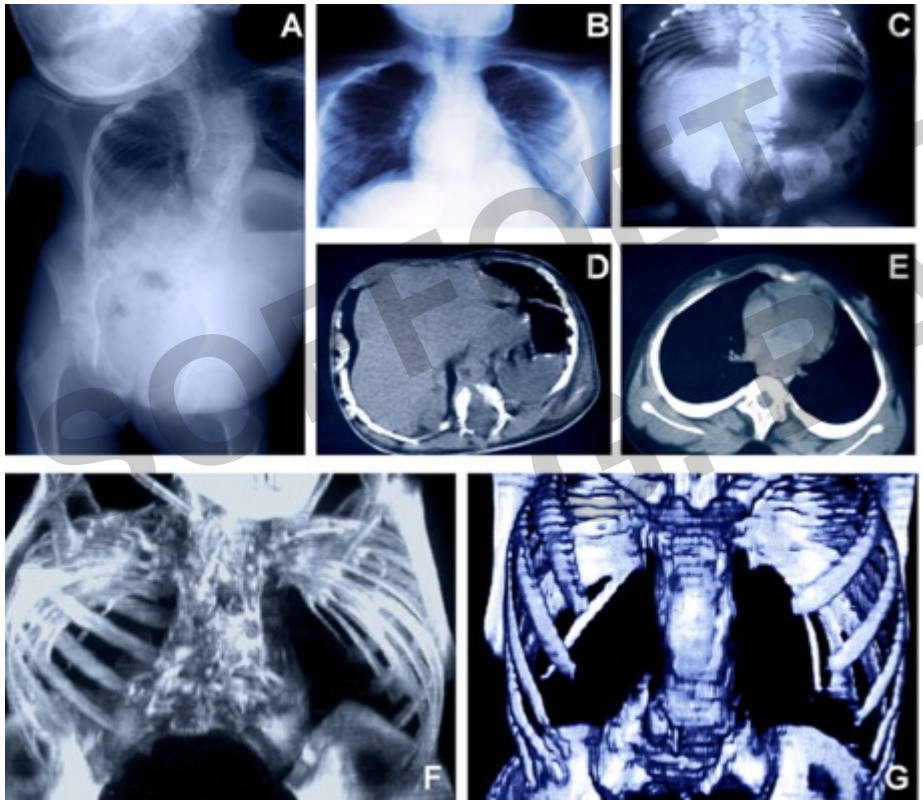
American Journal of Medical Genetics 128A:120–126 (2004)

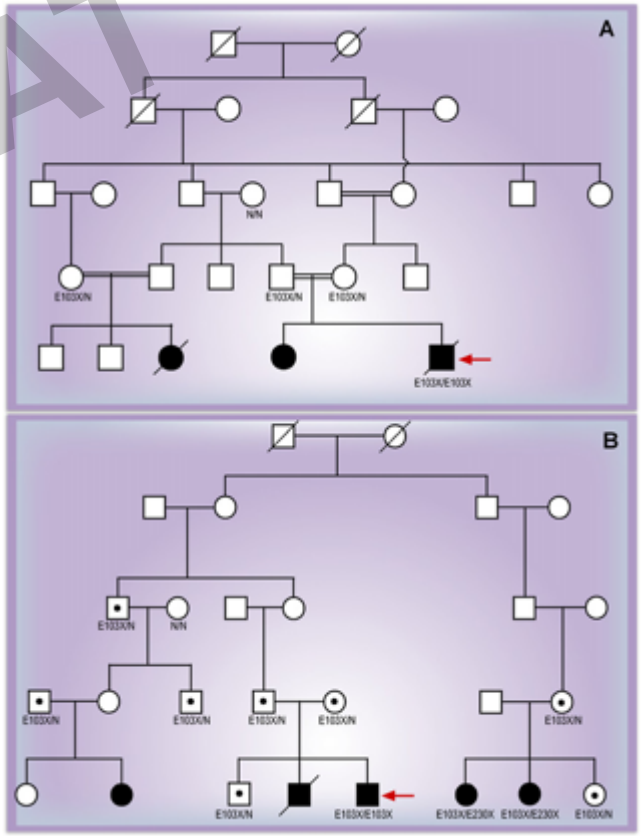
Mutations homozygotes de *MSP2* E103X (*origine Portoricaine*)

REPORT

Mutations in the *MESP2* Gene Cause Spondylothoracic Dysostosis/Jarcho-Levin Syndrome

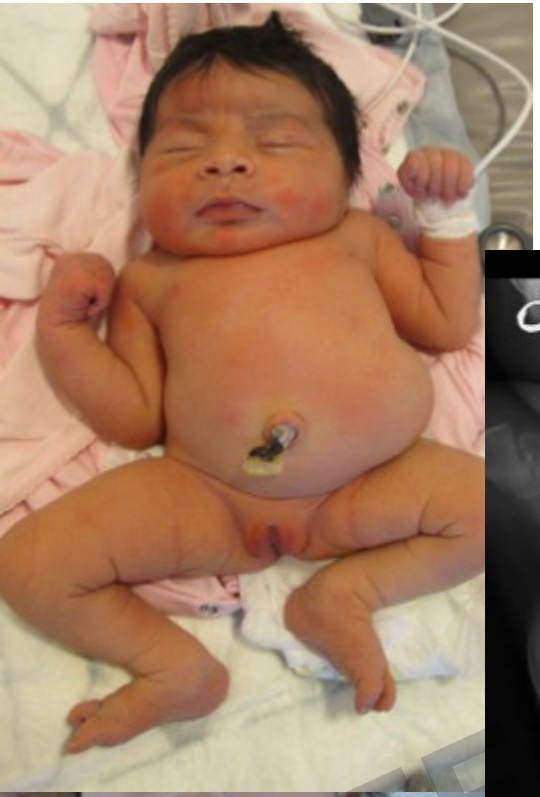
Alberto S. Cornier,[1,2,11] Karen Staehling-Hampton,[3,11] Kym M. Delventhal,[3] Yumiko Saga,[4] Jean-Francois Caubet,[5] Nobuo Sasaki,[4] Sian Ellard,[6] Elizabeth Young,[6] Norman Ramirez,[7] Simon E. Carlo,[1,8] Jose Torres,[2] John B. Emans,[5] Peter D. Turnpenny,[9] and Olivier Pourquié[10,*]

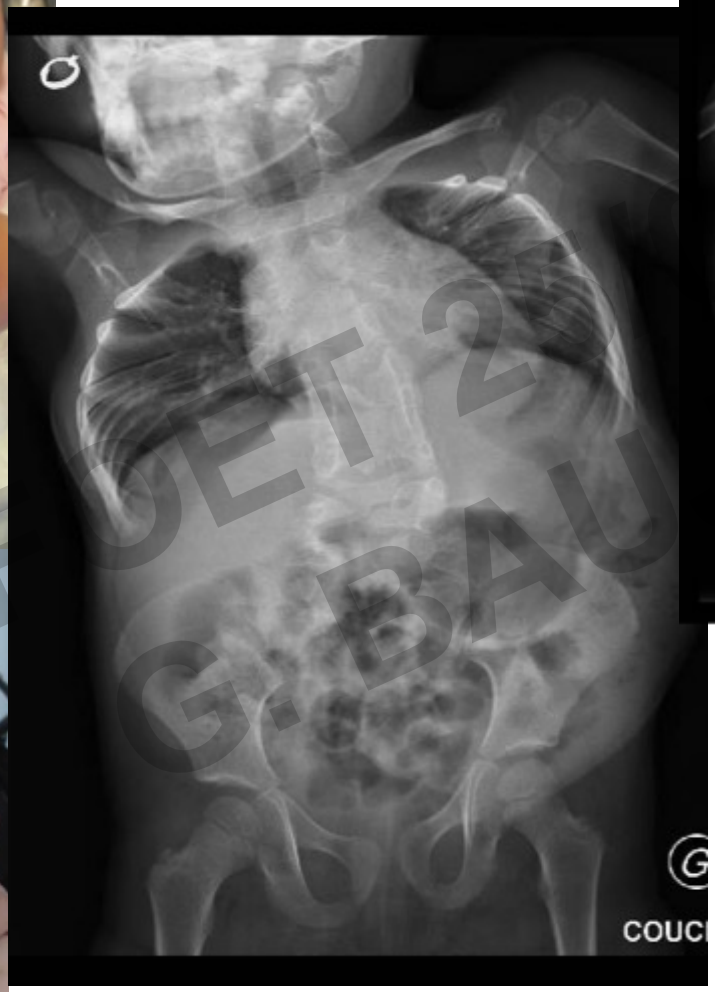


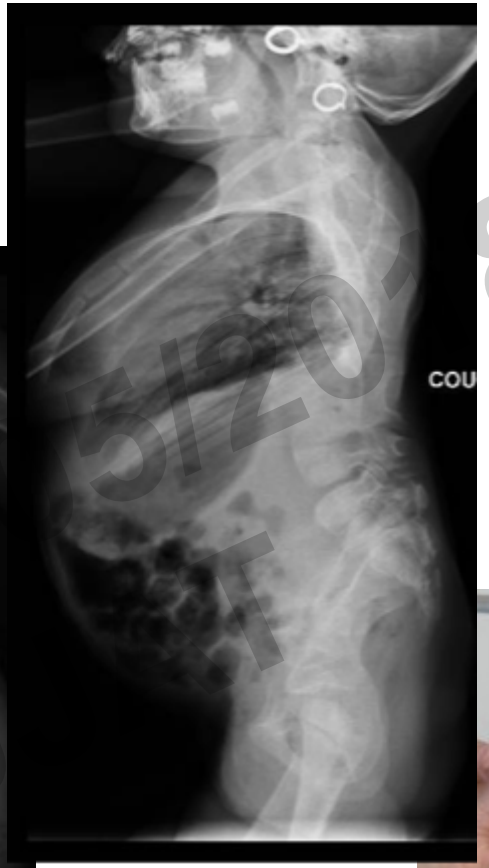


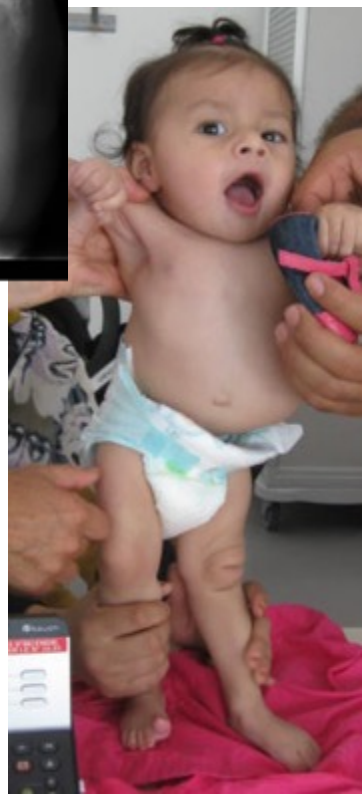
et hétérogénéité moléculaire

The American Journal of Human Genetics Volume 78 January 2006



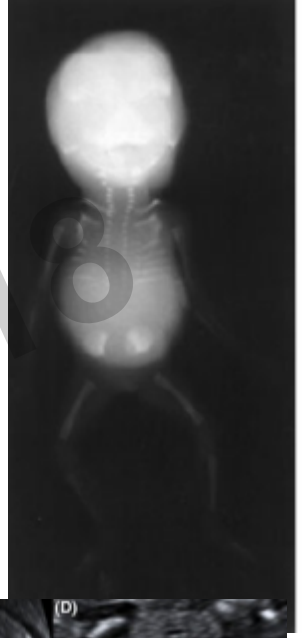


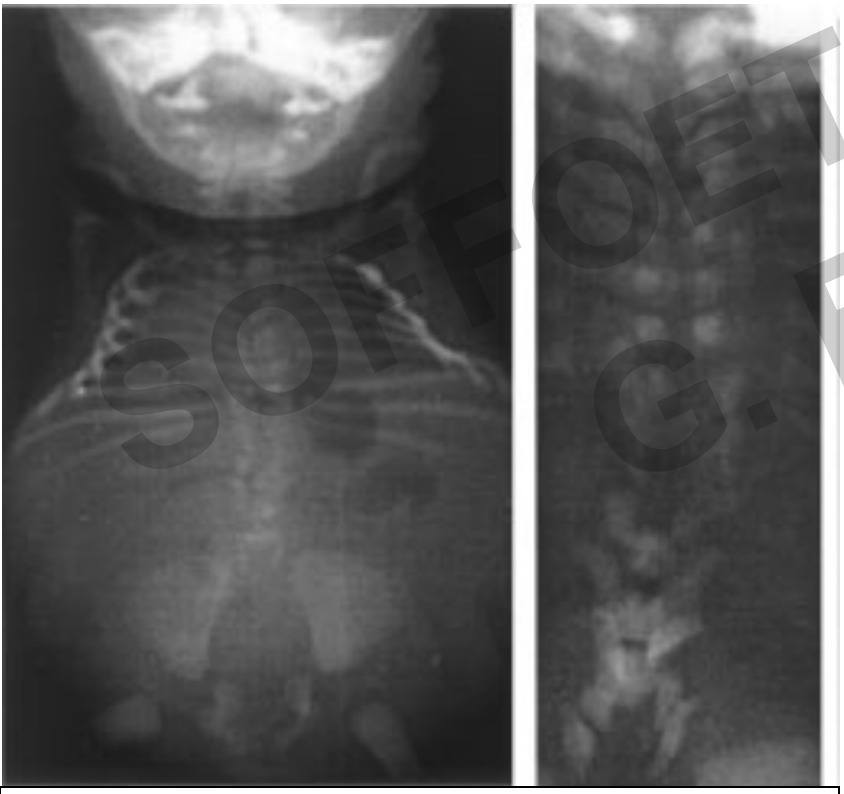




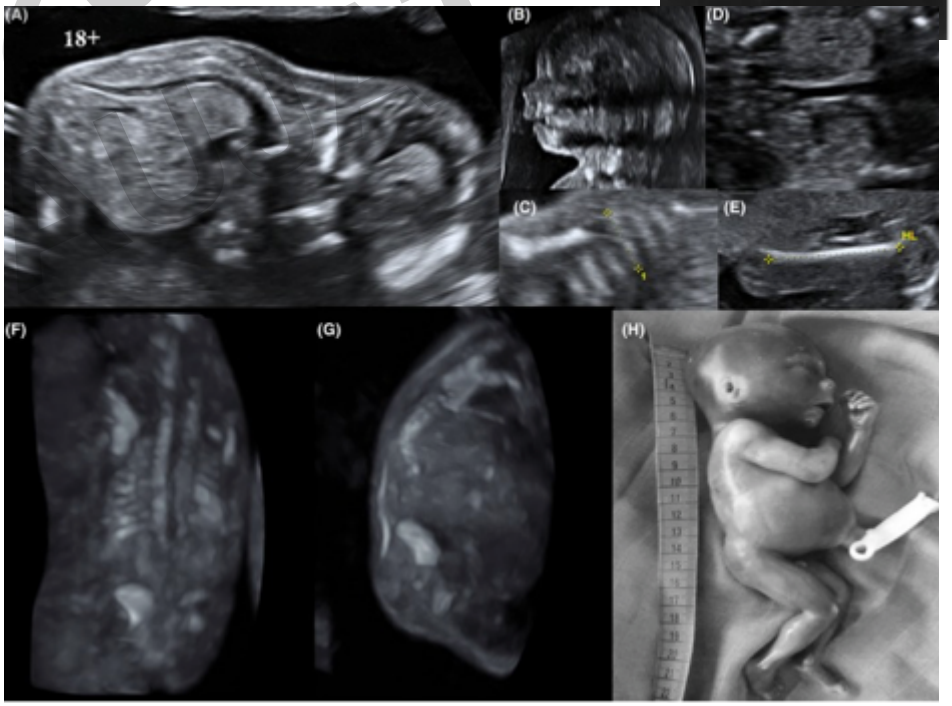
Diaphanospondylodysostose

- Dysostose spondylocostale +/- étendue
- Absence de fusion des corps vertébraux
- Éperon ostéo-dural central (du CV)
- Hypertrichose/ spina bifida / élargissement du canal rachidien
- +/- kystes rénaux, néphroblastomatose
- *BMPER*





Gonzales et al , AJMG136A:373–376 (2005)

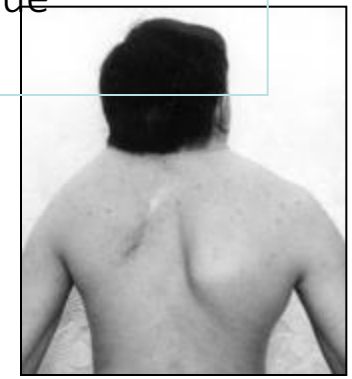


Hofstaetter 2018

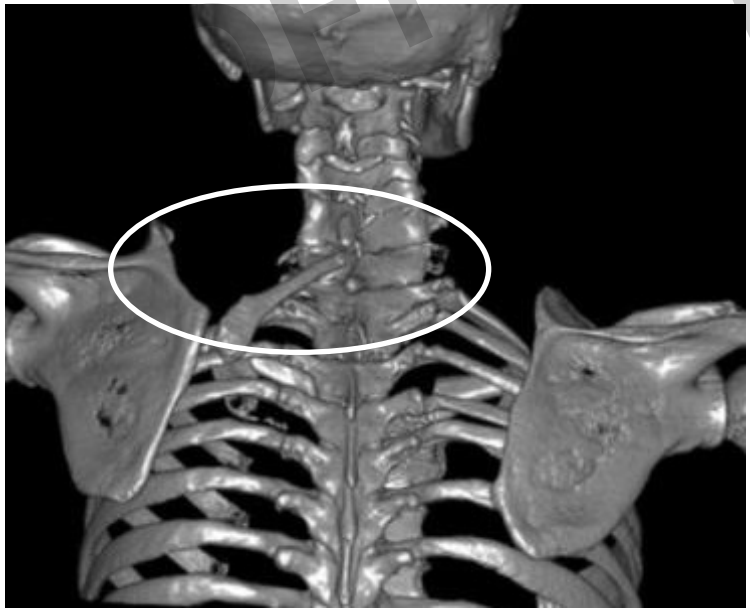
Troubles de la segmentation rachidienne syndromique **cervicale**

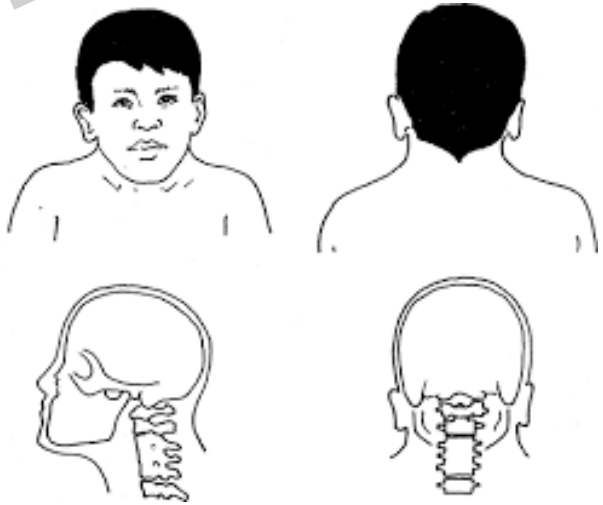
Anomalie de Klippel Feil

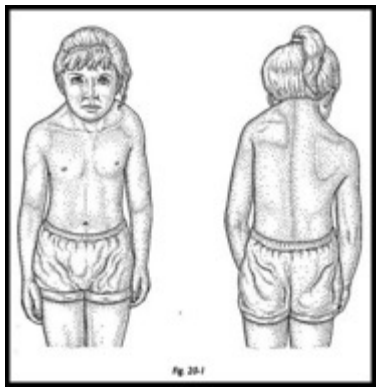
- Anomalie des vertèbres cervicales et dorsales avec hemivertebre et fsuion vertébrales, ptérygium colli, implantation basse des cheveux
- formes décrites RA, DA et sporadique



✓+/- anomalie de Sprengel
✓+/- os omovertebral
✓ Pronostic = f(extension anomalies)
✓ classifications
- ✓ Gunderson, 1967 (/ radio)
  - I / Fusion complète du rachis cervical
  - II / Synostose de 2 vertèbres
  - III/ Anomalies cervicales + dorsales + lombaires
- ✓ Clarke, 1995 (/ transmission)







KFS1 : autosomique dominant : *GDF6*

RESEARCH ARTICLE

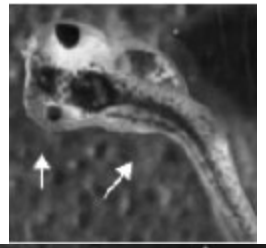
Mutations in GDF6 Are Associated With Vertebral Segmentation Defects in Klippel-Feil Syndrome

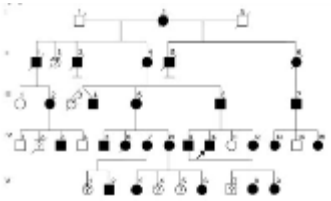
May Tassabehji,[1] Zhi Ming Fang,[2] Emma N. Hilton,[1,3] Julie McGaughran,[4] Zhongming Zhao,[5] Charles E. de Bock,[2] Emma Howard,[6] Michael Malass,[1] Dian Donnai,[1] Ashish Diwan,[7] Forbes D.C. Manson,[3] Dédée Murrell,[7] and Raymond A. Clarke[2,7,8]*

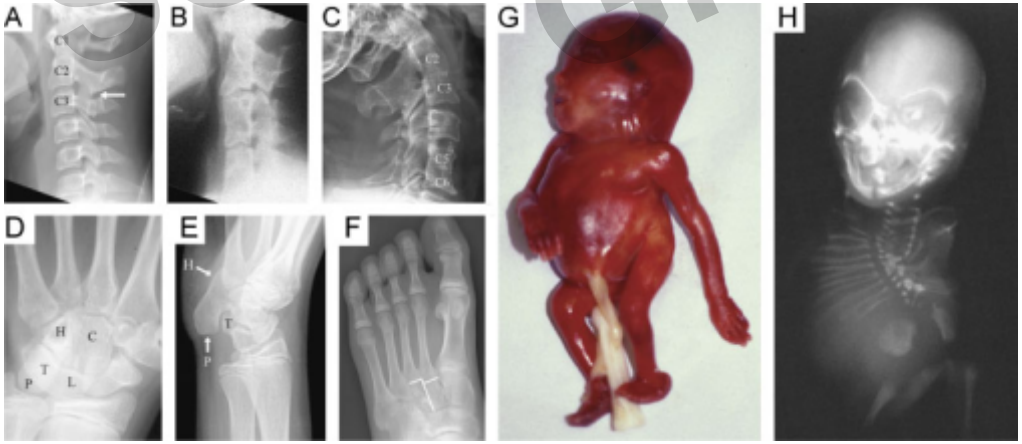
- 1 famille avec inversion paracentric en 8q22q23 contenant GDF6
- 2 cas sporadiques et 1 large famille
- Squelette, ORL, palais, articulations
- Missense mutation de *GDF6*, BMPs/ TGFβ superfamily
- Mutation récurrente C.866C>T avec fusion carpo-tarsale
- Modèles murin et xenopus: espace intervertébral, articulations
- Xenopus model: anomalies oculaires + axiales
- Mouse studies : carpo-tarsal fusions + axial defect

TABLE 1. Correspondence Between Discrete Gdf6 Expression Patterns and Cartilage, Bone, Ligament, and Joint anomalies of Family KF2-01

	Gdf6 Expression in mouse embryos			Human Family KF2-01
Cartilage/ ligament structure	Endogenous [Settle et al., 2003]	LacZ [Merlock et al., 2003]	Gdf6 −/− [Settle et al., 2003]	Phenotype (% affected)
Vertebral interspaces	Vertebral joints	Vertebral joints	Intervertebral cartilage reduced, scoliosis	Fusion of vertebral bodies and lamina (100); scoliosis in thoracic and lumbar spine (100)
Dorsal neural tube		Craniocaudal gradient		Craniocaudal fusion frequency gradient
Ear				
Pinna cartilage		Pinna cartilage		Absent pinna cartilage or ears low set (90)
Meatus cartilage		Facial cartilage		Restricted auditory canal and/or microtia (80)
Middle ear joints	Middle ear joints	Middle ear joints	Middle ear joints reduced	Conductive hearing impairment (30)
Larynx Cartilages	Laryngeal cartilages	Thyroid and cricoid cartilage		Malformed thyroid and cricoid cartilages; infantile epiglottis and narrow glottic chink
Vocal folds	Vocal folds	Vocal folds		Completely aphonic; no fold vibration; one female; short misaligned vocal folds; severe vocal impairment (80); learning difficulties (50)
Palate Face and mouth	Palate Teeth	Palate Teeth		High palate Microstomia, micrognathia and/or short tongue (80)
Carpal joints	Carpal joints	Carpal joints	Bilateral carpal coalition	Bilateral carpal coalition (50); gradation of pisiform expansion (100)
Tarsal joints Talus joint Tendons of feet and hands	Tarsal joints Talus joint	Tarsal joints	Tarsal coalition Talus coalition	Bilateral tarsal coalition Talocalcaneal coalition Difficulty grasping, writing, and toe-walking (100)
Elbow joint	Elbow joint	Elbow joint	Negative ulna variance	Restricted elbow movement (100); negative ulna variance
Hip joint Scapula	Hip joint	Hip joint Edge of scapula		Perthes; one male affected family member Elevated scapula; Sprengel anomaly (50)







Human Mutation 2008, 29:1017

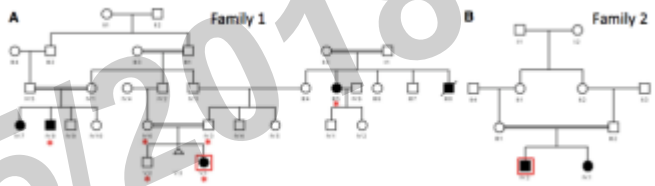
KFS2 : autosomique récessif : MEOX1

REPORT

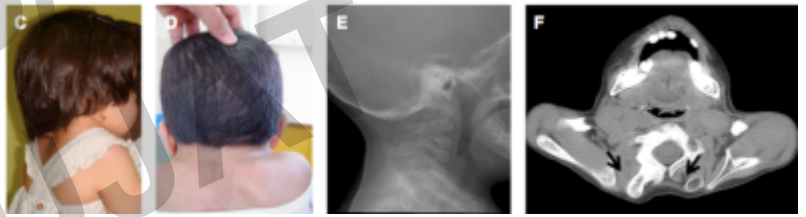
Mutations in *MEOX1*, Encoding Mesenchyme Homeobox 1, Cause Klippel-Feil Anomaly

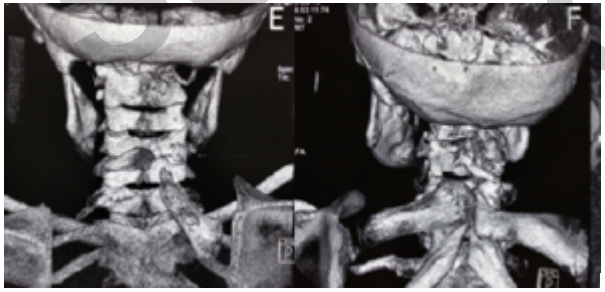
Jawahir Y. Mohamed,[1] Eissa Faqeih,[2] Abdulmonem Alsiddiky,[3] Muneera J. Alshammari,[1,4] Niema A. Ibrahim,[1] and Fowzan S. Alkuraya[1,5,*]

The American Journal of Human Genetics *92*, 157–161, January 10, 2013



2 familles consanguines
KFS isolé
MEOX1
Mutation tronquantes et deletion frameshift
Facteur de transcription, somitogenèse
Différentiation du sclérotome

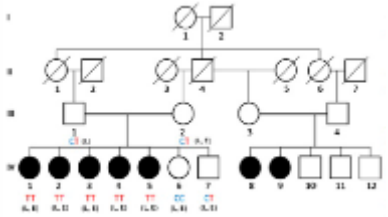




Mutation in *MEOX1* gene causes a recessive Klippel-Feil syndrome subtype

Fatih Bayrakli[1,2*†], Bulent Guclu[3†], Cengiz Yakicier[4], Hatice Balaban[5], Ugur Kartal[2], Bekir Erguner[6], Mahmut Samil Sagiroglu[6], Sirin Yuksel[4], Ahmet Rasit Ozturk[7], Burak Kazanci[3], Unal Ozum[1] and Hamit Zafer Kars[1]

Bayrakli *et al. BMC Genetics* 2013, **14**:95

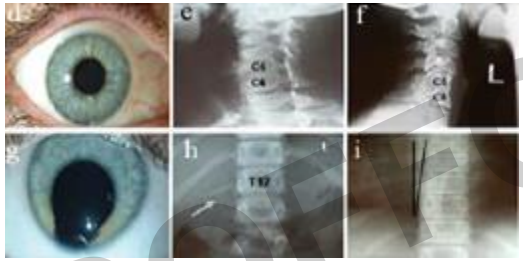


KFS3, autosomique dominant : *GDF3*

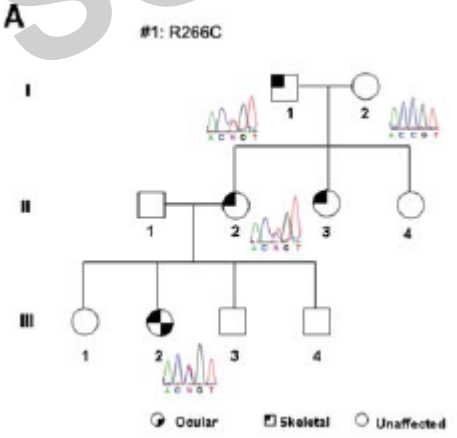
Mutation of the bone morphogenetic protein GDF3 causes ocular and skeletal anomalies

Ming Ye1,3{, Karyn M. Berry-Wynne2{, Mika Asai-Coakwell1,3, Periasamy Sundaresan4, TimFootz3, Curtis R. French2, Marc Abitbol5, Valerie C. Fleisch2, Nathan Corbett6, W. Ted Allison2,Garry Drummond1, Michael A. Walter1,3, T. Michael Underhill6, Andrew J. Waskiewicz2and Ordan J. Lehmann1,3,

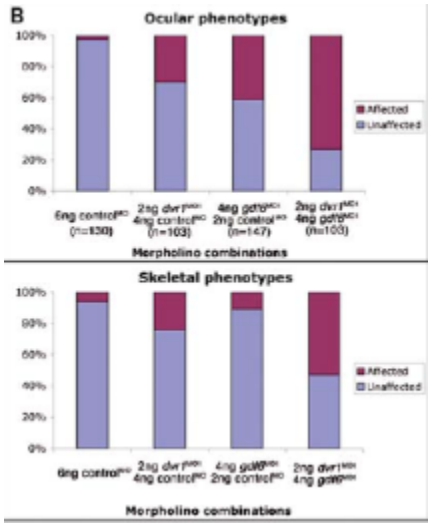
Human Molecular Genetics, 2010, Vol. 19, No. 2



Mutation	Phenotypes		Inheritance	Designation	Region
	Ocular	Skeletal			
R266C	None	Scoliosis	Autosomal dominant	#1.I-1	North America
R266C	None	Klippel–Feil and vertebral fusion	Autosomal dominant	#1.II-2	North America
R266C	None	Klippel–Feil and vertebral fusion	Autosomal dominant	#1.II-3	North America
R266C	Unilateral iris and retinal coloboma	Rudimentary 12th ribs, mild scoliosis	Autosomal dominant	#1.III-2[a]	North America
L305P	Unilateral microphthalmia	None	Incomplete penetrance	#2.1	Asia
L305P	None	None	–	#2.2	Asia
R266C	Bilateral coloboma, microphthalmia, nystagmus	None	Autosomal dominant	#3.1[b]	Europe
R266C	Bilateral coloboma, mild microphthalmia	Unknown	Autosomal dominant	#3.2	Europe
R266C	Bilateral coloboma and microphthalmia	Anomalous right temporal bone	Not known	Proband 4	Europe
R195Q	Unilateral microphthalmia	None	Autosomal dominant	Proband 5	Europe
R274W	Bilateral microphthalmia and coloboma	None	Not known	Proband 6	Asia
L305P	Bilateral iris coloboma	None	Not known	Proband 7	Asia



- Ophtalmo : colobome, microphtalmie
- Squelette : KFS, scoliose, côtes
- Stratégie gène candidat
- *GDF3* : missense variants
- Pénétrance incomplète



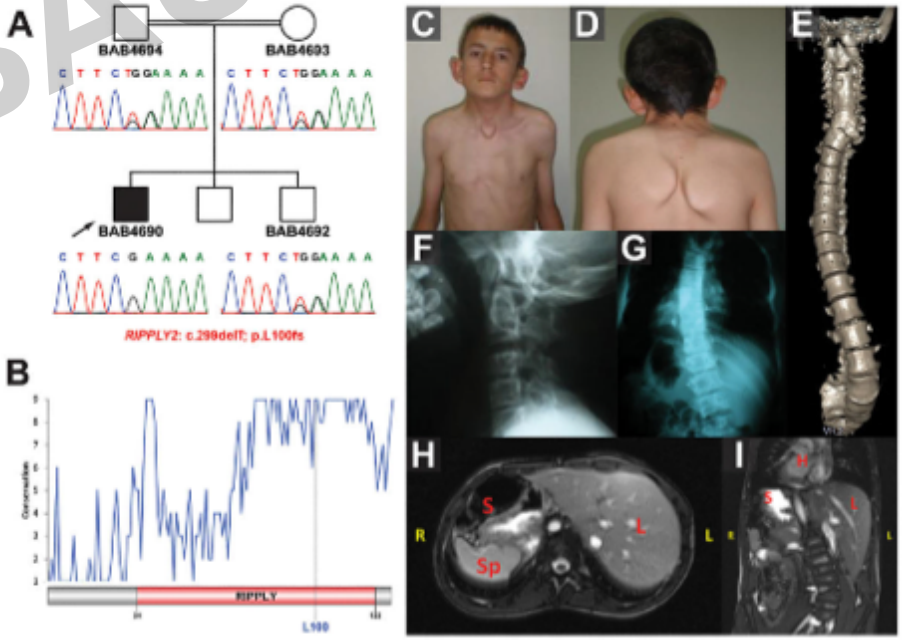
KFS4, autosomique récessif, *RYPPL*

Am J Med Genet A. Author manuscript; available in PMC 2016 April 20.

Published in final edited form as:
Am J Med Genet A. 2015 November ; 167A(11): 2795–2799. doi:10.1002/ajmg.a.37263.

Rare Variants in the Notch Signaling Pathway Describe a Novel Type of Autosomal Recessive Klippel–Feil Syndrome

Ender Karaca[1], Ozge O. Yuregir[2], Sevcan T. Bozdogan[3], Huseyin Aslan[4], Davut Pehlivan[1], Shalini N. Jhangiani[1,5], Zeynep C. Akdemir[1], Tomasz Gambin[1], Yavuz Bayram[1], Mehmed M. Atik[1], Serkan Erdin[6,7], Donna Muzny[1,5], Richard A. Gibbs[1,5], James R. Lupski[1,5,8,9,*], and The Baylor-Hopkins Center for Mendelian Genomics

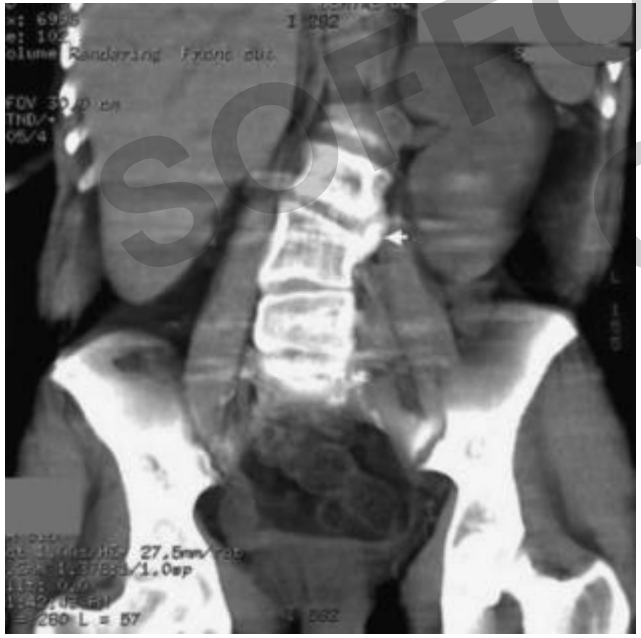


anomalies caudales

- Agénésies lombosacrées
  - Sporadique ++++
  - Anomalie de la régression caudale`
  - Favorisée par le diabète maternel
  - Isolées ou associées
- Le syndrome de Currarino
  - *HLXB9,* microdeletion 7q36
- MURCS + DSC
- Casamassima

MURCS association

- Mullerienne, Utérine, Rénale, Cervicothoraciques
  - Hypo ou aplasie des dérivés mulléríens
  - Rein
  - Anomalies cervico-thoraciques
  - Klippel Feil
- Surdité, hypoplasie radiale décrites (≠ VACTERL)
- bases moléculaires ? hétérogénéité



Occipitoatlantoaxial Junction Malformation and Early Onset Senile Ankylosing Vertebral Hyperostosis in a Girl With MURCS Association

Ali Al Kaissi,[1,2]* Farid Ben Chehida,[3] Maher Ben Ghachem,[2] Franz Grill,[4] and Klaus Klaushofer[1]

Am J Med Genet Part A 149A:470–474.

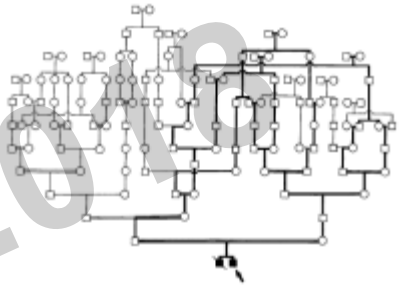
Casamassima Syndrome

- Dysostose spondylo-costale sévère, pluri-étagée
- Anomalies génito-urinaires
- Atrésie anale
- Autosomique récessif

-5 cas décrits (dont 1 fœtus)

-Base moléculaire ?

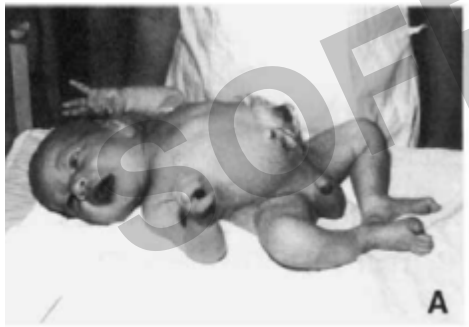
-t(5;9) d'allure équilibrée/ 2eme evt ?

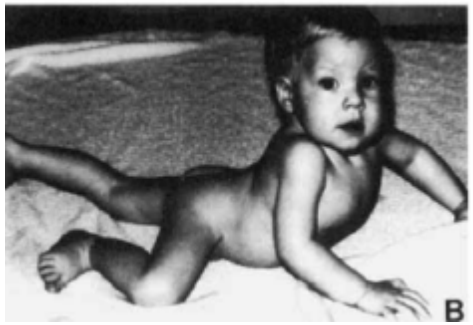


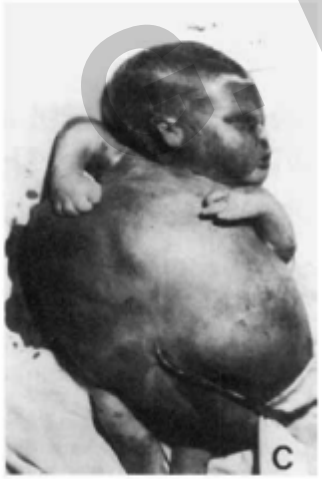
Spondylocostal Dysostosis Associated With Anal and Urogenital Anomalies in a Mennonite Sibship

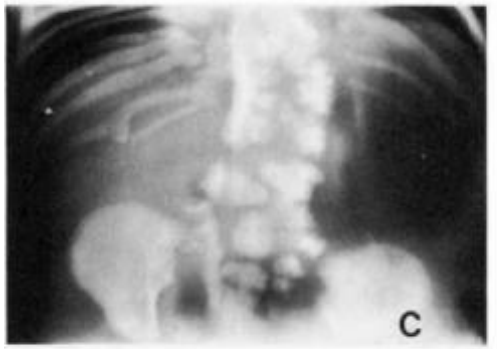
Anthony C. Casamassima, Cynthia Casson Morton, Walter E. Nance, Michael Kodroff, Robin Caldwell, Thaddeus Kelly, and Barry Wolf

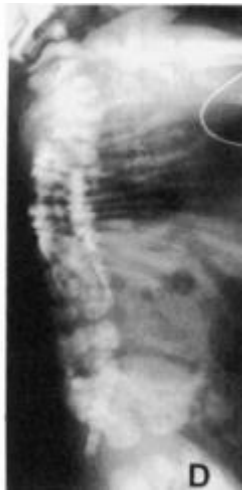
American Journal of Medical Genetics 8:117–127 (1981)











Syndrome de Currarino

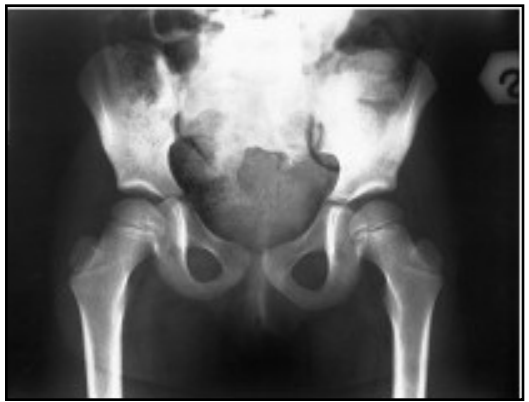
Triade

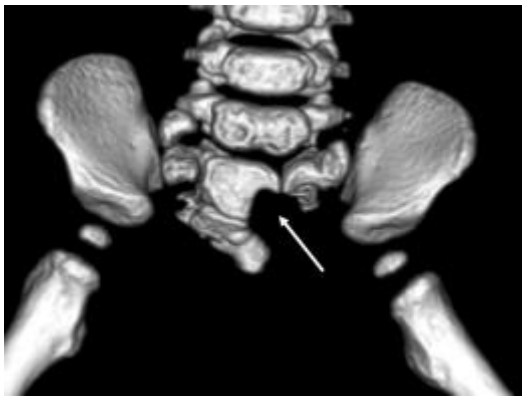
1. Agénésie partielle du sacrum (cimeterre) > S2
2. Tumeur pré-sacrée malformative

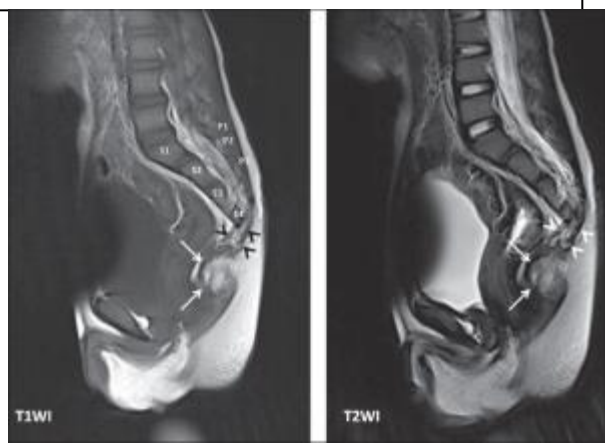
   Tératome, méningocele, moelle attachée basse, kyste entérique
3. Anomalie anatomique et/ou fonctionnelle colique

+/- anomalies uro-génitales

- Agénésies, malformations rénales, duplications rénales ou urétérales,
- reflux vésico-urétéral, hydronéphrose,
- vessies neurologiques, utérus bicornes, hypospadias

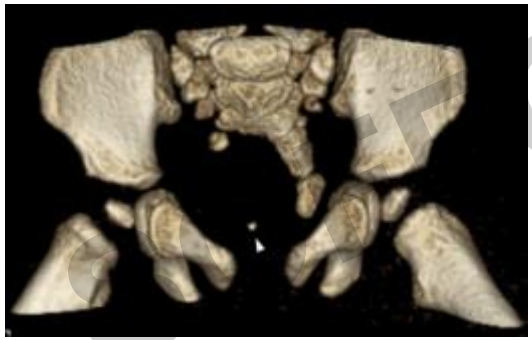


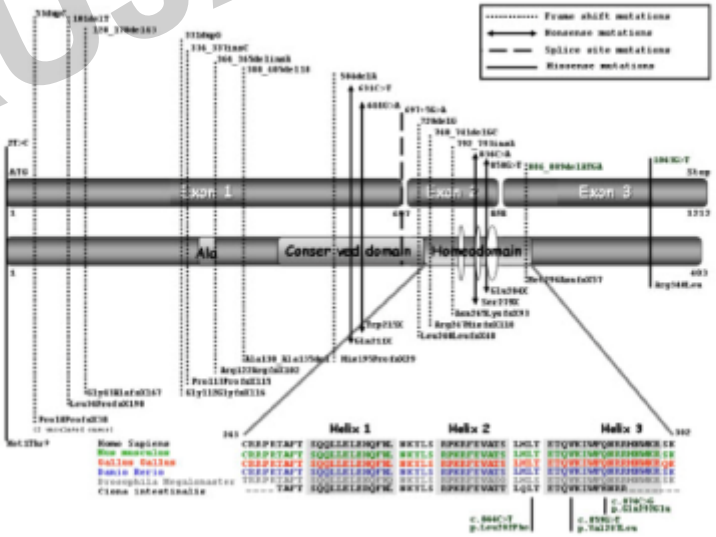




Syndrome de Currarino, *MNX1*

- AD, pénétrance incomplète et expressivité variable
- gène homéotique *HLXB9* (*MNX1*) : locus 7q36
- facteur de transcription avec homéodomaine
  - 3 exons (transcrit: 1203 pdb)
  - Code la protéine HB9





HUMAN MUTATION 29(7), 903–910, 2008

Spectrum of *HLXB9* Gene Mutations in Currarino Syndrome and Genotype–Phenotype Correlation

C. Crétolle,[1,2] A. Pelet,[1] D. Sanlaville,[3] M. Zérah,[4] J. Amiel,[1] F. Jaubert,[5] Y. Révillon,[2] L. Baala,[1] A. Munnich,[1] C. Nihoul-Fékété,[2] and S. Lyonnet[1]*

Syndromes avec atteinte **costo-vertébrale** prédominante

Syndrome cérébro-costo-mandibulaire

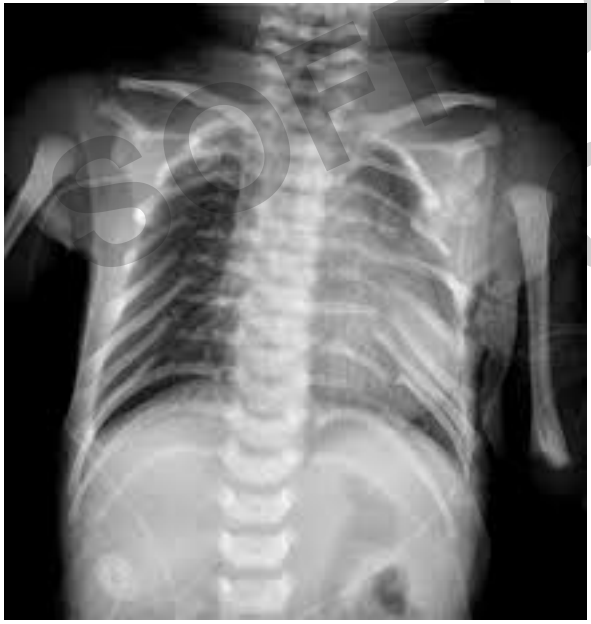
- Pierre Robin, fente palatine
- Failure to thrive
- Thorax tres étroit
- « Gaps » costaux
- Microcephalie
- AD
- ***SNRPB***

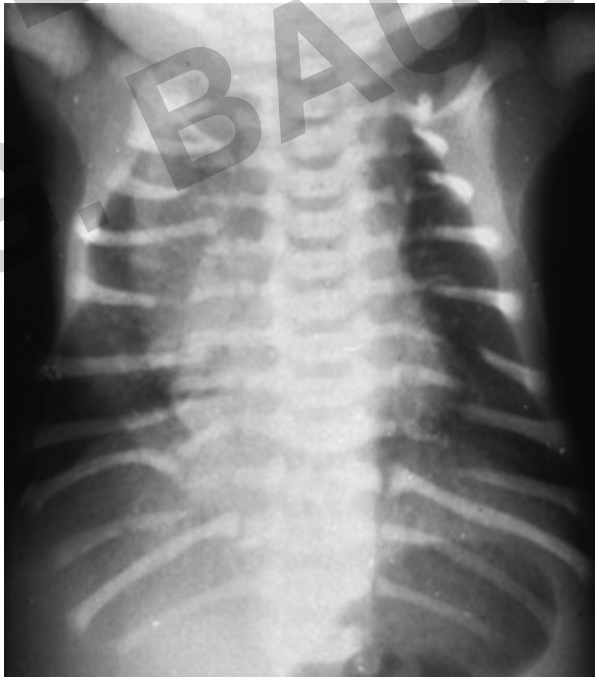
Mutations in *SNRPB*, Encoding Components of the Core Splicing Machinery, Cause Cerebro-Costo-Mandibular Syndrome

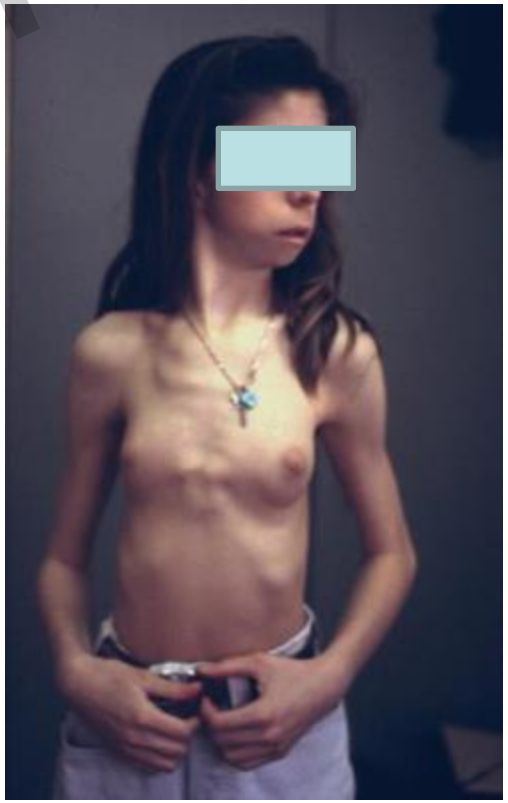
HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

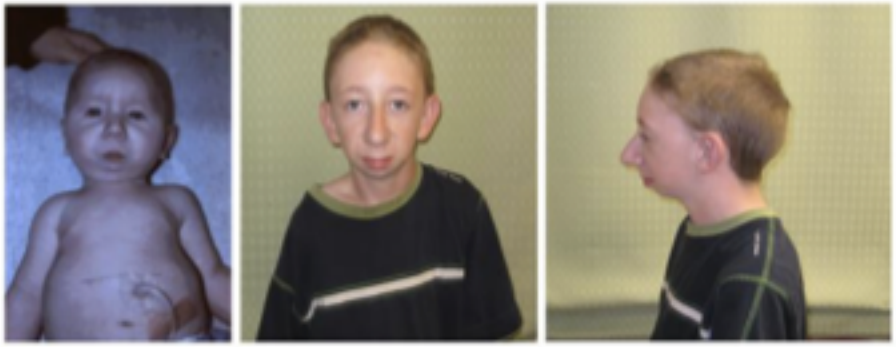
Séverine Bacrot,[1] Mathilde Doyard,[1] Céline Huber,[1] Olivier Alibeu,[2] Niklas Feldhahn,[3] Daphné Lehalle,[1] Didier Lacombe,[4] Sandrine Marlin,[1] Patrick Nitschke,[5] Florence Petit,[6] Marie-Paule Vazquez,[7] Arnold Munnich,[1] and Valérie Cormier-Daire[1]*

Hum Mutat 36:187–190, 2015.









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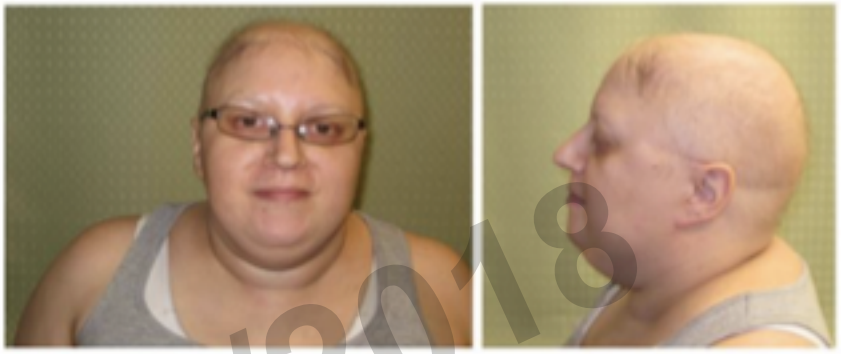

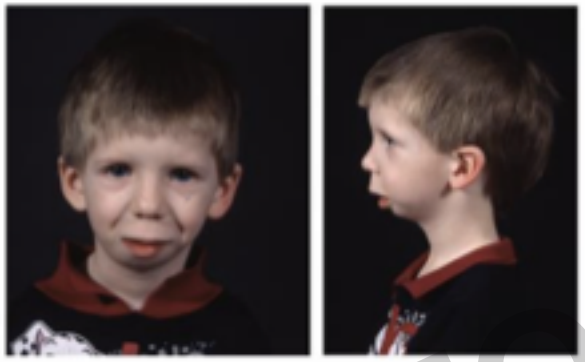

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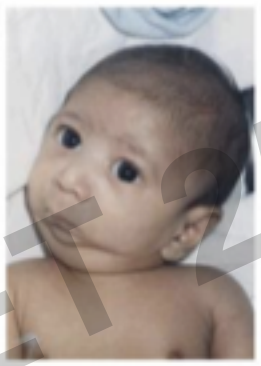

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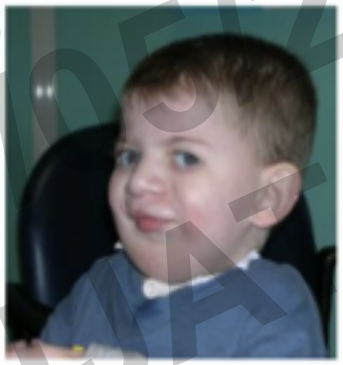

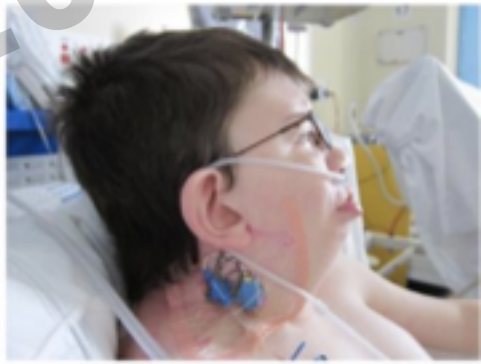

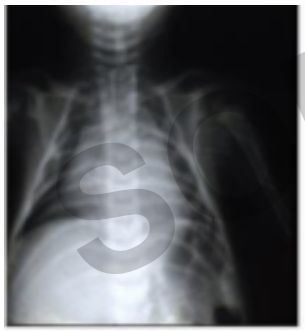

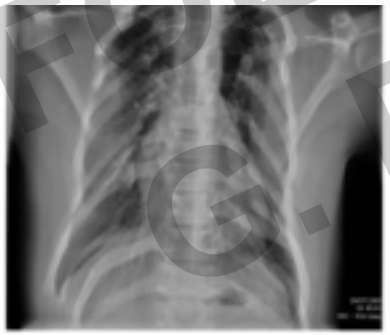

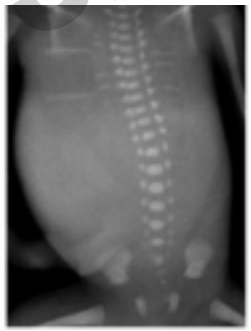

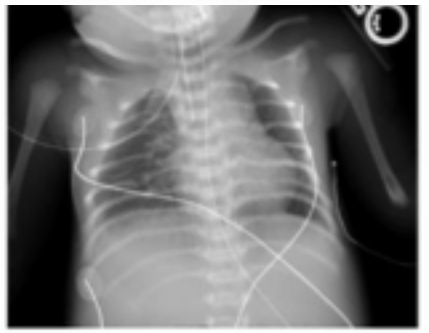

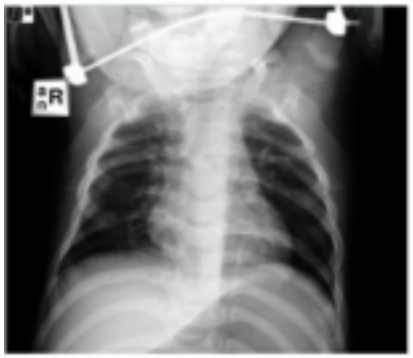

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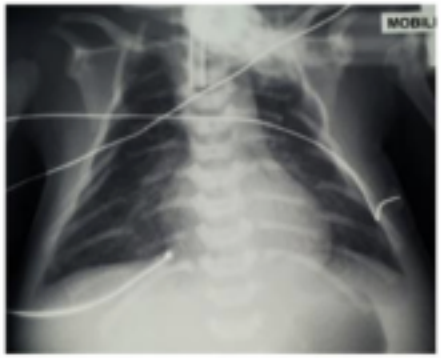

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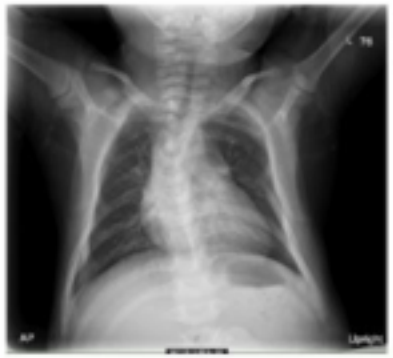
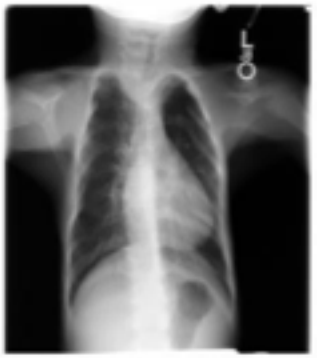


J II-1

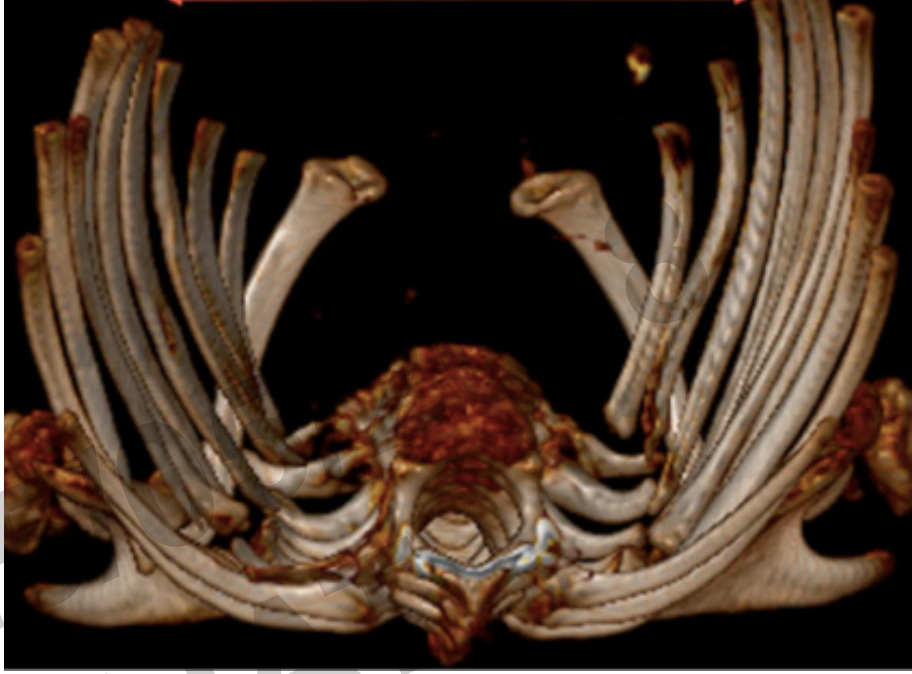


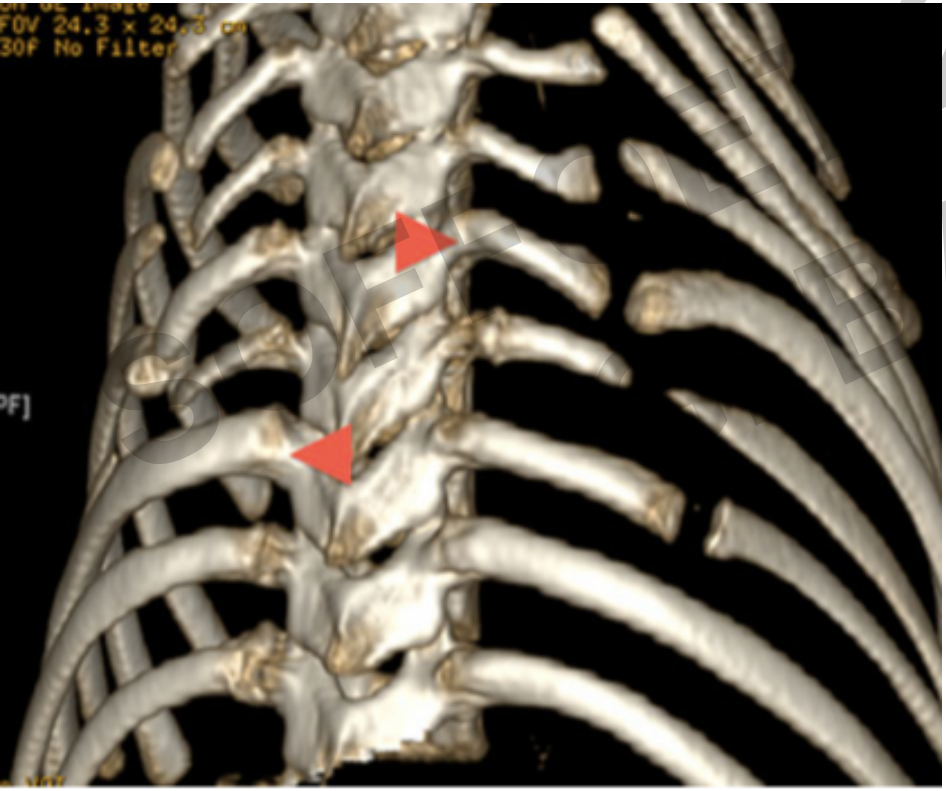
Skeletal Radiol (2014) 43:263–266
DOI 10.1007/s00256-013-1732-2

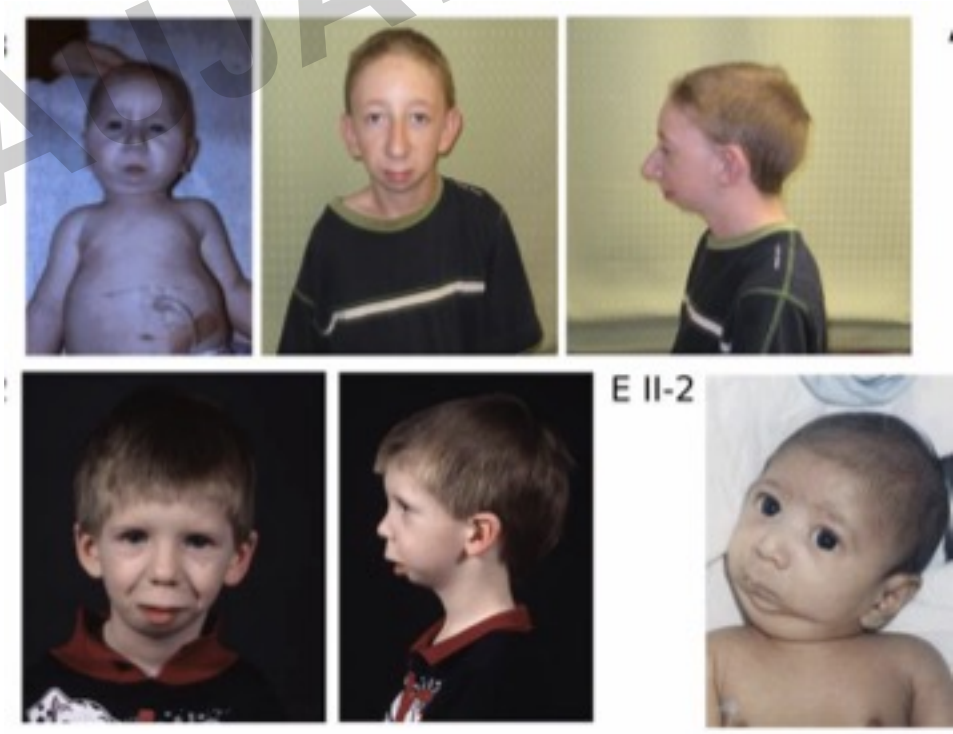
CASE REPORT

Multi-detector thoracic CT findings in cerebro-costo-mandibular syndrome: rib gaps and failure of costo-vertebral separation

Tom Anthony Watson · Owen John Arthurs · Nagarajan Muthialu · Alistair Duncan Calder







Syndrome cérébro-costo-mandibulaire - like

Cerebrocostomandibular-like syndrome and a mutation in the conserved oligomeric Golgi complex, subunit 1

Renate Zeevaert[1], François Foulquier[2,3], Boyan Dimitrov[2], Ellen Reynders[4,5], Rita Van Damme-Lombaerts[1], Emil Simeonov[6], Wim Annaert[4,5], Gert Matthijs[2] and Jaak Jaeken[1,*]

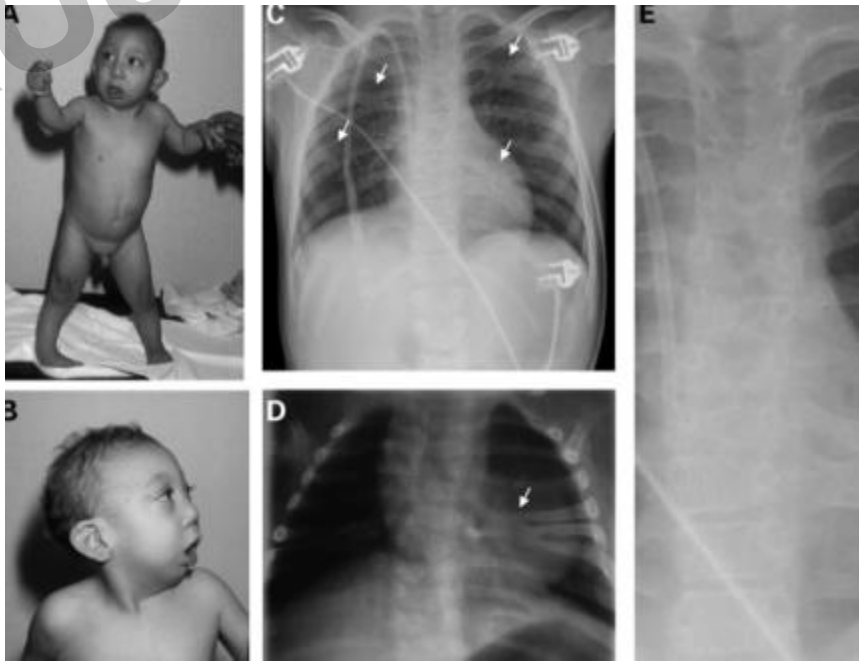
2 patients turcs/ grecs

- P. Robin
- RCIU + RC postnatal, microcéphalie
- Hypotonie, décalage acquisitions
- Hypoplasie vermienne
- Mega grande citerne
- maculopathie
- Anomalies costales (gap)
- Anomalies vertébrales
  - Fusions costales, gaps
  - Hémivertébres
  - Vertébres en papillon

COG1, protéine du Golgi, traffic intracellulaire

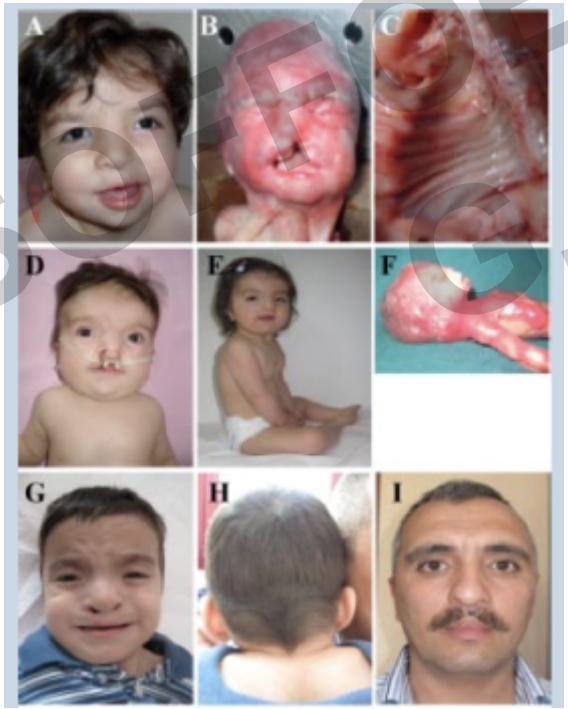
AR

Human Molecular Genetics, 2009, Vol. 18, No. 3



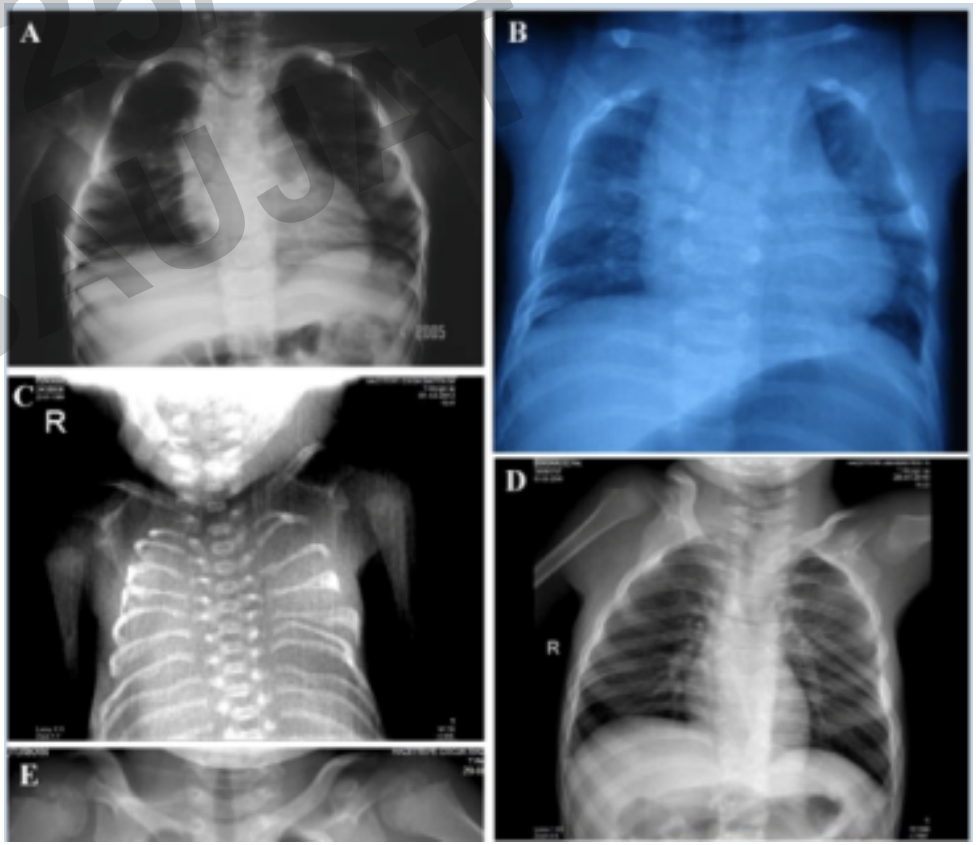
Syndrome cérébro-facio-thoracique

- Déficience intellectuelle variable
  - Macrocranie
  - Malformations cérébrales
- Fente vélo-palatine
- hypertélorisme
- Malformations vertébrales et costales
- AR, ***TMCO1*** (rôle ?)



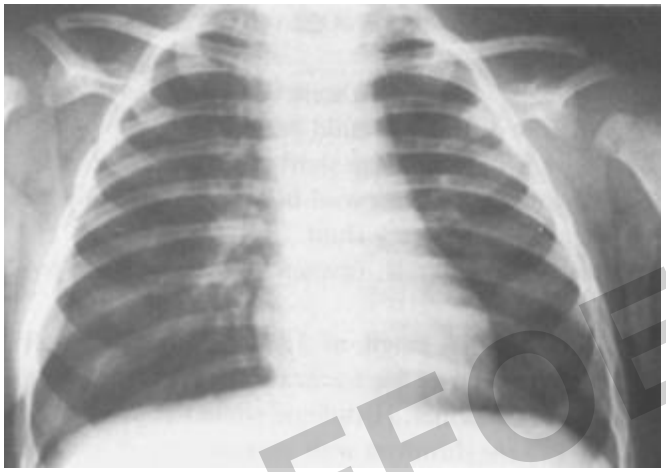
TMCO1 Deficiency Causes Autosomal Recessive Cerebrofaciothoracic Dysplasia

Yasemin Alanay,[1,2] Bekir Ergüner,[3] Eda Utine,[1] Orçun Haçarız,[4] Pelin Ozlem Simsek Kiper,[1] Ekim Zihni Taşkıran,[5] Ferda Perçin,[6] Elif Uz,[5,7] Mahmut Şamil Sağıroğlu,[3] Bayram Yuksel,[4] Koray Boduroglu,[1] and Nurten Ayse Akarsu[5]*



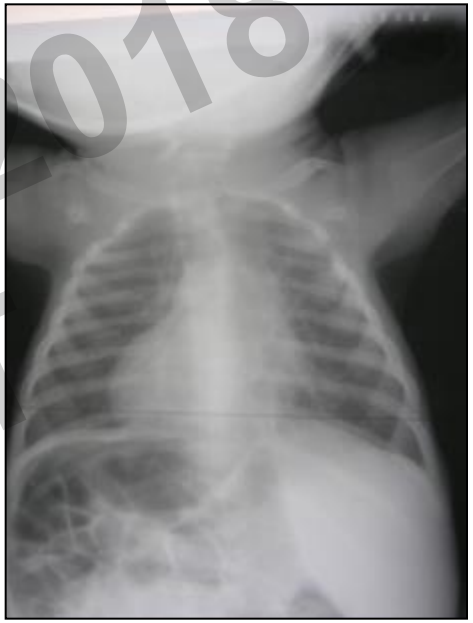
Anomalie vertébrale et ostéochondrodysplasies

Dysplasies campomélique et ischio-vertébrale

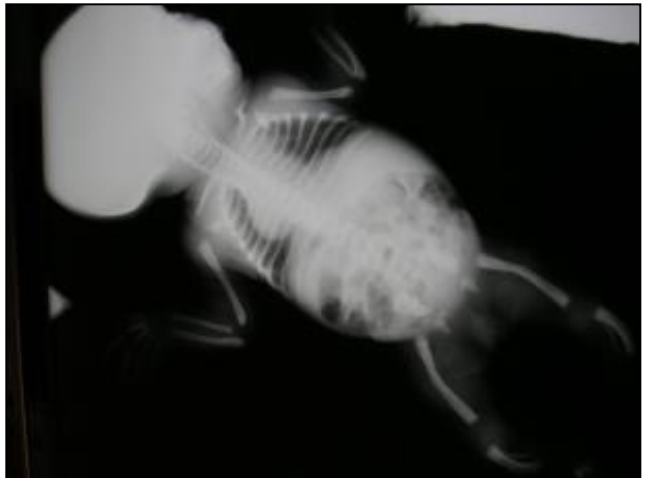


- Mortalité périnatale
- Incurvation os longs
- Hypoplasie scapula, bassin
- Pierre Robin
- Déficit statural
- Anomalies génitales c/o 2/3

- *SOX9*



The Campomelic Syndrome: Review, Report of 17 Cases, and Follow-up on the Currently 17-Year-Old Boy First Reported by Maroteaux et al in 1971



RADIOLOGIC ASPECTS

The diagnostic radiologic changes of the CS are the curved femora and tibiae, hypoplastic pedicles of the thoracic vertebrae, and extremely small scapulae. No other syndrome known to us has this constellation of findings. In addition, these infants have a relatively large calvaria, often with bathrocephaly, small midface, micrognathia, other vertebral anomalies (absent C1, C5, fusion, spina bifida), thin ribs, often only 11 pairs of ribs, abnormally aligned or dislocated hips, absence of distal femoral and proximal tibial ossification centers at birth, small middle phalanges of fingers, shortness and clinodactyly of fifth fingers, widely spaced ischial bones, unusually narrow iliac bones, unossified pubes, dislocation of elbows, and delay in the appearance of sternal centers and of the talus. This *combination* of changes associated with bowing of femora, fibiae, and the severe TEQV is diagnostic, though *individual* components of the radiologic picture are both nonobligatory and nonpathognomonic.

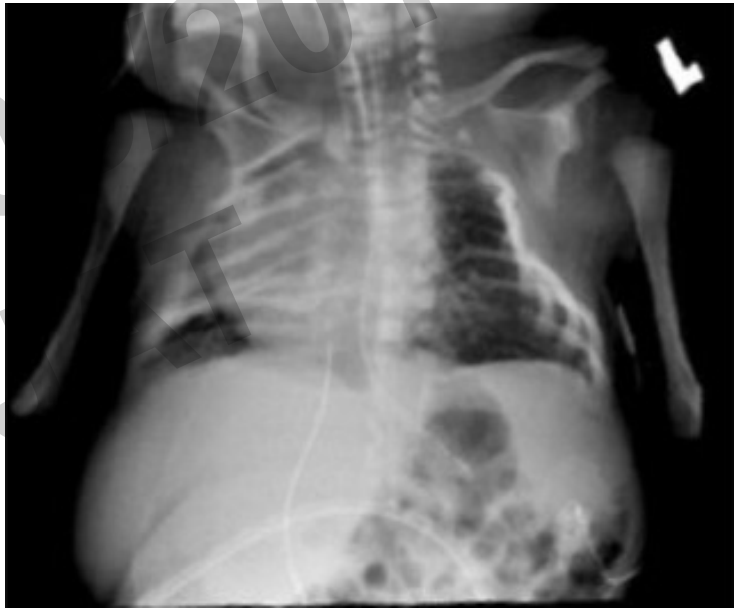
American Journal of Medical Genetics 15:3–28 (1983)

Diaphanospondylodysostose, *BMPER*

BMPER Mutation in Diaphanospondylodysostosis Identified by Ancestral Autozygosity Mapping and Targeted High-Throughput Sequencing

Vincent A. Funari,[1,2,*] Deborah Krakow,[1,3,4,5] Lisette Nevarez,[1] Zugen Chen,[4] Tara L. Funari,[1] Nithiwat Vatanavicharn,[6] William R. Wilcox,[1,2] David L. Rimoin,[1,2,4,7] Stanley F. Nelson,[2,4] and Daniel H. Cohn[1,2,4,*]

The American Journal of Human Genetics *87*, 532–537, October 8, 2010



GENATLAS PHENOTYPE

last update : 25-10-2010

Symbol	DIASD
Location	7p14.3
Name	diaphanospondylodysostosis
Corresponding gene	BMPER
Main clinical features	• perinatal lethal skeletal disorder • a small chest, abnormal vertebral segmentation, and posterior rib gaps containing incompletely differentiated mesenchymal tissue, craniofacial features include ocular hypertelorism, epicanthal folds, a depressed nasal bridge with a short nose, and low-set ears • extraskeletal finding is nephroblastomatosis with cystic kidneys
Genetic determination	autosomal recessive

Bone morphogenetic protein - binding endothelial cell precursor-derived regulator.

antagoniste mais aussi agoniste de la voie des BMP2, 4, 6

Kuchinskaya *et al. Orphanet Journal of Rare Diseases* (2016) 11:1
DOI 10.1186/s13023-015-0380-0

Orphanet Journal of Rare Diseases

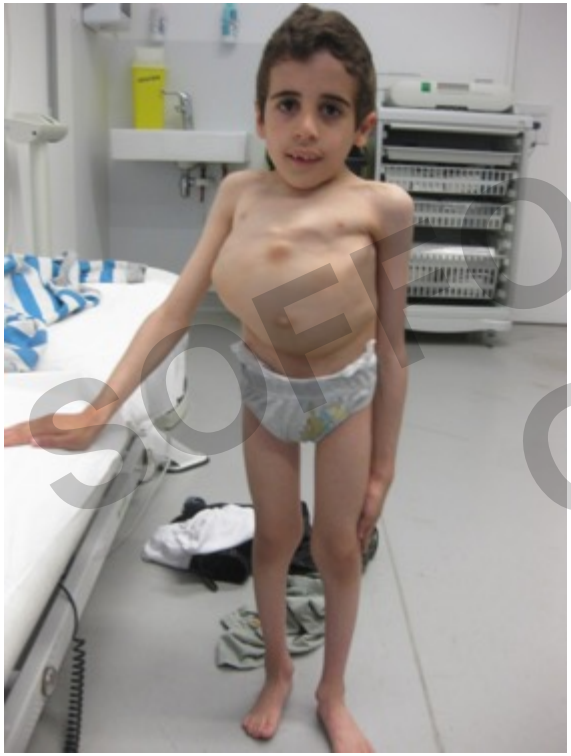
LETTER TO THE EDITOR Open Access

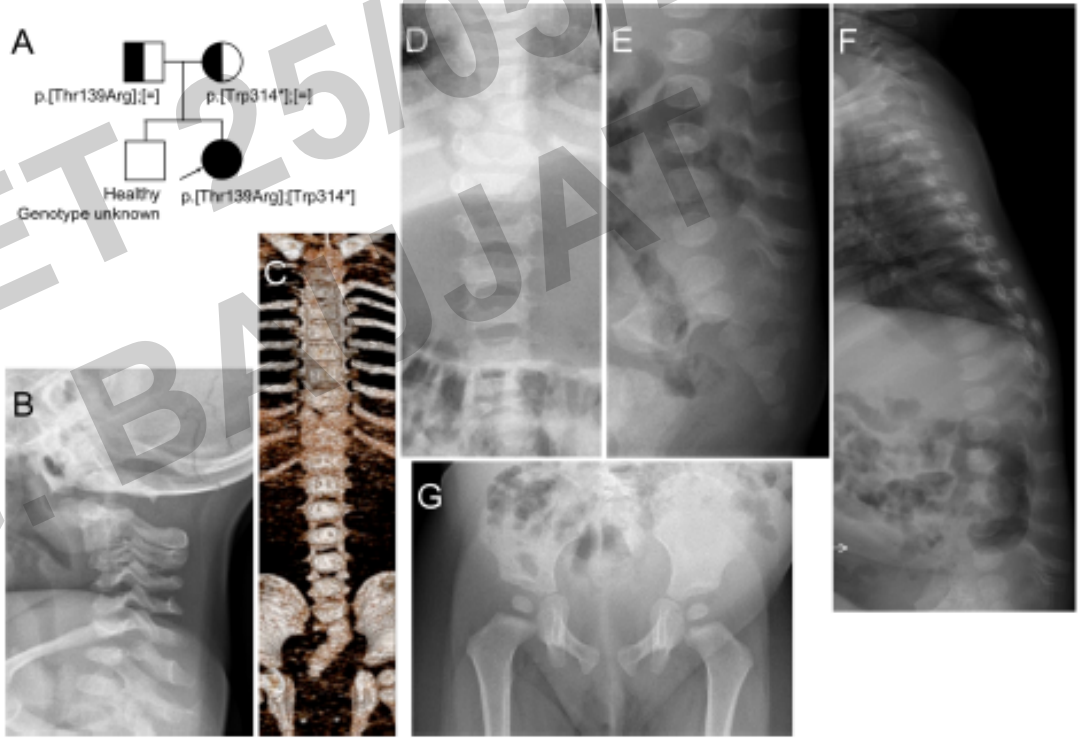
Extending the phenotype of *BMPER*-related skeletal dysplasias to ischiospinal dysostosis

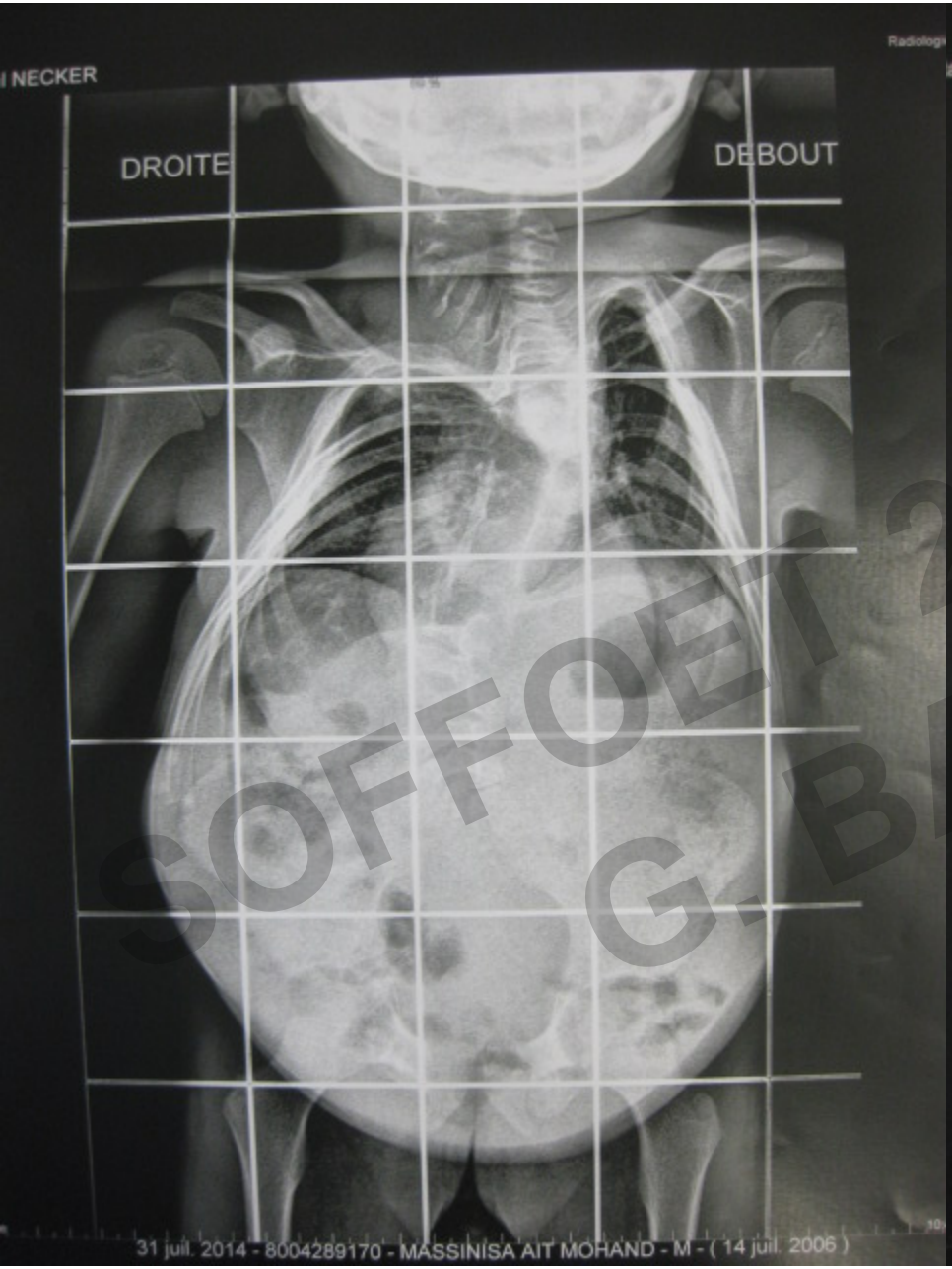
Ekaterina Kuchinskaya[1†], Giedre Grigelioniene[2,3*†], Anna Hammarsjö[2,3], Hye-Ran Lee[4], Lotta Högberg[5], Gintautas Grigelionis[2], Ok-Hwa Kim[6], Gen Nishimura[7] and Tae-Joon Cho[5*]

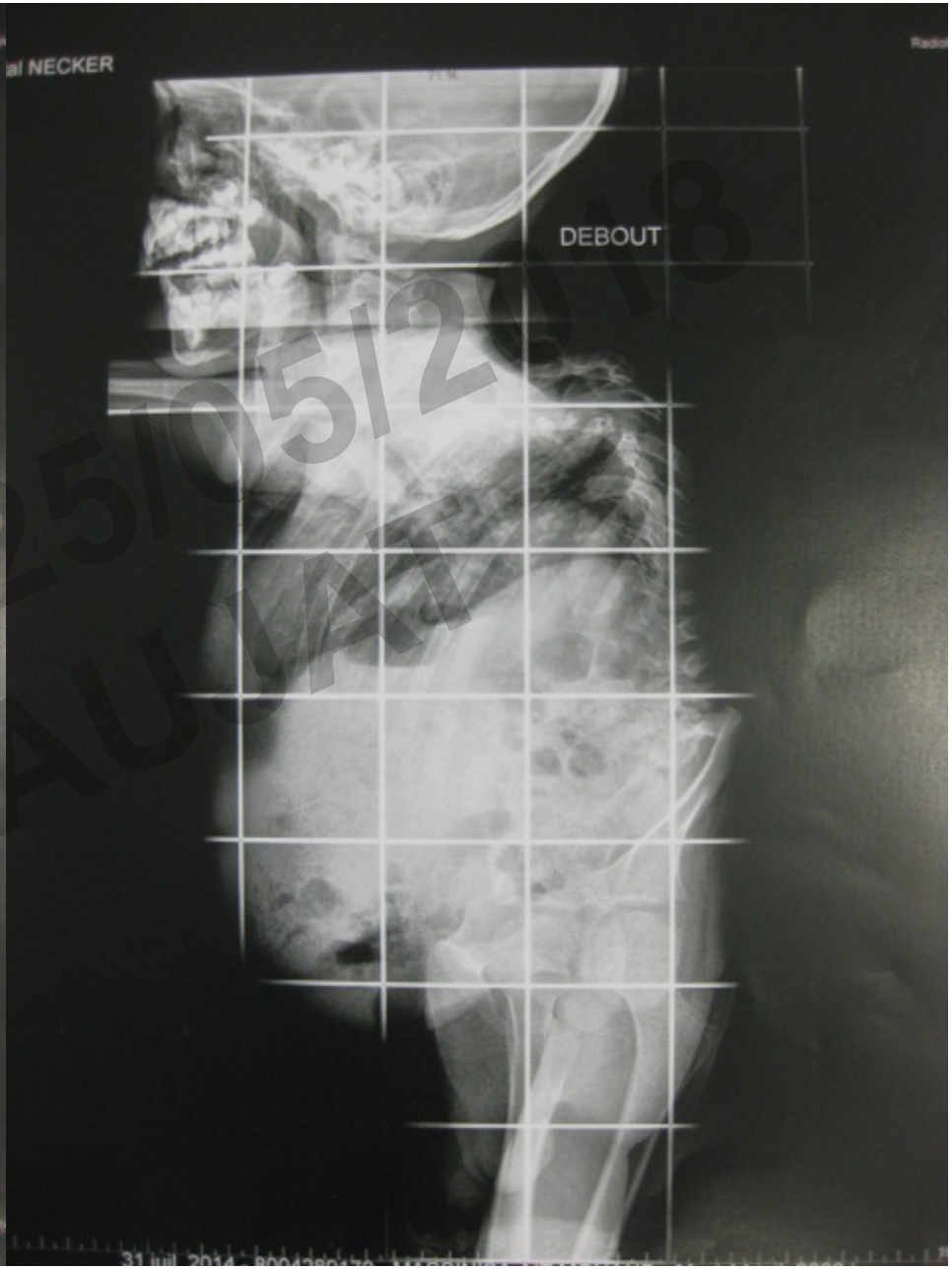
- Trouble de segmentation plus sévère
- Pas de retrognathisme
- Possible solution de continuité des côtes

AR, BMPER





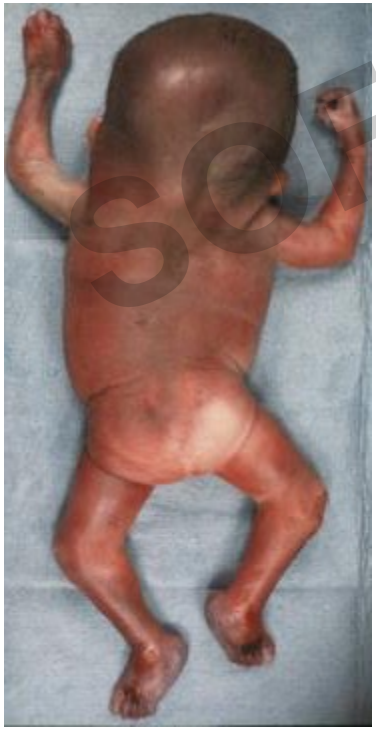


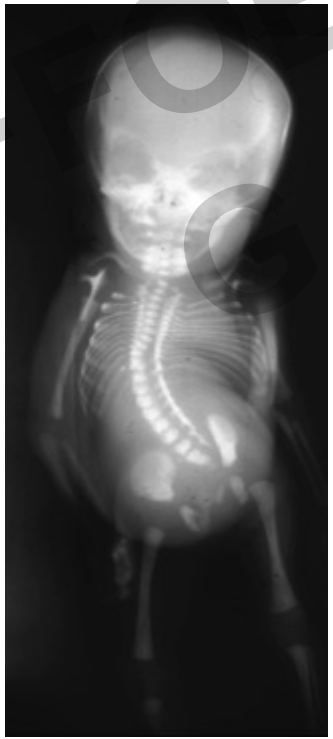


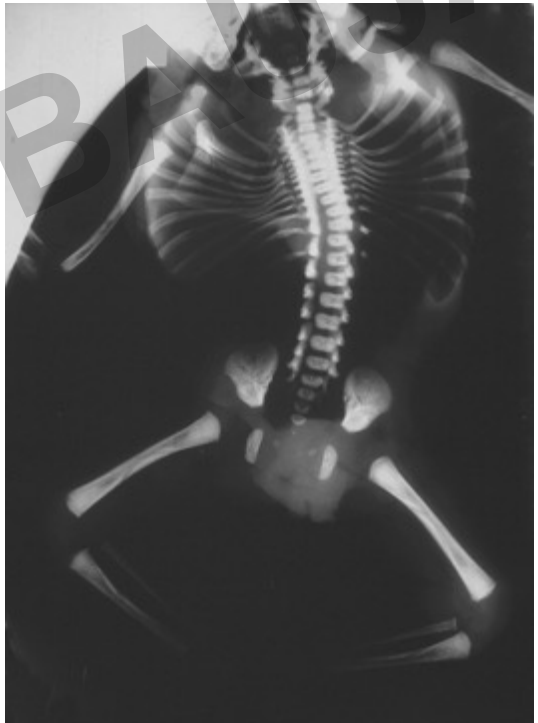
Synspondylismes, hétérogénéité

Synspondylisme congenital / sd ptérygo acro vertebral : formes foetales

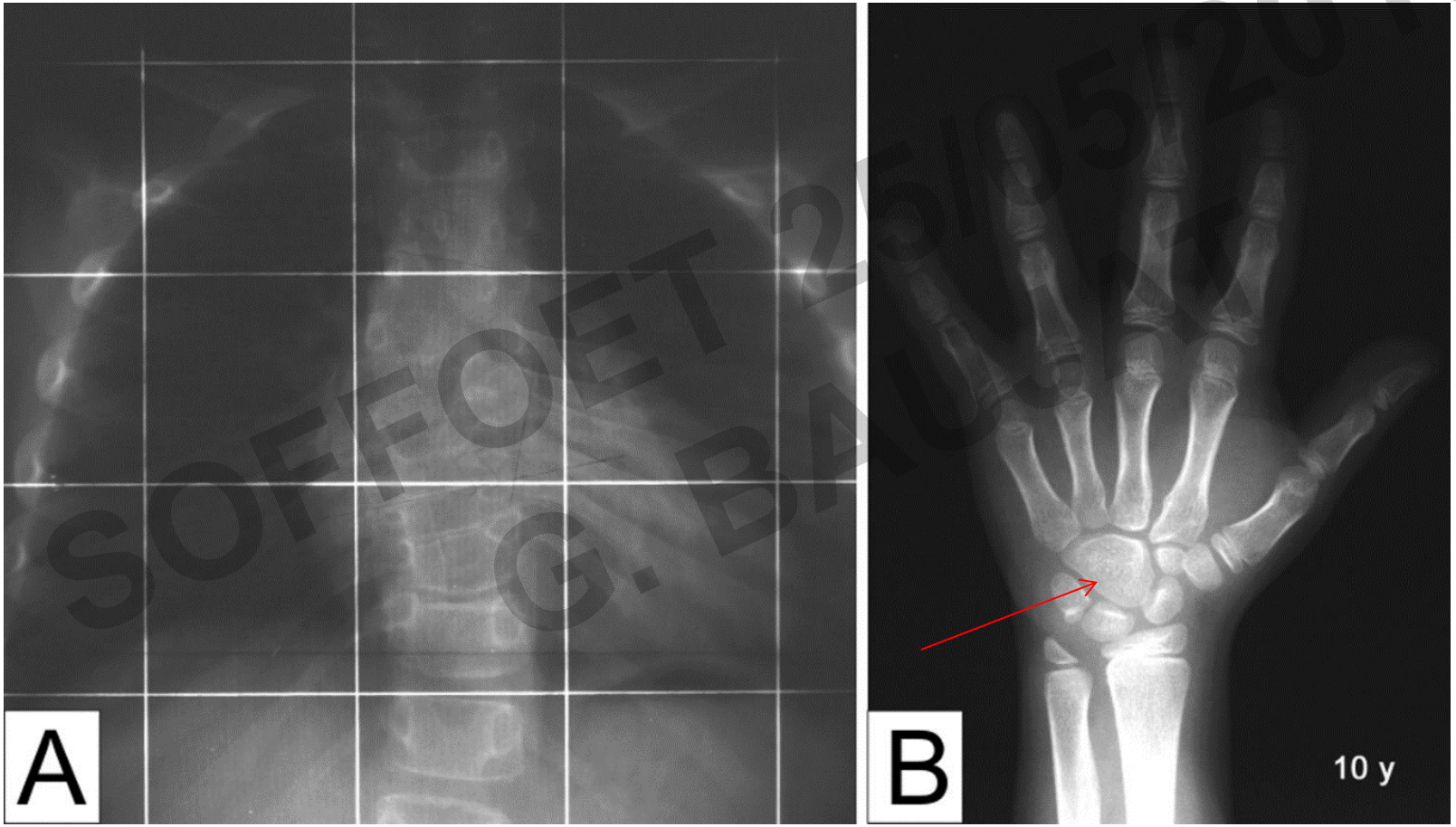
- Tronc et cou court
- Hyperlordose
- Fusion étagée des vertèbres dorsales , cervicales et parfois lombaires sup, touchant les corps vertebraux et les épineuses
- Associée ou non à des camptodactylies et des ptérygium
- Formes DA et RA ; bases moléculaires ?







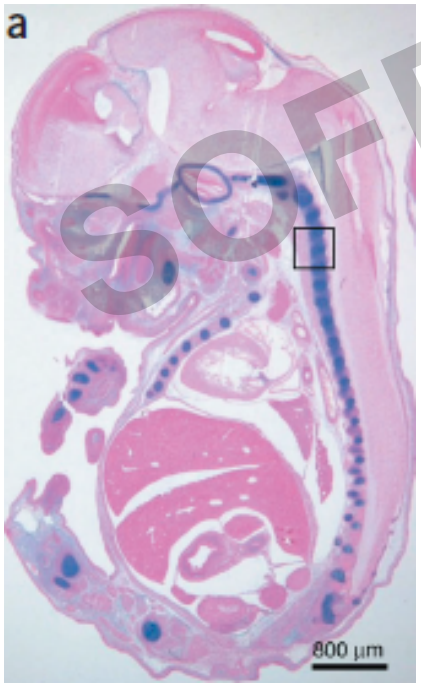
- Forme récessive
  - Mutation stop homozygote de la Filamine B (Larsen, Ateloostéogénèse)

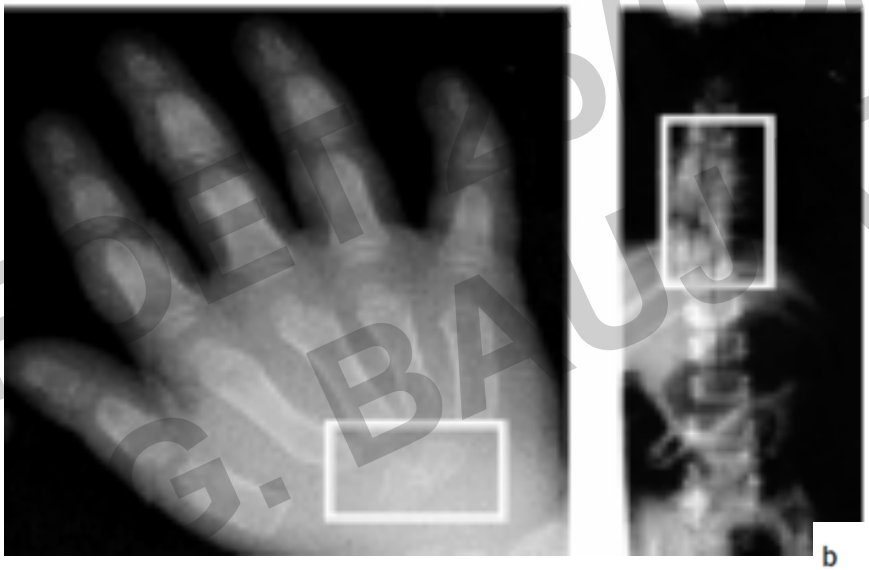


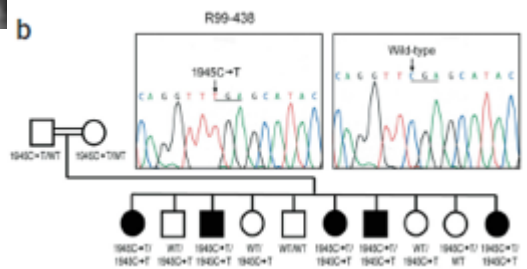
Am J Med Genet A. 2008 May 1; 146A(9): 1230–1233

Syndrome de fusion spondylo-carpo-tarsienne

- Forme récessive (SCT recessive form)
- Localisation en 3p14 (Steiner 2004)
- Identification mutations tronquantes *FLN B* en 2004 chez 4 patients







NATURE GENETICS VOLUME 36 | NUMBER 4 | APRIL 2004

Syndrome spondylo-carpo-tarsal, f. dominante

- Transmission dominante
- Exclusion *NOG* et *FLN B*

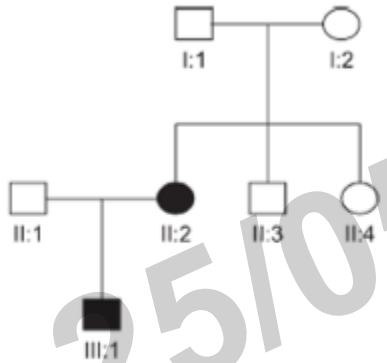


FIG. 1. Pedigree: patient 1 (II:1) and 2 (III:1).

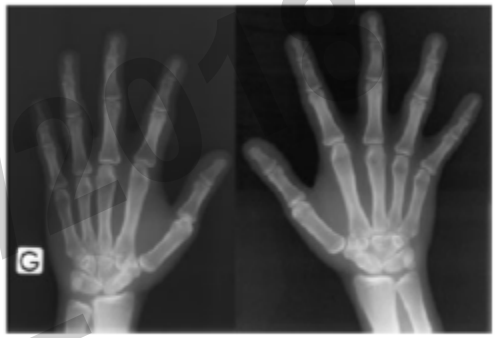
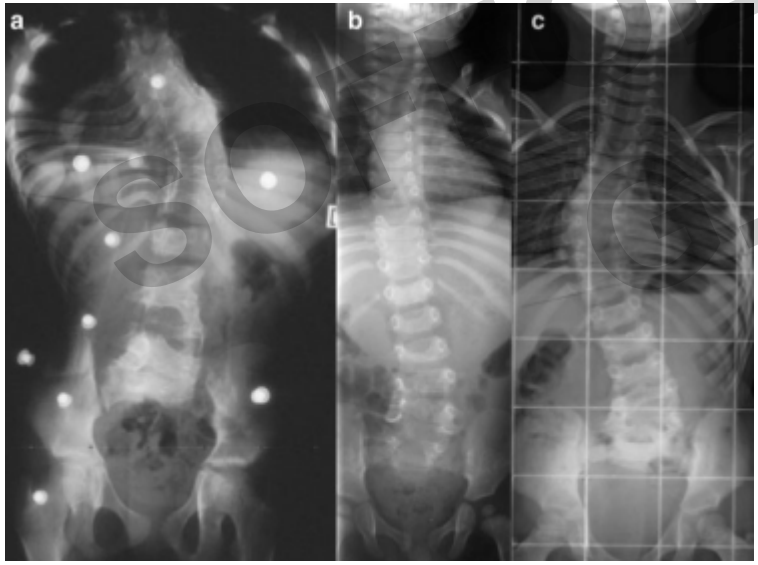


FIG. 2. Patient 1 at 26 years old. Radiograph of both hands. Lunate-triquetral and trapezium-scaphoid fusions of both hands. Capitate–hamate fusion on the right hand.



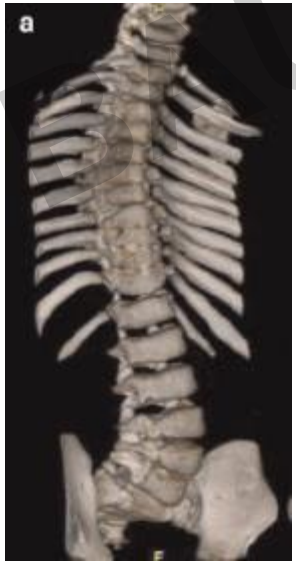


TABLE I. Comparison of Clinical Manifestations in 25 Reported Cases With Those in Our Two Patients

	Literature review	Our patients	
	25 patients	1	2
Sex (M/F)	10/25	F	M
Consanguinity	5 families	–	–
Mild developmental delay	2/25	+	+
Short stature	23/25	+	+
Spine anomalies			
Short trunk	21/25	+	+
Thoracolumbar fusions	24/25	+	+
Scoliosis	21/25	+	+
Lordosis	17/25	+	+
Cervical fusion	11/25	+	–
Short neck	8/25	+	+
Sacral anomaly	3/25	+	+
Fusion of spinous process	10/25	–	–
Limbs anomalies			
Carpal fusion	23/25	+	[a]
Tarsal fusion	9/25	+	[a]
Joint mobility limitation	11/25	+	+
Clinodactyly 5th	7/25	+	+
Brachydactyly	5/25	–	–
Club foot	2/25	–	–
Flat foot	11/25	–	–
Bowed humerus	2/25	–	–
ORL			
Hearing deficit	11/25	+	+
High arched/cleft palate	4/25	+	+
Kidney anomalies	2/25	–	–
Inguinal hernia	2/25	–	+
Heart anomaly	3/25	–	–
Facial anomalies			
Dentition/enamel anomaly	9/25	–	–
Dysmorphic face	10/25	+	+
Ocular findings	2/25	–	–

Autosomal Dominant Spondylocarpotarsal Synostosis Syndrome; B. Isidor

Am J Med Genet Part A 146A:1593–1597.

Table 1 Clinical findings and mutations in diseases associated with *FLNB*

Family	Phenotypic findings									Mutation			
Diagnosis	ID#	Craniofacial abnormalities	Vertebral fusions	Vertebral abnormalities	Carpal or phalangeal abnormalities	Tarsal abnormalities	Joint dislocations	Other congenital abnormalities[a]	DNA mutations	Exon	Protein consequence	Protein ABD or repeat
SCT	R99-438	+	+	+	+	+	–	+	1945C→T	13	R649X	5
SCT	R03-062	+	+	–	+	–	–	–	7029T→G	43	Y2343X	22
SCT	R00-084	–	–	–	+	–	–	–	2452C→T	16	R818X	6
									4819C→T	28	R1607X	14
SCT	R00-008	–	+	+	+	–	–	–	6408delC	39	S2137fs	20
Larsen	319	+	–	+	+	+	+	–	482T→G	2	F161C	CHD2
Larsen	380	+	–	–	+	+	+	–	679G→A	4	E227K	CHD2
Larsen	318	+	–	+	+	+	+	–	4711_4713delAAT	28	1571delN	14
Larsen	334	+	–	+	U	U	+	–	4756G→A	29	G1586R	14
Larsen	225	+	U	U	+	U	+	–	5071G→A	31	G1691S	15
AOI	R95-326	U	–	+	+	U	–	–	518C→T	2	A173V	CHD2
AOI	R96-320	+	+	+	U	–	+	–	604A→G	3	M202V	CHD2
AOI	R97-016	+	–	+	+	U	+	–	562T→C	3	S188P	CHD2
AOIII	R83-120	+	+	+	+	+	+	–	2251G→C	15	G751R	6
AOIII	R94-363	+	–	+	+	+	+	–	604A→G	3	M202V	CHD2

JMG Online First, published on February 19, 2018 as 10.1136/jmedgenet-2017-104939

ORIGINAL ARTICLE

Diagnostic strategy in segmentation defect of vertebrae: a retrospective study of 73 patients

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Saint-Onge Judith,[2] Anne Bazin,[6] Lucile Pinson,[7] Tania Attie-Bitach,[4]
Clarisse Baumann,[8] Melanie Fradin,[9] Genevieve Pierquin,[10] Sophie Julia,[1]
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Laetitia Lambert,[13] Nadine Bachmann,[14] Didier Lacombe,[15,16] Bertrand Isi
Nicole Laurent,[18] Roume Joelle,[19] Patricia Blanchet,[7] Sylvie Odent,[9]
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Alice Goldenberg,[26] Salima El Chehadeh,[5] Christine Francannet,[27] Benedi
Yannis Duffourd,[2] Christel Thauvin-Robinet,[1,2] Alain Verloes,[8] Valerie Corn
Jean Baptiste Riviere,[2] Laurence Faivre,[1,2] Julien Thevenon[1,2,29]

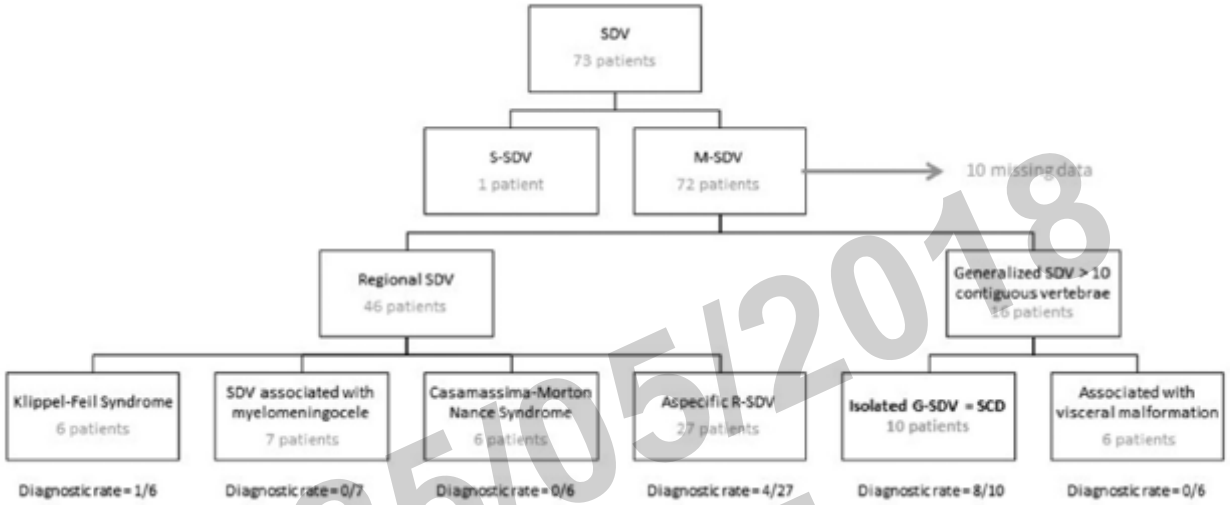


Table 1 Causal variants identified in the SDV cohort

Patient	Gene	Mutation cDNA	Protein	Status	ExAC frequency	Phenotype	Reference
M-SDV							
73	*TBX6*	Del 16p11.2 BP4-BP5 haplotype	/	Haploinsufficient		CS	25
84	*TBX6*	Del 16p11.2 BP4-BP5 haplotype	/	Haploinsufficient		CS	25
32	*TBX6*	Del 16p11.2 BP4-BP5 NM_004608.3: c.661C>A	/p.His221Asn	Haploinsufficient	0	M-SDV	19
36	*MEOX1*	NM_004527.3: c.614C>T	p.Ala205Val	Homozygous (consanguinity)	0.0000587245	KFS	
78	*FLNB*	NM_001457.3: c.3446_3455delGTGAAGCTGG NM_001457.3: c.4768_4771delATTG	p.Gly1149Alafs*41 p. Ile1590Glufs*38	Compound heterozygosity	0 0	Spondylocarpotarsal synostosis	
SCD							
62	*TBX6*	NM_004608.3: c.699G>C NM_004608.3: c.422T>C	p.Trp233Cys p.Leu141Pro	Compound heterozygosity	0.000815567 0	SCD	19
2	*DLL3*	NM_016941.3: c.1138C>T NM_016941.3: c.1164C>A	p.Arg380Cys p.Cys388*	Compound heterozygosity	0 0	SCD	
15	*DLL3*	NM_016941.3: c.616_617insGCGGT NM_016941.3: c.1183_1184insCGCTGC	p.Pro202Alafs*41 p. Cys395delinsSerLeuArg	Compound heterozygosity	0 0	SCD	
55	*MESP2*	NM_001039958.1: c.376G>T	p.Glu123*	Homozygous (consanguinity)	0	SCD	
81	*HES7*	NM_032580.3: c.86A>G	p.Asn29Ser	Homozygous (consanguinity)	0 0	SCD	
17	*LFNG*	NM_001040167.1: c.583T>C NM_001040167.1: c.842C>A	p.Trp195Arg p.Thr281Lys	Compound heterozygosity	0 0.00005831	SCD	
18	*LFNG*	NM_001040167.1: c.44dupG	p.Ala16Argfs*135	Homozygous	0	SCD	

CS, congenital scoliosis; ExAC, Exome Aggregation Consortium; KFS, Klippel-Feil syndrome; M-SDV, multiple SDV; SCD, spondylocostal dysostosis; SDV, segmentation defects of the vertebrae

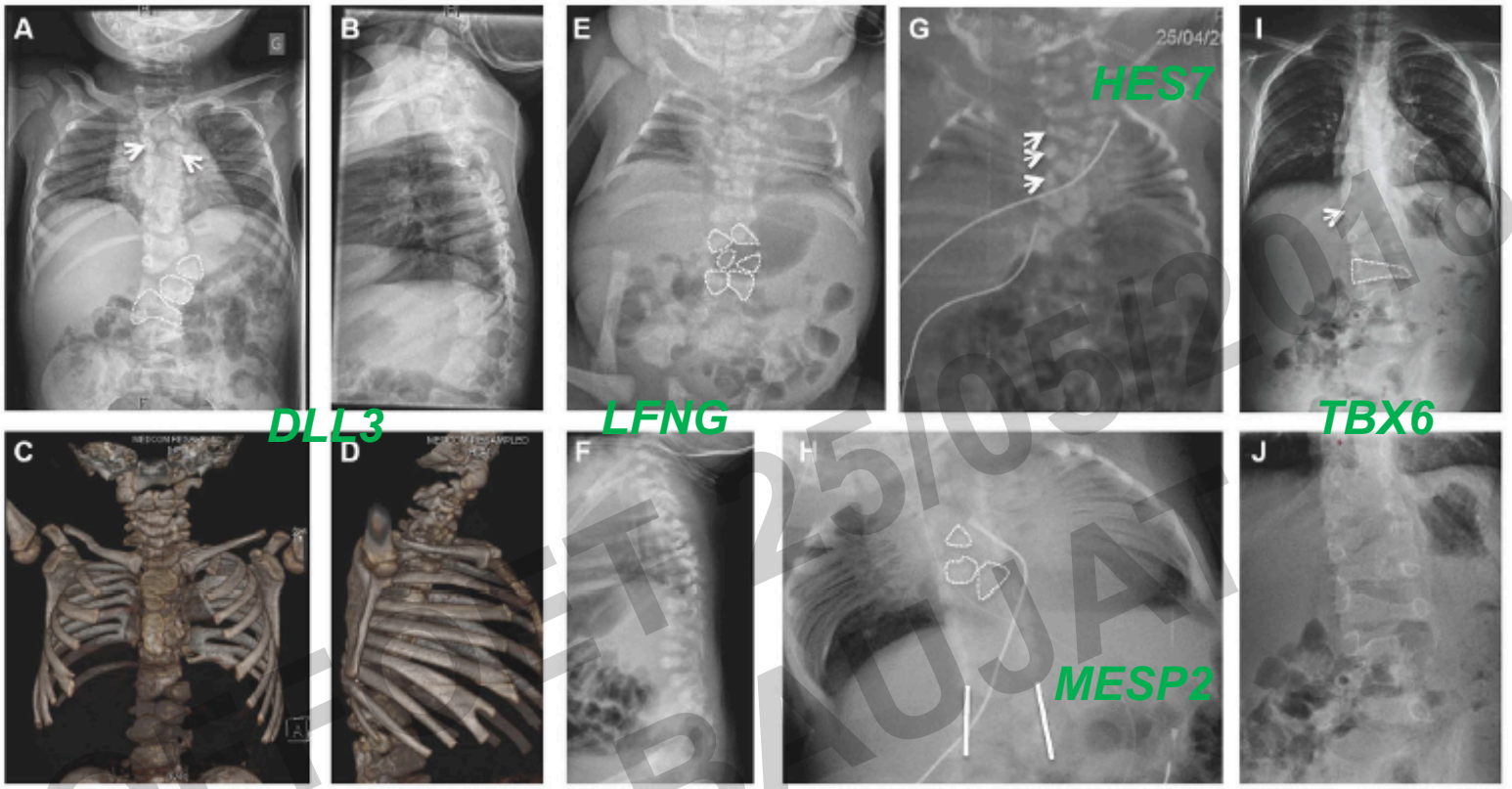
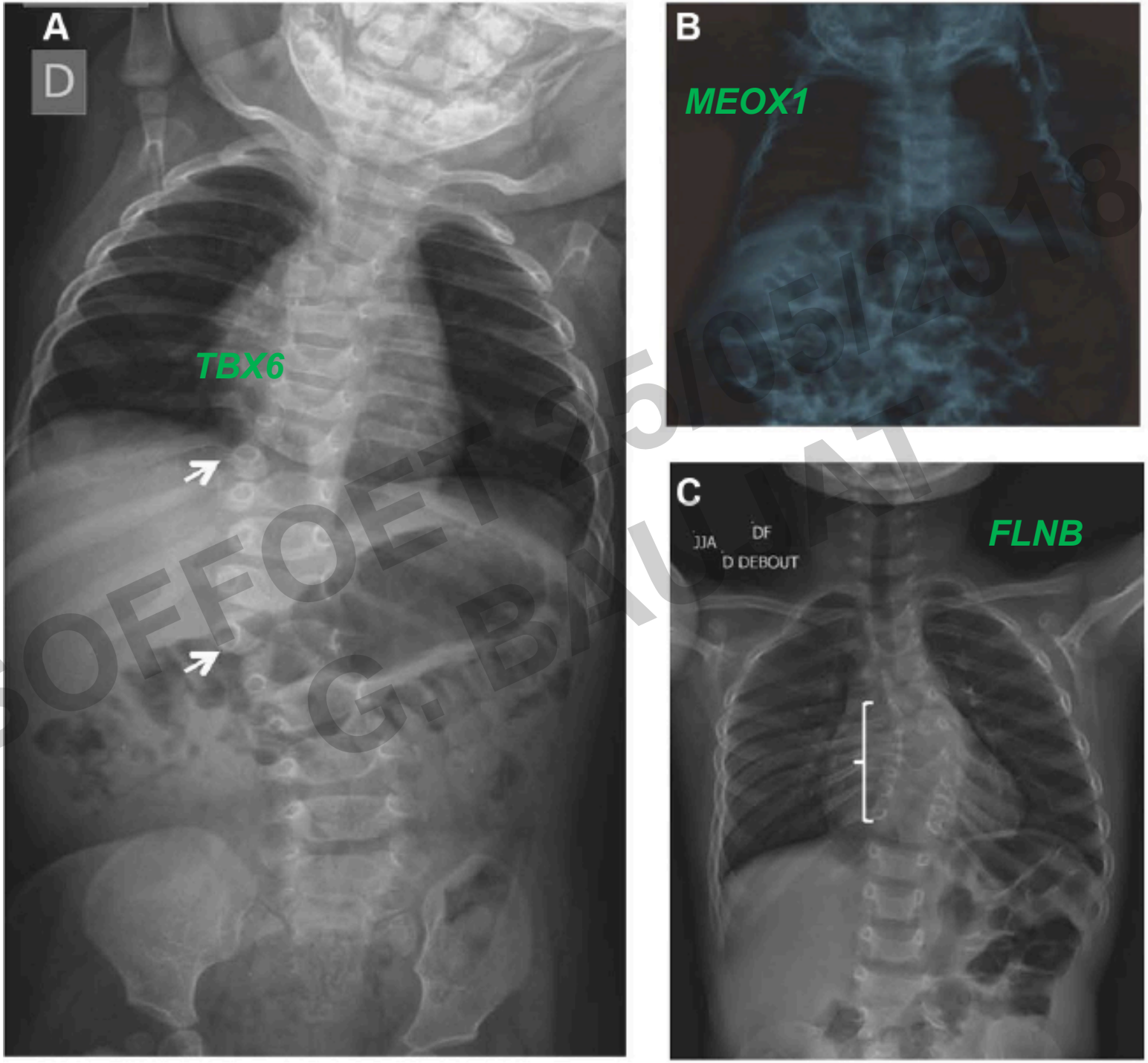
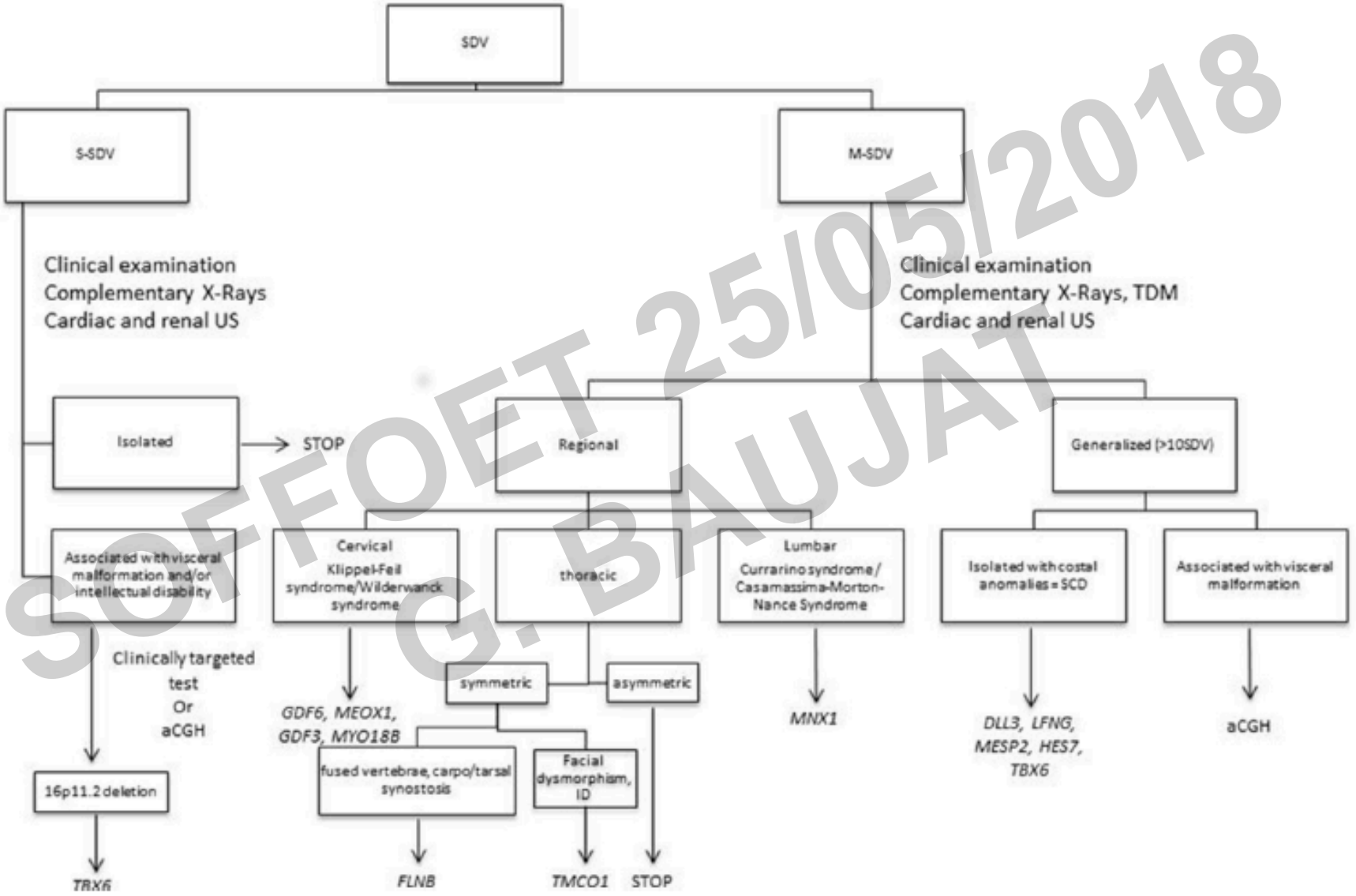


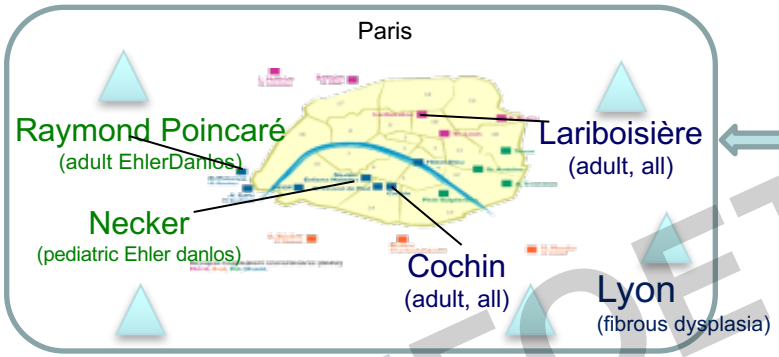
Figure 2 Radiological features identified in patients with SCD: (A,B) extended SDV with multiple hemivertebrae (arrows) and ovoid vertebral bodies (dotted lines) with a pebble beach appearance at age 1 year in patient 15 mutated in *DLL3* (A,B: X-rays; C,D: three-dimensional tomodensitometry); (E,F) SDV of the entire spine with angulated vertebral bodies (dotted lines) at birth in patient 18 mutated in *LFNG*; (G) severe extended SDV of the whole spine with enlarged pedicles (arrows) at birth in patient 81 mutated in *HES7*; (H) extended SDV with angulated vertebral bodies (dotted lines) and enlarged pedicles with a railway line appearance (full lines), ribs are posteriorly fused with a crab-like appearance at age 1 year in patient 55 mutated in *MESP2*; (I,J) extended SDV from the cervical to the lumbar vertebrae with platyspondyly, cuneiform vertebrae (dotted lines) and hemivertebrae (arrow), and one missing rib at age 10 years in a patient with a biallelic *TBX6* mutation. SCD, spondylocostal dysostosis; SDV, segmentation defects of the vertebrae.





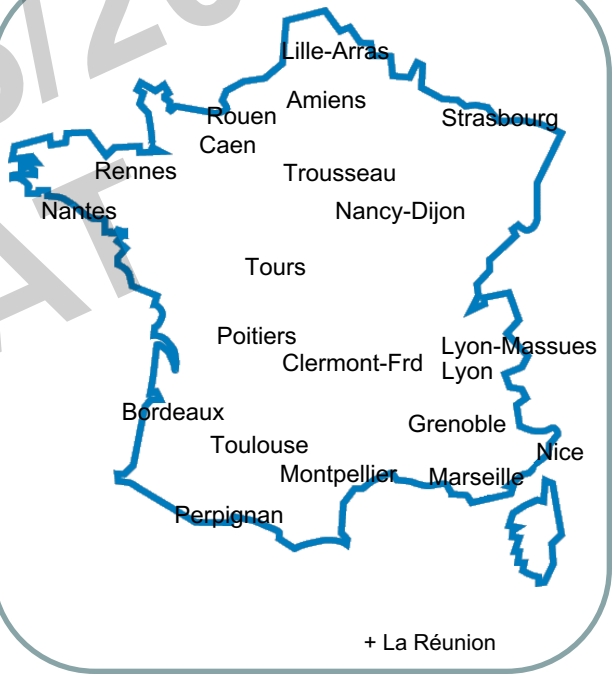
French Bone Disorders network

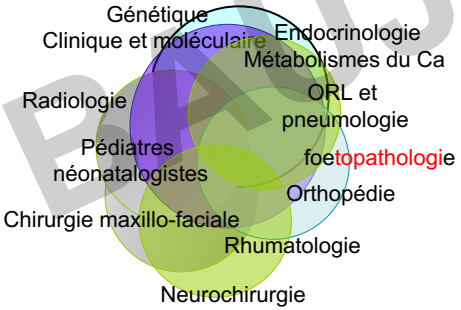
5 Constituent Centres of Reference

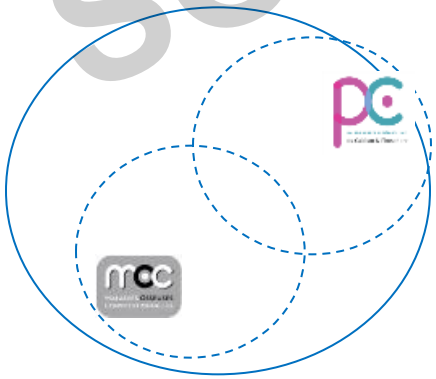


Coordination
NECKER (Paris)

29 Competence regional Centres







OSCAR FILIÈRE SANTÉ MALADIES RARES

SoFFœt
Société Française de Fœtopathologie

Merci de votre attention

nous de parlerons pas des sd comprenant une dysostose vertébrale

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1. #608022 - DIAPHANOSPONDYLODYSOSTOSIS
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   Cytogenetic locations: 3p14.3
   OMIM: 272460
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3. #214300 - KLIPPEL-FEIL **SYNDROME** 2, AUTOSOMAL RECESSIVE; KFS2
   Cytogenetic locations: 1pter-p36.13, 17q21.31
   OMIM: 214300
   Gene summaries Genetic tests Medical literature

4. #277300 - SPONDYLOCOSTAL DYSOSTOSIS 1, AUTOSOMAL RECESSIVE; SCDO1
   Cytogenetic locations: 19q13.2
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5. #118100 - KLIPPEL-FEIL **SYNDROME** 1, AUTOSOMAL DOMINANT; KFS1
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   OMIM: 118100
   Gene summaries Genetic tests Medical literature

6. 212135 - CARDIOSKELETAL **SYNDROME**, KUWAITI TYPE
   OMIM: 212135
   Gene summaries Genetic tests Medical literature

7. %141400 - HEMIFACIAL MICROSOMIA WITH RADIAL DEFECTS
   OMIM: 141400
   Gene summaries Genetic tests Medical literature

8. #268310 - ROBINOW **SYNDROME**, AUTOSOMAL RECESSIVE; RRS
   ROBINOW **SYNDROME**, AUTOSOMAL RECESSIVE, WITH APLASIA/HYPOPLASIA OF PHALANGES AND METACARPALS/METATARSALS, INCLUDED
   Cytogenetic locations: 9q22.31
   OMIM: 268310
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Some syndromes and conditions including abnormal vertebral segmentation

- Acrofacial dysostosis
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- Alagille
- Antalt
- Atelosteogenèse III
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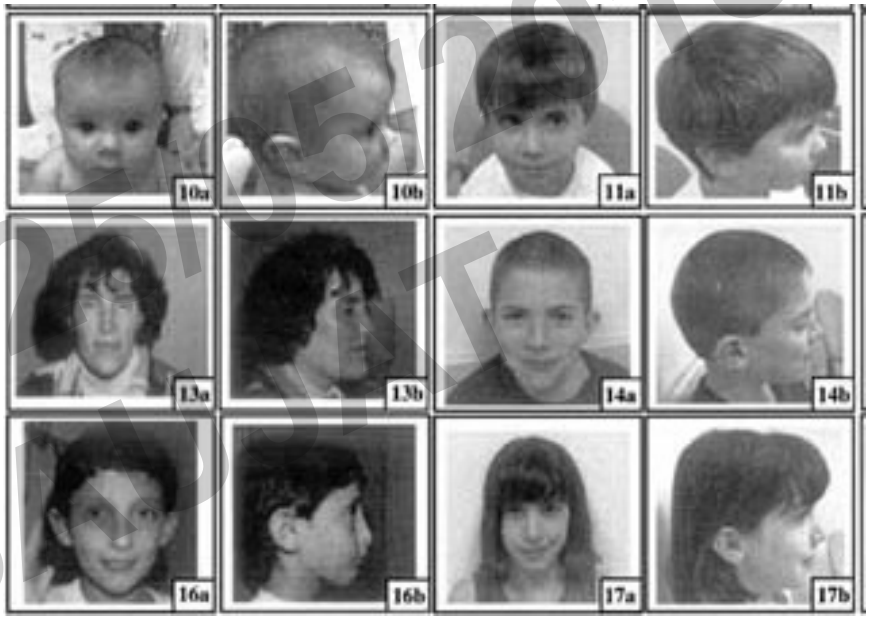
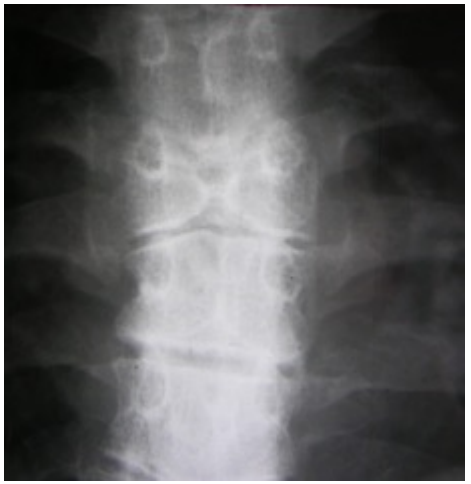
- Casamassima
- Caudal regression
- CHARGE
- Covesdem
- Currarino
- De la Chapelle
- Di Georges
- FFU
- FOP
- Frontonasal dysplasia
- Fryns Moerman
- Guieon Almeda
- OAV/ Goldenhar specrrum
- Holmes – Sqchimke
- Kabuki
- Klippel feil
- Larsen
- Diabete maternel
- MURCS association
- Multiple Pterygium syndrome
- Pascual-Castroviejo
- PHAVER
- RAPADILINO
- Robinow
- Simpson Golabi Behmel
- Sirenomelia
- Spondylocarpotarsal dysostosis
- Thakker-Donnai
- Toriello
- Urioste
- VATER/ VACTERL
- Verhove-Vanhorick
- Wiedemann Steiner
- Zimmer

- Chromosomal rearrangements
- ……..

le syndrome d'Alagille

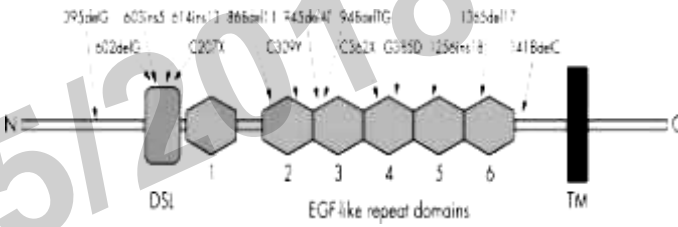
- Cholostase par pauvreté des voies biliaire
- Stenose pulmonaire et vasculopathie
- Dysmorphie faciale
- Anomalie de la chambre antérieure
- Vertébre en aile de papillon, fusion, hemivertèbre
- Autres malf surdité et retard dans les délétions du chromosome 20p12 (7%)





Syndrome d'Alagille, *JAG-1* et *NOTCH2*

- *JAG-1,* ligand de *NOTCH1* (94%)
- *JAG1* : délétions 20p12 (7%), mutations tronquantes 67%
- *NOTCH2* rare



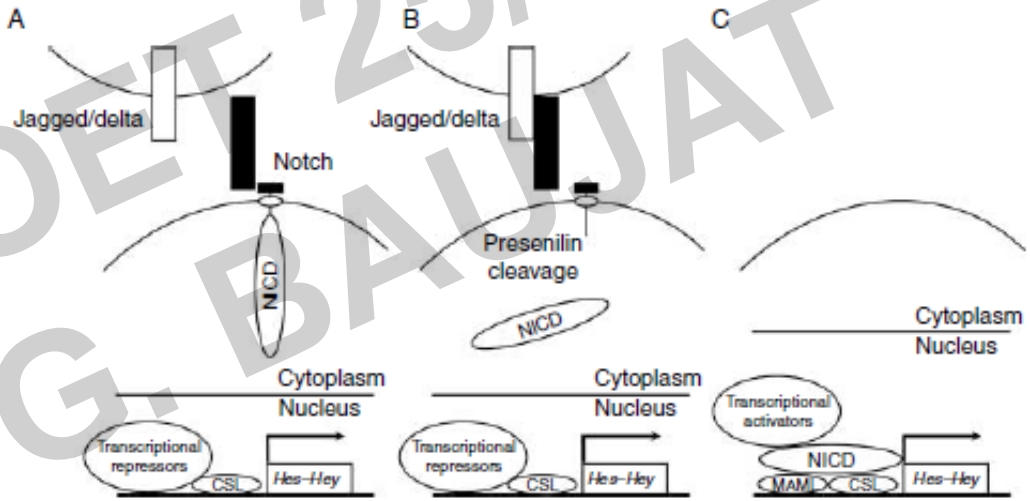


Figure 1 Activation of Notch signaling. (A) Notch receptors and Jagged/delta ligands are expressed as single-pass transmembrane proteins. Epstein–Barr virus latency C promoter-binding factor 1, suppressor of hairless, Lag1 (CSL), also termed Rbpjk, is bound to DNA and inhibits gene expression by recruiting transcriptional repressors. (B) Receptor–ligand interactions lead to the cleavage of the Notch receptor mediated by Presenilin and release of the Notch intracellular domain (NICD) to the cytoplasm. (C) NICD translocates to the nucleus and forms a ternary complex with CSL and Mastermind-like (MAML), replacing transcriptional repressors with transcriptional activators and inducing expression of Notch target genes, such as Hairy enhancer of split (*Hes*) and Hes-related with YRPW motif (*Hey*).

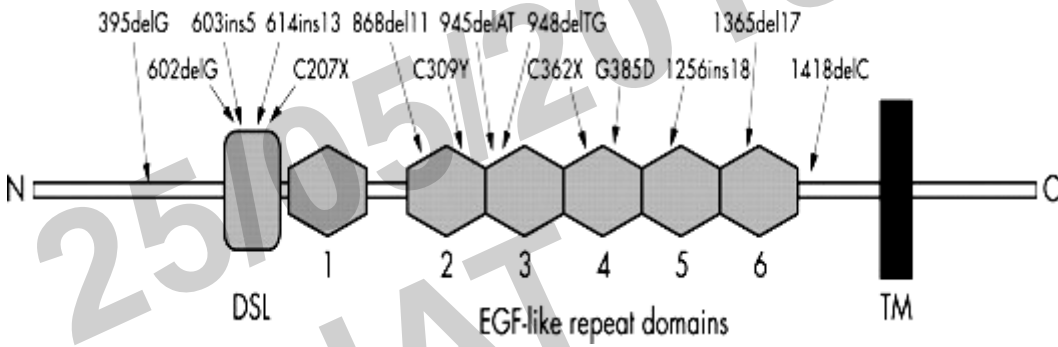
Notch signaling in skeletal health and disease

Stefano Zanotti and Ernesto Canalis

European Journal of Endocrinology **168** R95–R103

Jag1

- DSL Ligand de Notch recepteur
- Famille de *delta-serrate*

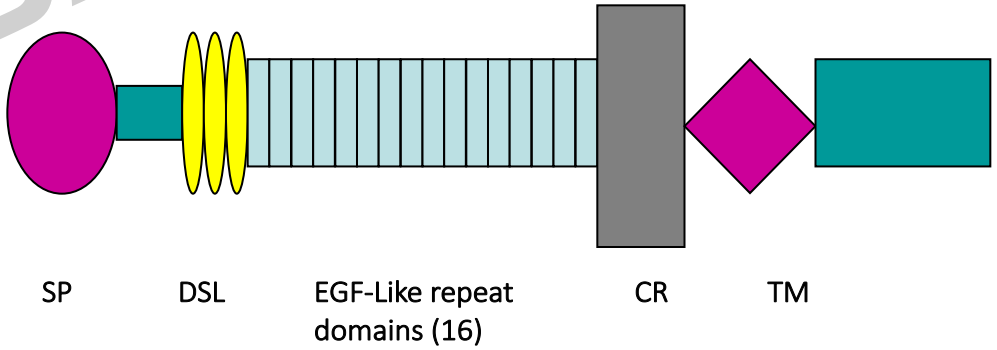


DLL3

- Délétions du chromosome 20p12 (7%)

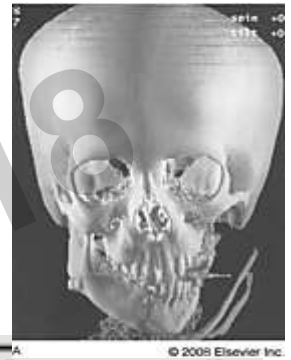
- Mutations troncantes 67%
- *de novo* dans 2/3 des cas

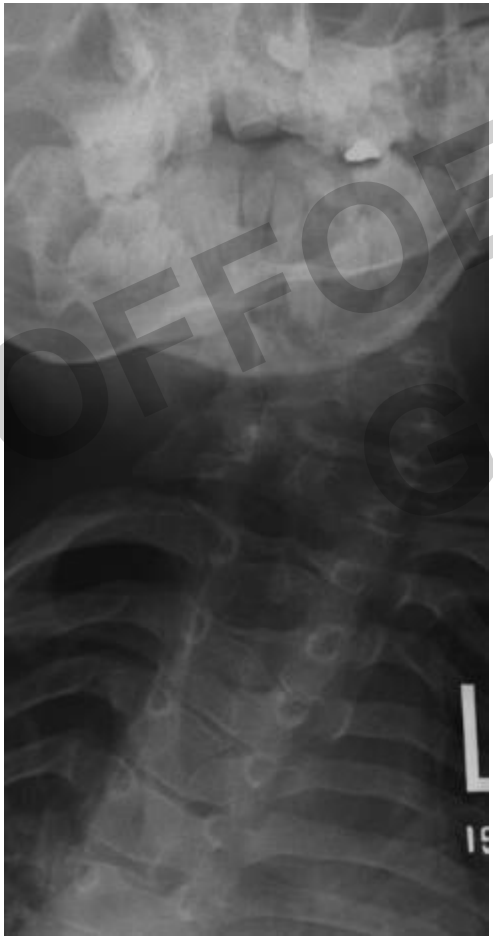
JAG1



Goldenhar/ oculo-auriculo-vertébral/ hemi-facial microsomie

- 1er et 2eme arcs
- asymétrie faciale, microtie , dermoide epibulbaire
- cortège de signes associés
- C1-C2 et vertèbres dorsales : fusion, hémi-, vertèbres surnuméraires





Principal anomalies	Study A (%)[8 9]	Study B (%)[7]	Study C (%)[10]
*Head and face**			
Hemifacial microsomia†	–	83	84
Macrocephaly	–	–	5
Microcephaly	–	8	–
Cleft lip/palate	15–22		18
Macrostomia/facial cleft	1762		13
Facial nerve palsy	10–45		–
Ear			
Anotia or microtia†	66–99	100‡	70
Preauricular tags†	34–61		67
Preauricular sinus/pit	6–9		7
Hearing loss	50–66§	85	68
Velopharyngeal insufficiency	35–55	–	–
Vertebral anomalies	16–60¶	53	35
Congenital heart defects	4–33	15	27
Anomalies of extremities	3–21	12	–

Table 4 Differential diagnoses of OAVS

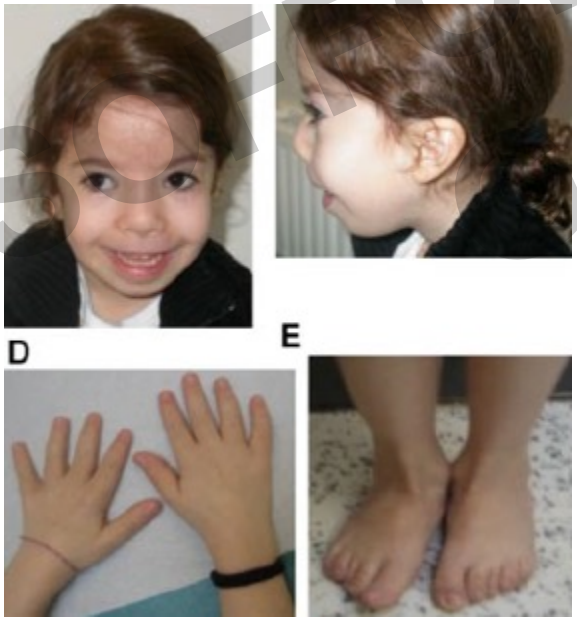
Diagnosis	Main clinical features	Gene	Ref.
Treacher Collins syndrome OMIM 154500, 613717, 248390	▶ Hypoplasia of the zygomatic bones and mandible ▶ External ear abnormalities frequently associated with hearing impairment ▶ Coloboma of the lower eyelid ▶ Absence of the lower eyelashes ▶ Preauricular hair displacement onto the cheeks ▶ Craniofacial involvement is generally symmetrical	*TCOF1*	86
Townes–Brocks syndrome OMIM 107480	▶ Imperforate anus ▶ Dysplastic ears (overfolded superior helices and preauricular tags) frequently associated with sensorineural and/or conductive hearing impairment ▶ Thumb malformations (triphalangeal thumbs, duplication of the thumb, preaxial polydactyly or hypoplasia of the thumbs) ▶ Renal impairment with or without structural abnormalities	*SALL1*	89
CHARGE syndrome OMIM 214800	▶ Coloboma of the iris, retina-choroid, and/or disc ▶ Unilateral or bilateral choanal atresia or stenosis ▶ Ear abnormalities (external ear malformation, ossicular malformations, Mondini defect of the cochlea and/or absent/hypoplastic semicircular canals) ▶ Cryptorchidism in males and hypogonadotrophic hypogonadism in both males and females ▶ Cardiovascular malformations ▶ Orofacial clefts ▶ Tracheoesophageal fistula ▶ Cranial nerve dysfunction	*CHD7*	90
Branchio-oto-renal spectrum disorders (branchio-oto-renal and branchio-otic syndromes) OMIM 113650, 610896, 602588	▶ Malformations of the outer, middle and inner ear ▶ Conductive, sensorineural, or mixed hearing impairment ▶ Branchial fistulae and cysts, ▶ Renal malformations ranging from mild renal hypoplasia to bilateral renal agenesis. ▶ Branchio-otic syndrome has the same features as branchio-oto-renal syndrome but without renal involvement.	EYA1, SIX5 and SIX1	91
Mandibulofacial dysostosis, Guion–Almeida—type OMIM 610536	▶ Oto-facial abnormalities (acrofacial dysostosis) ▶ Oesophageal atresia ▶ Thumb anomalies ▶ Intellectual disability ▶ Zygomatic anomalies ▶ Microcephaly	*EFTUD2*	92 93

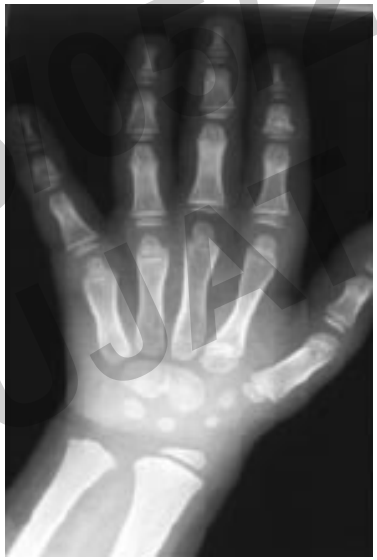
Autre forme de synspondylie dominante non liée à *FLNB*

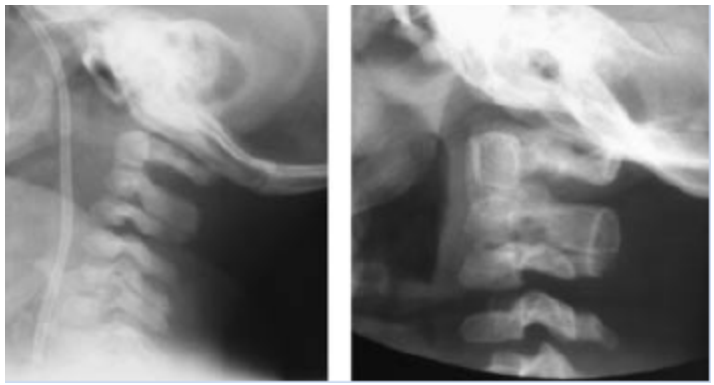
Postnatal Growth Retardation, Facial Dysmorphism, Spondylocarpal Synostosis, Cardiac Defect, and Inner Ear Malformation (Cardiospondylocarpofacial Syndrome?)—A Distinct Syndrome?

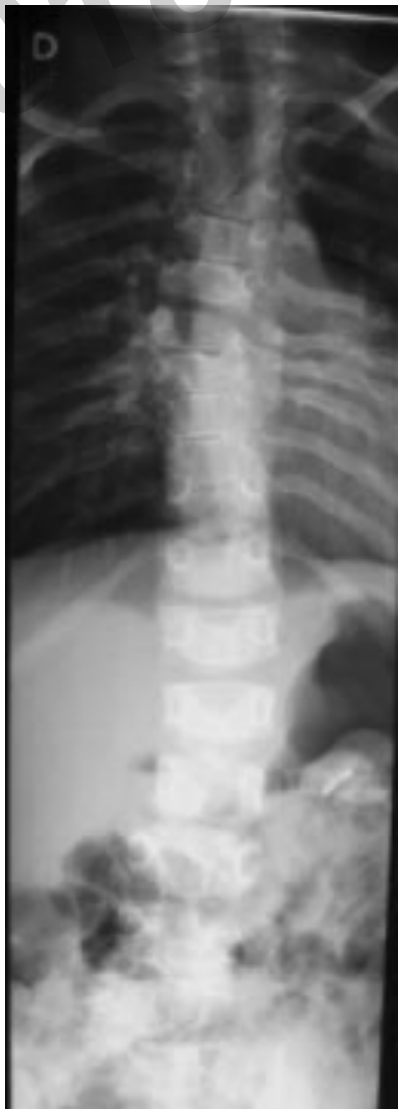
Sérgio B. Sousa,[1,2] Geneviéve Baujat,[1] Véronique Abadie,[3] Damien Bonnet,[4] Daniel Sidi,[4] Arnold Munnich,[1] Deborah Krakow,[5,6] and Valérie Cormier-Daire[1]*

Am J Med Genet Part A 152A:539–546.



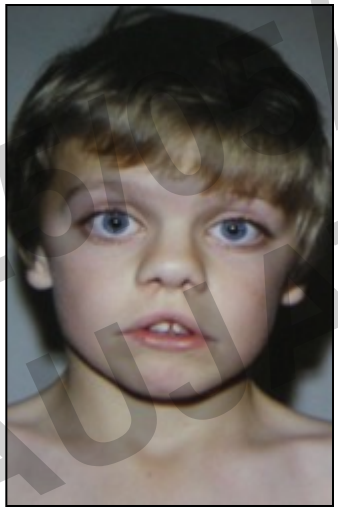


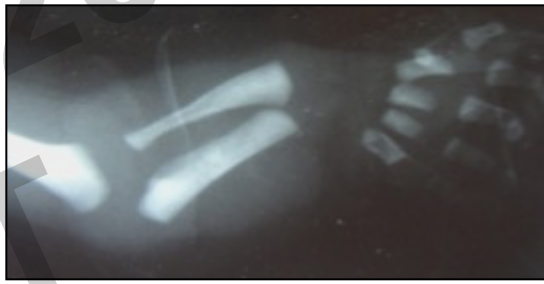


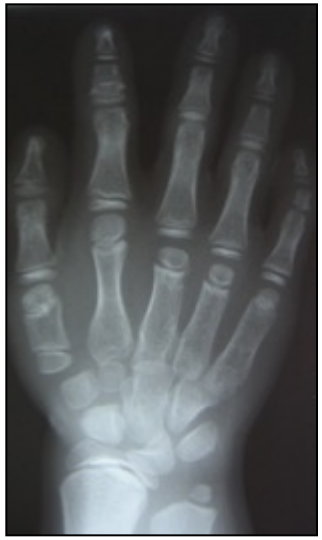


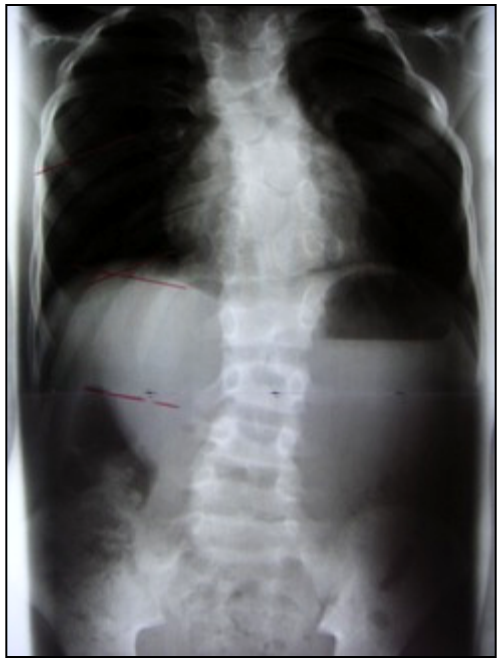
Les anomalies de segmentation rachidiennes et les osteochondrodysplasies

- Le syndrome de Robinow
  - Dysplasie mésomélique
  - Doigts court
  - Face « fetale »
  - hypogénitalisme









Forme RA et DA: ROR2

- DSC++

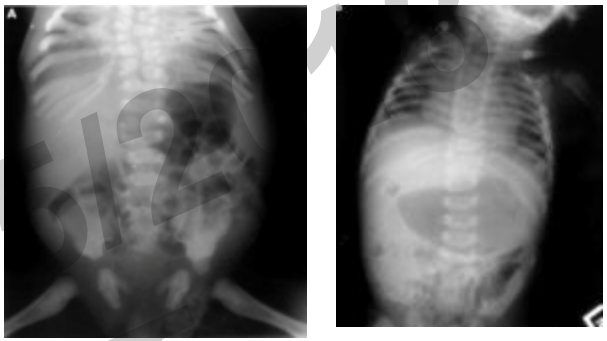
(Brachydactylie de type B)

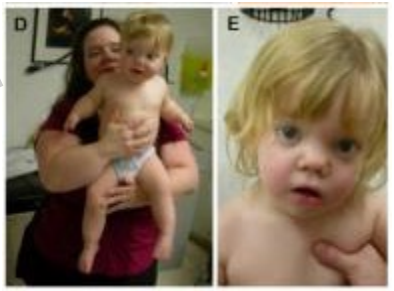
Forme DA : WNT5A

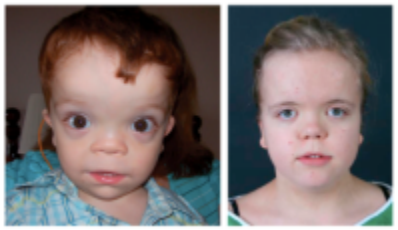
- Pas de DSC
- Hernie ombilicale et dents surnuméraires

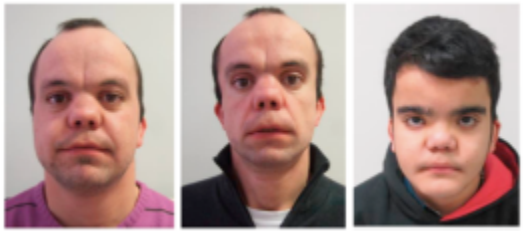
Syndrome de Robinow, bases moléculaires

- *ROR2*
  - AR et AD
  - Mutations perte de fn, domaine EC
  - **DSC ++++**
- *WNT5A*
  - DA
  - Pas de DSC
  - Hernie ombilicale et dents surnuméraires
- *DVL1*
  - AD
  - Effet gain de fonction ou dominant negatif, Wnt
  - Macrocéphalie +++, taille normale
  - Pas de DSC







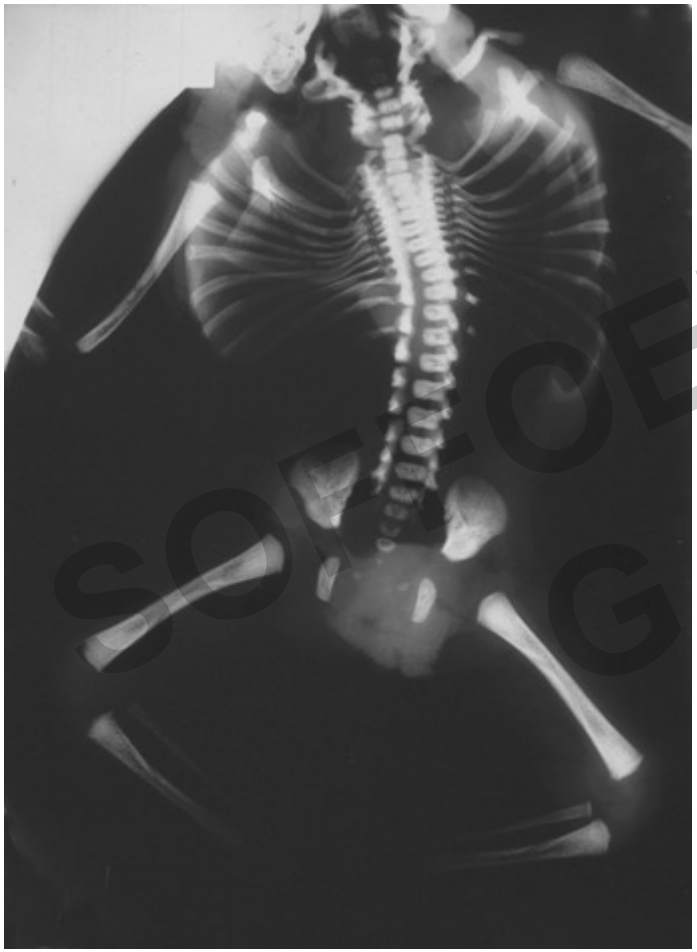


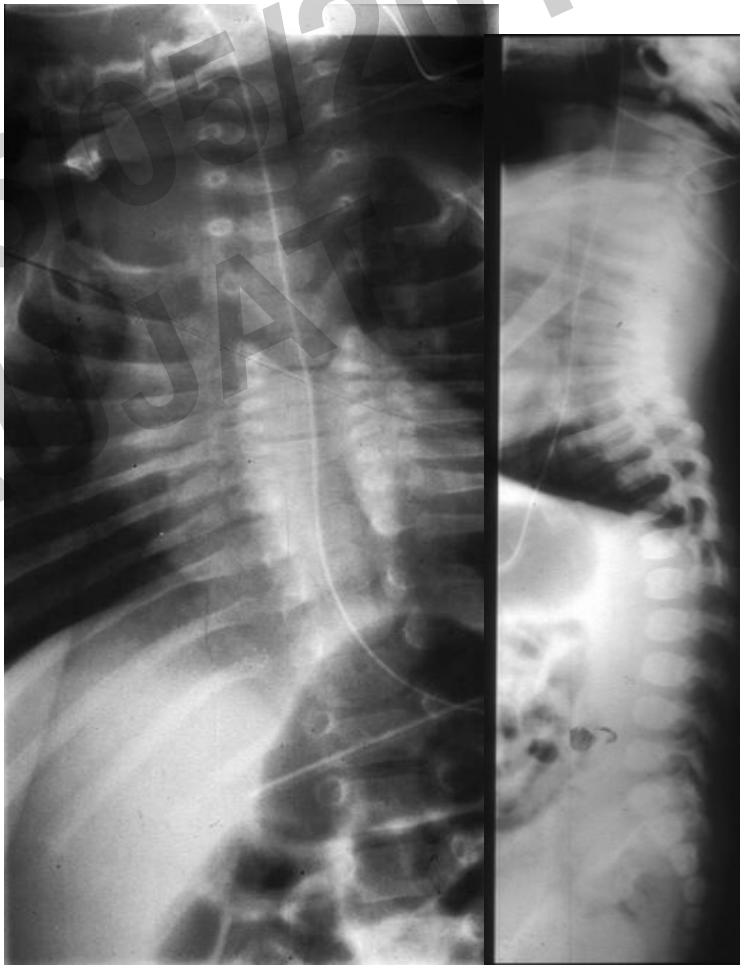
DVL1 Frameshift Mutations Clustering in the Penultimate Exon Cause Autosomal-Dominant Robinow Syndrome

Janson White,[1,17] Juliana F. Mazzeu,[2,3,17] Alexander Hoischen,[4] Shalini N. Jhangiani,[5] Tomasz Gambin,[1,6] Michele Calijorne Alcino,[7] Samantha Penney,[1] Jorge M. Saraiva,[8,9] Hanne Hove,[10] Flemming Skovby,[10] Hülya Kayserili,[11,12] Elicia Estrella,[13] Anneke T. Vulto-van Silfhout,[4] Marloes Steehouwer,[4] Donna M. Muzny,[5] V. Reid Sutton,[1,14] Richard A. Gibbs,[1,5] Baylor-Hopkins Center for Mendelian Genomics, James R. Lupski,[1,5,14,15] Han G. Brunner,[4,16] Bregje W.M. van Bon,[4] and Claudia M.B. Carvalho[1,7,*]

The American Journal of Human Genetics *96*, 612–622, April 2, 2015

Autres formes de synspondylie non liée a FLNB





22q11.2 microdeletion

Pediatr Radiol (2008) 38:766–771
DOI 10.1007/s00247-008-0903-0

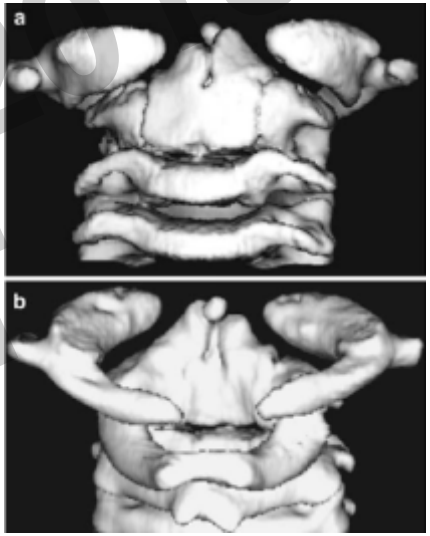
ORIGINAL ARTICLE

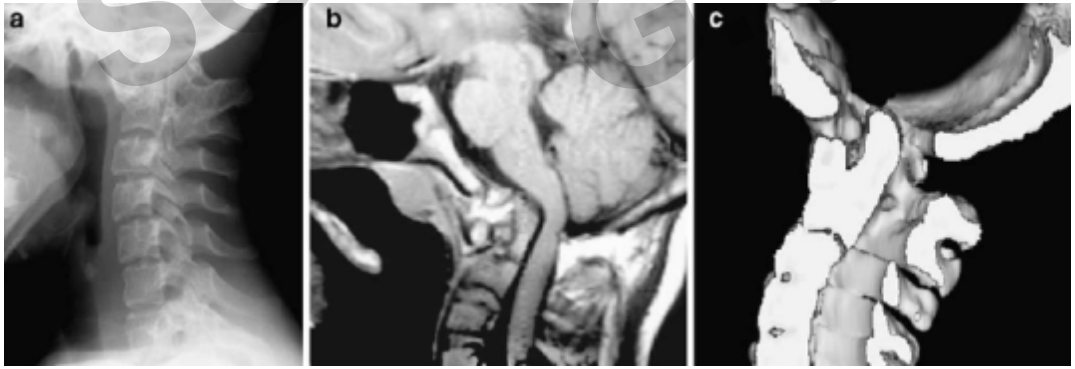
C1-2 vertebral anomalies in 22q11.2 microdeletion syndrome

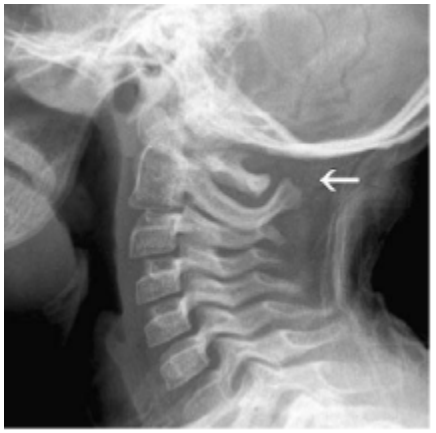
Osnat Konen · Derek Armstrong · Howard Clarke · Nancy Padfield · Rosanna Weksberg · Susan Blaser

Materials and methods Sequential CT scans performed for presurgical carotid assessment in 76 children (45 children positive for chromosome 22q11.2 deletion and 31 negative for the deletion) with VPI were retrospectively evaluated for assessment of C1-2 anomalies.

Results C1-2 vertebral anomalies, specifically midline C1 defects, uptilted or upswept posterior elements of C2 and fusions of C2-3, were nearly universal in our cohort of 22q11DS patients with VPI. They were strikingly absent in the majority of non-22q11DS patients with VPI.







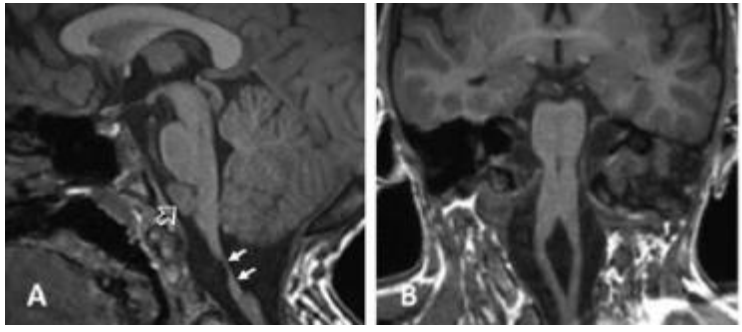
Anomalie de C1 –C2 chez 97% des patients 22q11.2 avec insuffisance vélo-palatine

Anomalie de Wildervank

- Klippel Feil + surdité congénitale de perception + Duane (uni ou bilatéral)
+/- tag pre-auriculaires, atrésie CAE, fente palatine , PF, anomalie oreille moyenne et interne
+/- anomalies SNC : fosse postérieure, hydrocéphalie
+/- anomalie rachidienne étendue (diastematomyelie), cardiaque

- Possible confusion avec le spectre de SALL4
-fille>>
-Microdeletion Xq26.3, emportant *FGF13* (*HOXA1, KIF21A, SALL4*, and *CHN1* N)
-FGF13 = FHF12 (FGF homolog factor) : développement SNC, oreille, squelette

♂

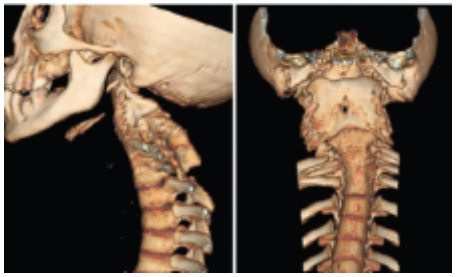


RESEARCH REPORT

Xq26.3 Microdeletion in a Male with Wildervanck Syndrome

Khaled K. Abu-Amero[1,4], Altaf A. Kondkar[1], Ibrahim A. Alorainy[2], Arif O. Khan[3], Leila A. Al-Enazy[4], Darren T. Oystreck[1,5], and Thomas M. Bosley[1]

Ophthalmic Genetics, 2014; 35(1): 18–24



© 2017. Published by The Company of Biologists Ltd | Development (2017) 144, 1743-1763 doi:10.1242/dev.148007

REVIEW

The developmental biology of genetic Notch disorders

Jan Mašek and Emma R. Andersson*

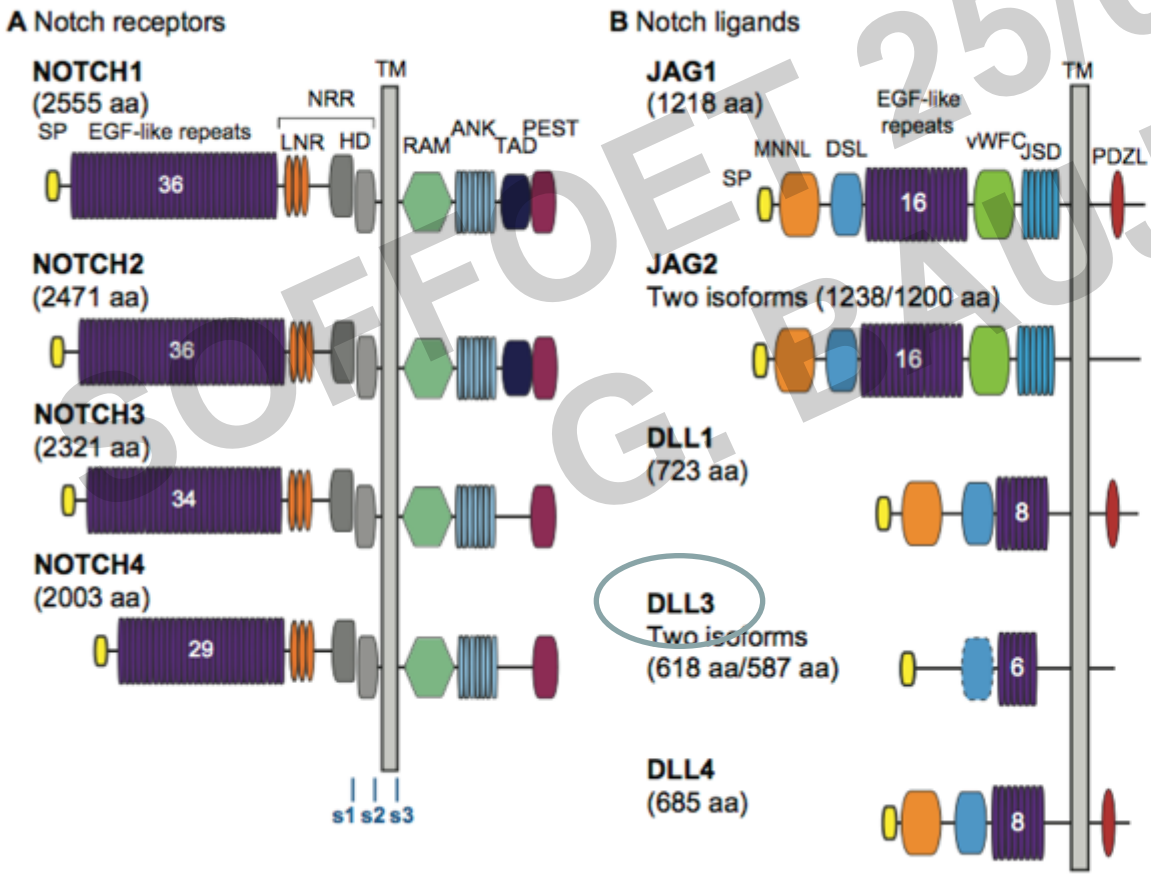


Fig. 2. The human Notch repertoire. Protein domain arrangement of human Notch receptors (A) and ligands (B). Structures are based on InterPro protein domain prediction and other studies (Ehebauer et al., 2005; Lubman et al., 2005). ANK, ankyrin repeats; DLL, Delta-like protein; DSL, Delta/Serrate/LAG-2 domain; EGF, epidermal growth factor; HD, heterodimerization domain; JAG, jagged; JSD, Jagged Serrate domain; LNR, Lin-Notch repeats; MNNL, Notch ligand N-terminal domain; NRR, negative regulatory region; PDZL, PDZ ligand domain [PDZ, post synaptic density protein (PSD95)]; PEST, proline (P), glutamic acid (E), serine (S) and threonine (T) degradation domain; RAM, Rbp-associated molecule domain; s, cleavage site; SP, signal peptide; TAD, transactivation domain; TM, transmembrane domain; vWFC, von Willebrand factor type C domain.