

SOFFOET
03 octobre 2024

Ciliopathies rénales

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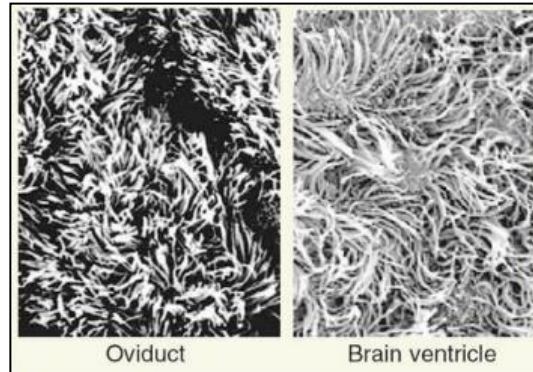
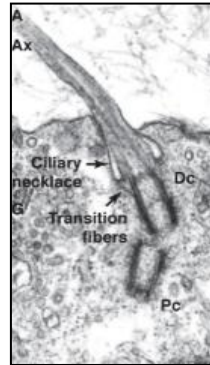
Le cil

Organelles, à la surface des cellules

Taille : 7 à 10 μm

Diamètre : 0,2 μm

Chaque cil est construit autour d'un complexe central, l'**axonème** qui naît du **centrosome**

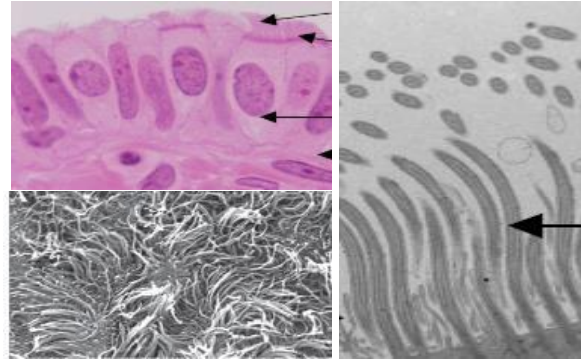
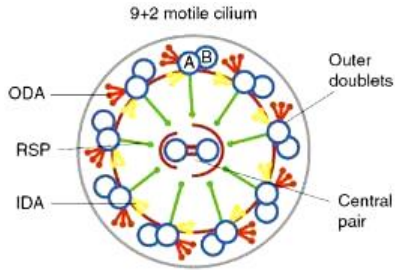


2 types de cils:
les cils mobiles et le cil primaire

Cils mobiles

Mouvement cellulaire

9+2

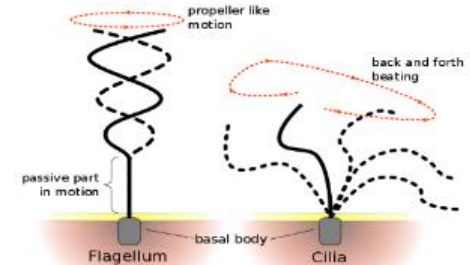
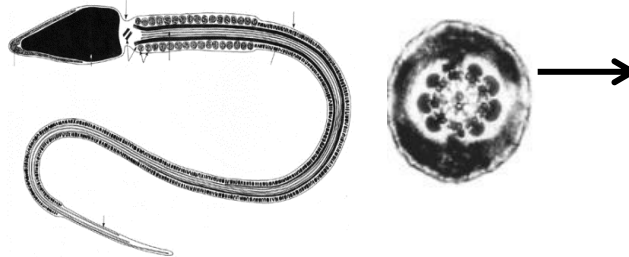


Cellules ciliées

Epithélium respiratoire
Epithélium voies génitales
Cellules épendymaires
Génération de flux

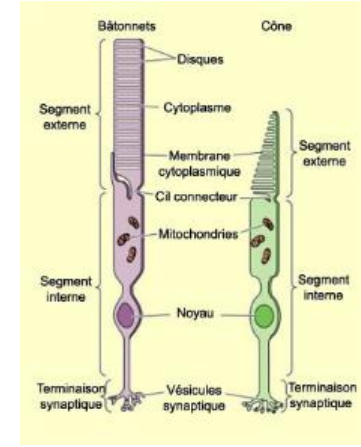
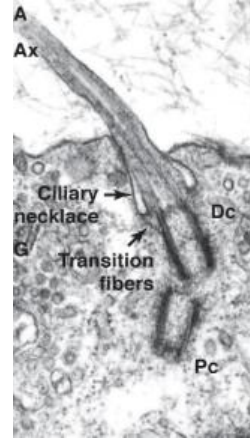
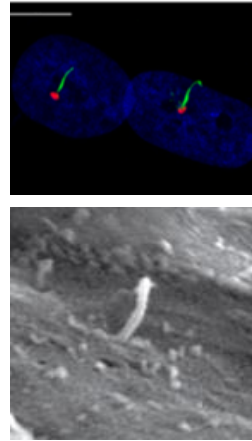
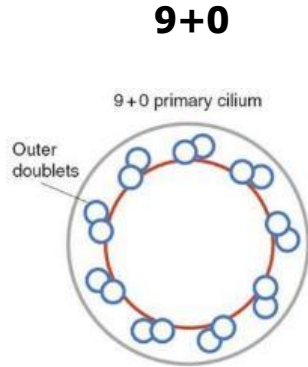


Flagelles



Cil primaire

Fonction sensorielle Signalisation



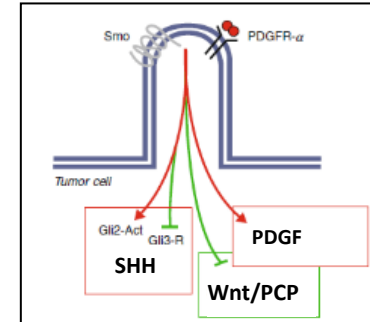
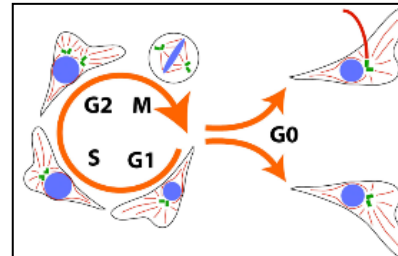
Cil connecteur
des cônes et
batonnets

Fonctions sensorielles diverses

« Antenne » cellulaire

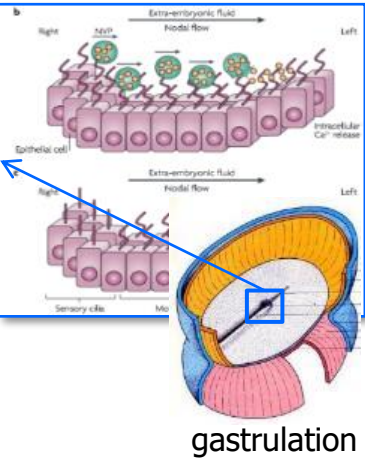
Photoréception
Réception chimique
Réception mécanique

Cellules au repos



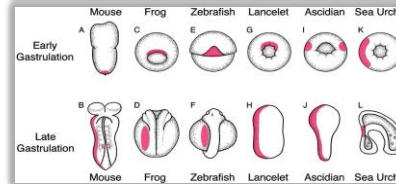
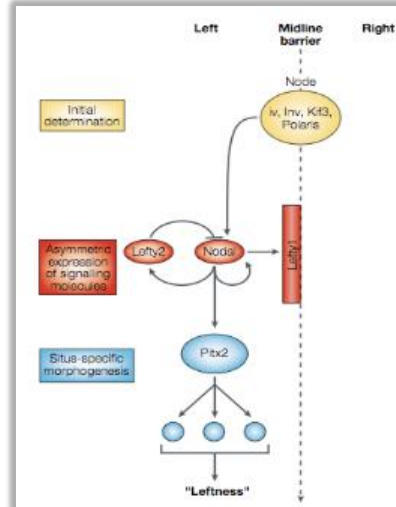
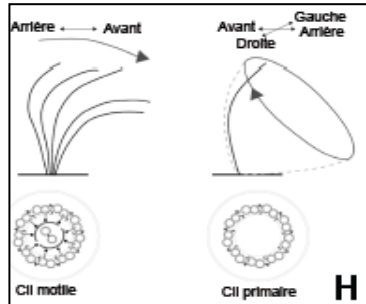
Le cil nodal : cil primaire... mais mobile

Mise en place de l'asymétrie G/D

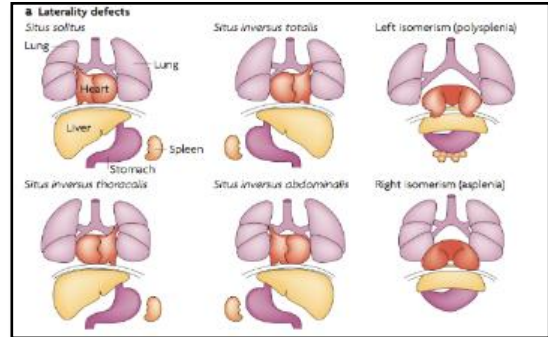


Droite

Gauche



Anomalies de l'asymétrie G/D, Hétérotaxie



- **Situs inversus totalis** : image en miroir complet du *situs solutus*, (1/6000 - 8000 naissances)
- **Situs ambiguus** : problème d'asymétrie d'au moins un organe, malformations graves possibles notamment cardiaques (1/10 000 naissances)
- **Isomérisme** : perte de l'asymétrie habituelle d'un ou plusieurs organes, menant à une symétrie pathologique de type G ou D

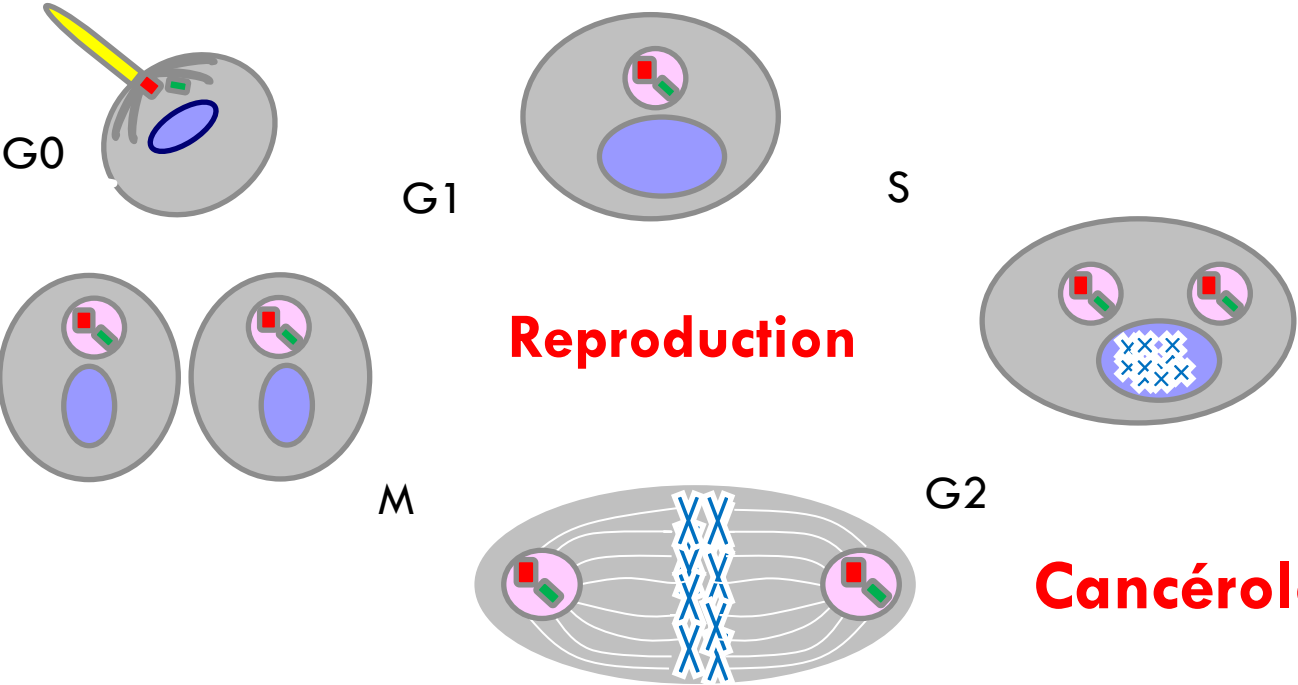
Manfred Fliegeauf et al., Nature (2007)

Hiroshi Hamada et al., Nature Reviews Genetics (2002)

<http://scienceblogs.com/pharyngula>

Centrosome et cil primaire: Fonctions cellulaires majeures

Anomalies du développement



Reproduction

Cancérologie

Cil et cancer

Examples of ciliary genes use in cancer clinical trials (from TTD—Therapeutic Target Database

<http://db.idrblab.net/ttd/> (accessed on 6 November 2019) [178].

Ciliary Genes	Type of Cancer	Name of Drug	Clinical Trial	References
<i>CTNNB1</i>	Solid cancer	Recombinant human endostatin	approved	[179,180]
<i>DRD5</i>	Solid cancer	DS-8273	Phase1	https://clinicaltrials.gov/ct2/show/NCT02076451
<i>GSK3B</i>	Acute myeloid leukemia, osteosarcoma	LY2090314, Tideglusib	Phase2	https://clinicaltrials.gov/ct2/show/NCT01214603 [181]
<i>PLK1</i>	Solid cancer, Acute myeloid leukemia	Rigosertib, Volasertib	Phase3, Phase3	[182,183,184,185,186,187,188,189]
<i>SMO</i>	Solid cancer, skin cancer	LDE225 LY2940680, BMS-833923, LEQ-506, TAK-441	Approved (basal cell carcinoma) Phase1, Phase2	[190,191,192,193,194,195,196,197,198,199,200]
<i>TTK</i>	Solid cancer	BAY1161909, BAY1161909	Phase1 Phase1	[201,202,203]
<i>VDAC3</i>	Solid cancer	PRLX93936	Phase1/2	https://clinicaltrials.gov/ct2/show/NCT01695590
<i>VHL</i>	Renal cell cancer	Pyrrolidine carboxamide derivative 1	Patented-recorded Target	[204,205]

Genes ciliaires fréquemment mutés dans les cellules tumorales (sein, colon)

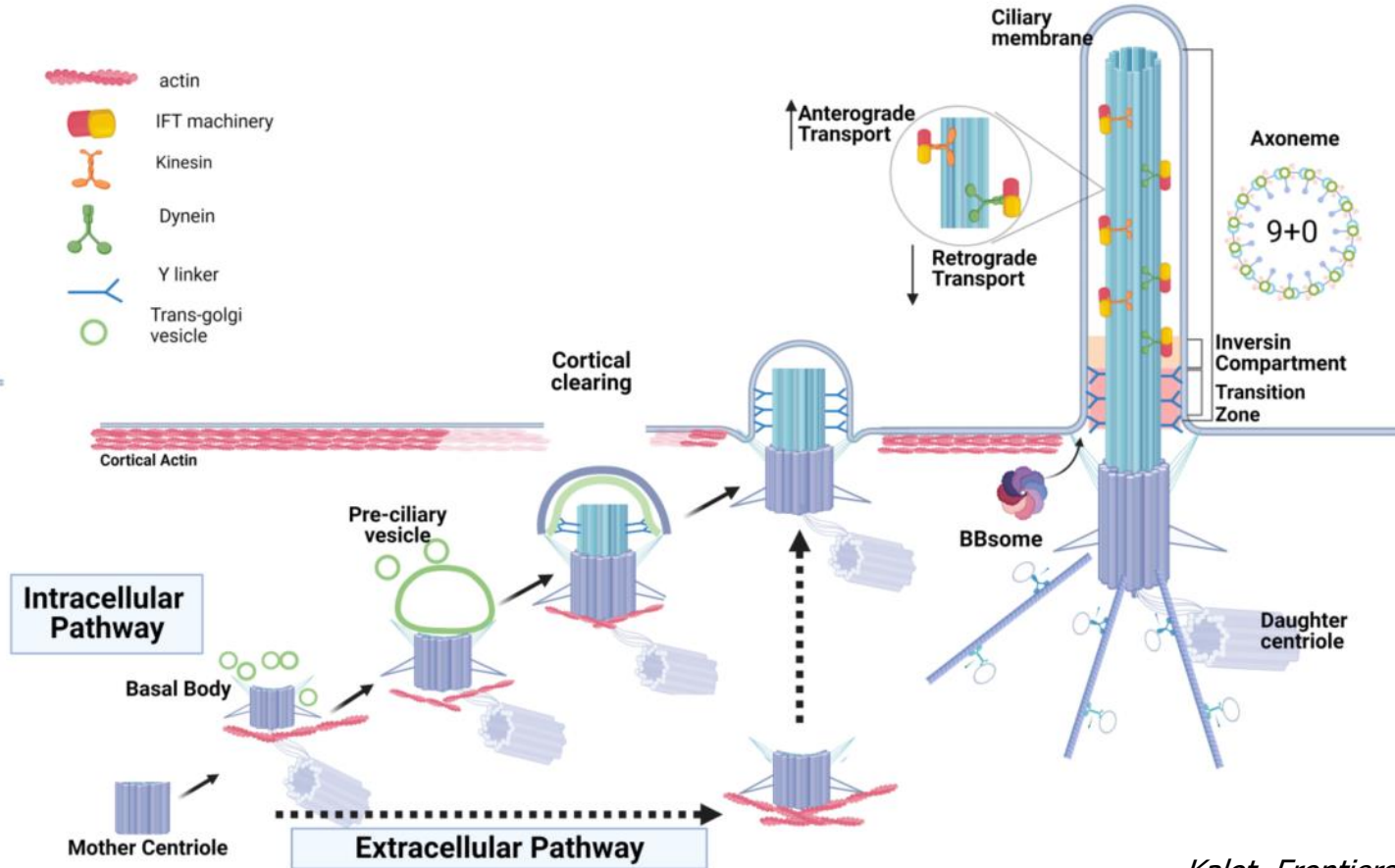
Sur 304 gènes ciliaires (website Syscilia) 8 codent pour des protéines ciblées par des molécules faisant l'objet d'essais cliniques

CTNNB1, *DRD5*, *GSK3B*, *PLK1*, *SMO*, *TTK*, *VDAC3*, *VHL*

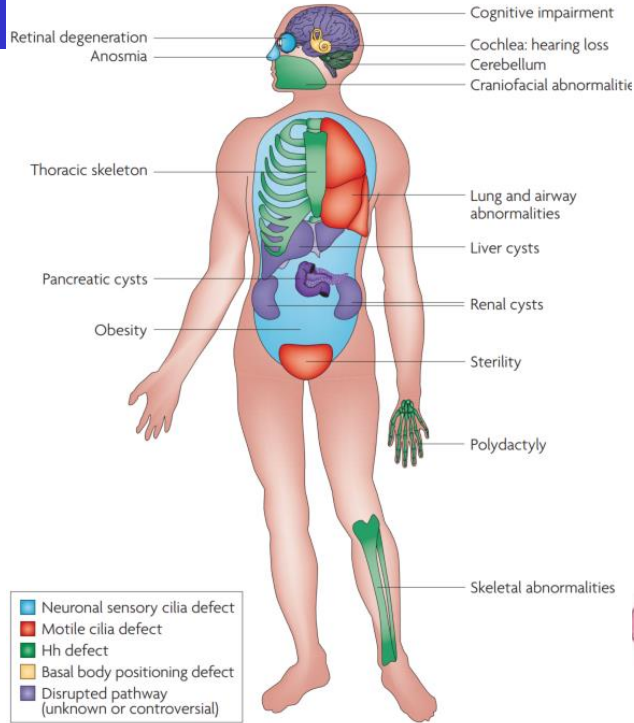
Cil, carcinome rénal (RCC) et VHL

- Les **carcinomes rénaux (CCR)** se manifestent souvent sur des reins kystiques
- Le **VHL est la cause génétique la plus fréquente de RCC, souvent précédé de kystes**
- **Nombre de cils primaires diminués dans les RCC**
 - Schraml P, et al. Sporadic clear cell renal cell carcinoma but not the papillary type is characterized by severely reduced frequency of primary cilia. *Mod Pathol* (2009) 22:31–6.
 - Basten SG, et al. Reduced cilia frequencies in human renal cell carcinomas versus neighboring parenchymal tissue. *Cilia* (2013) 2:2.
- **VHL, suppresseur de tumeur: dynamique des microtubules : orientation et la stabilization des MT -> ciliogenèse**
 - Schermer B, et al. The von Hippel-Lindau tumor suppressor protein controls ciliogenesis by orienting microtubule growth. *J Cell Biol* (2006) 175:547–54.
 - Hergovich A et al.,. Regulation of microtubule stability by the von Hippel-Lindau tumour suppressor protein pVHL. *Nat Cell Biol* (2003) 5:64–70. 233. Kuehn EW, Walz G, Benzing T. Von hippel-lindau: a tumor suppressor links microtubules to ciliogenesis and cancer development. *Cancer Res* (2007) 67:4537–40.
 - Lolkema MP, et al. The von Hippel-Lindau tumor suppressor protein influences microtubule dynamics at the cell periphery. *Exp Cell Res* (2004) 301:139–46.

Deux voies de la ciliogenèse



Pathologies du cil primaire



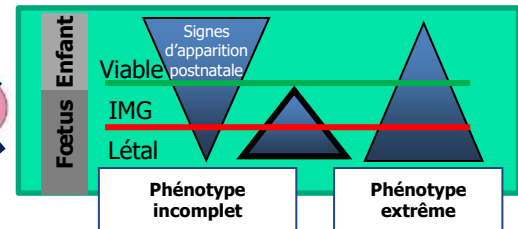
Goetz & Anderson, Nat review Genet, 2010

Chevauchement clinique

	Leber	NPHP	SNLS	ADPKD	ARPKD	BBS	JBS	MKS	SRTD / EVC	HYLS / ACLS	OFD
Anomalies rénales		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anomalies rétinienne	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Polydactylie		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Obésité		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anomalies hépatiques		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anomalies craniofaciales		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anomalies cérébrales		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dysplasie squelettique		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓



Spectre phénotypique



La polykystose rénale AD

1/400-1/1000

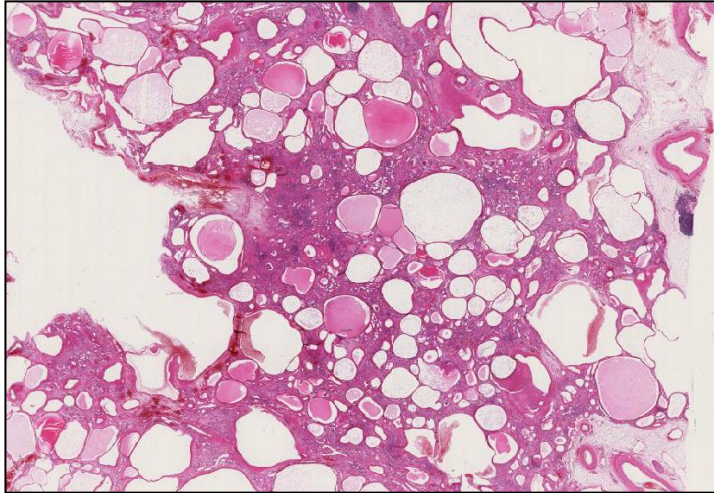
Kystes rénaux, hépatiques
Hypertrophie du VG
Anévrismes artériels

2 gènes

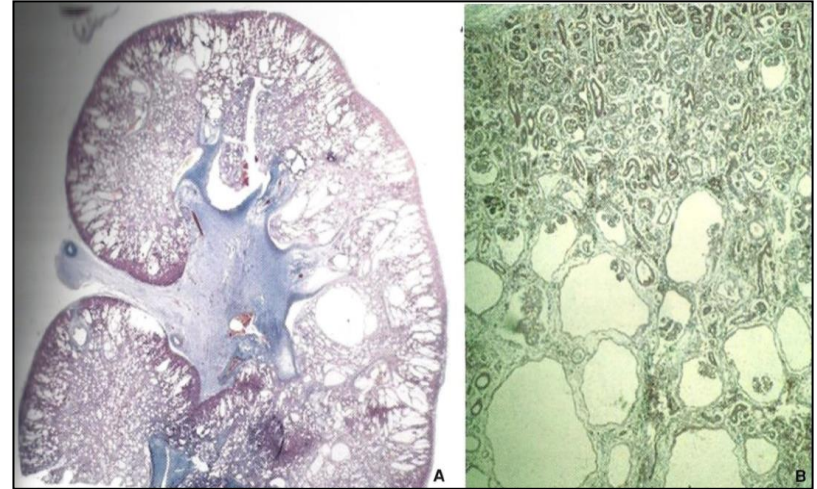
PKD1 : polycystin-1, 78 %

PKD2 : polycystin-2, 15 %

Adulte



Fœtus de 25 SA



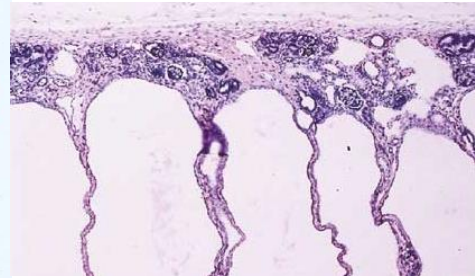
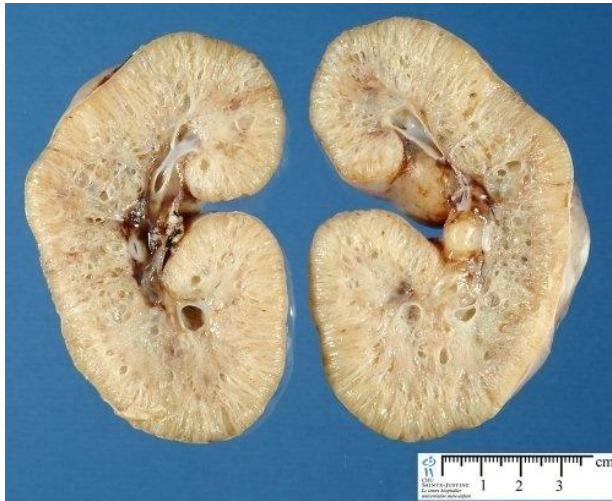
Dilatation de n'importe quel segment du néphron
kystes glomérulaires fréquents

La polykystose rénale AR

1/50 000 naissances

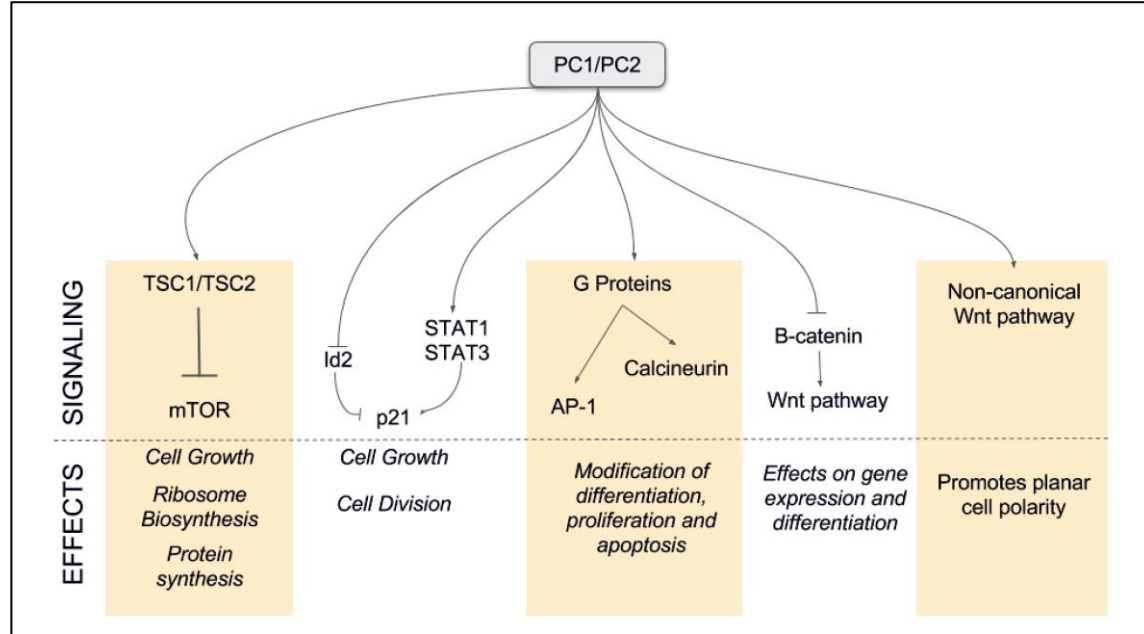
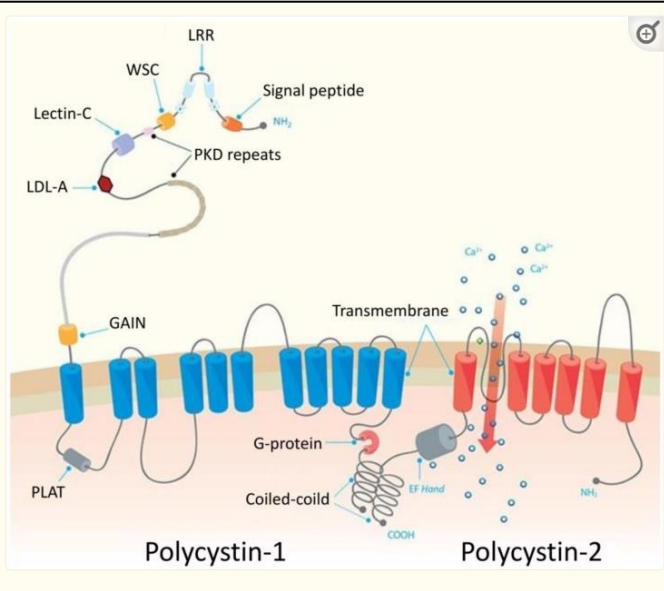
Malformation de la plaque ductale aboutissant à une fibrose hépatique congénitale (FHC).

Gène: *PKHD1* -> fibrocystine

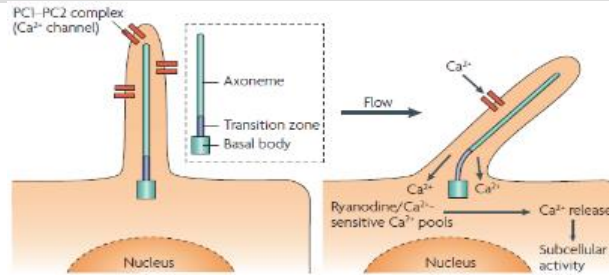


Dilatation des tubes collecteurs
Aspect radiaire
Néphrons généralement normaux

PKD : voies de signalisation impliquées

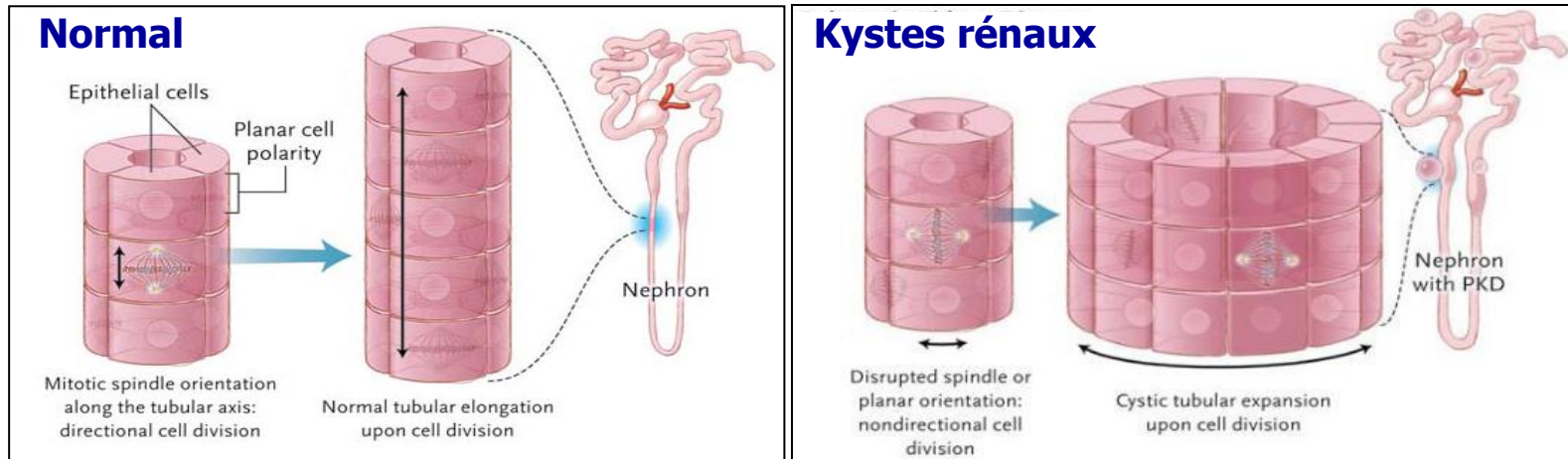


Cil primaire et polarité planaire (Wnt/PCP)



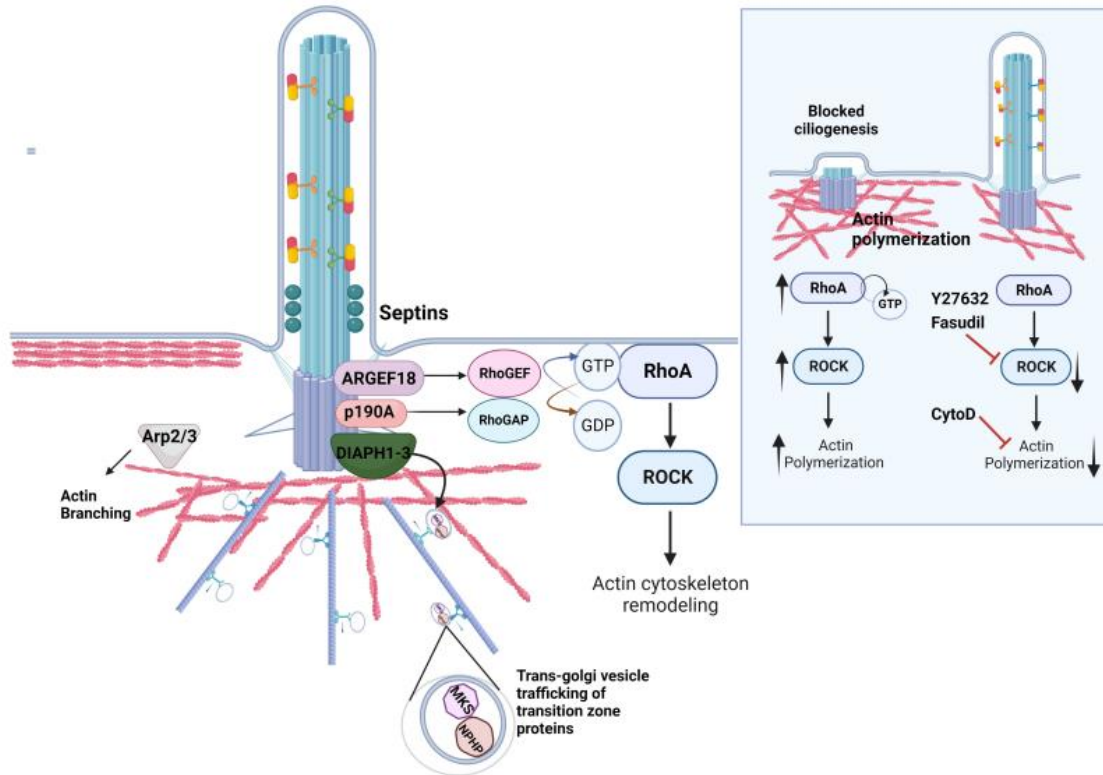
Cellule tubulaire rénale
Mécano-récepteur
(sens du flux)

Fliegauf Nature 2007



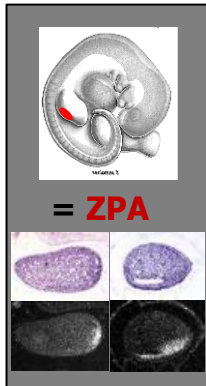
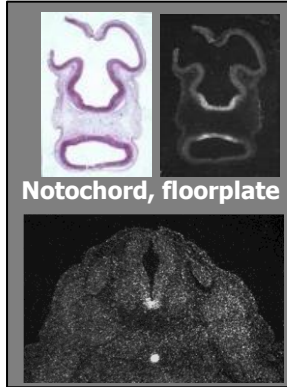
Hildebrandt & Katsanis NEJM 2011

Rôle émergent de l'actine dans les ciliopathies



La dynamique de l'actine est perturbée dans toutes les ciliopathies rénales
→ transformation kystique
→ fibrose

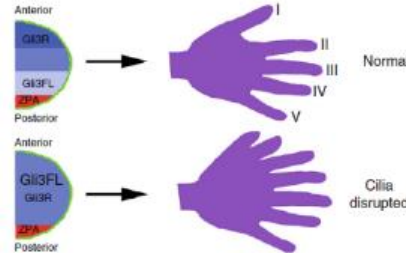
Cil primaire et voie Sonic hedgehog (SHH)



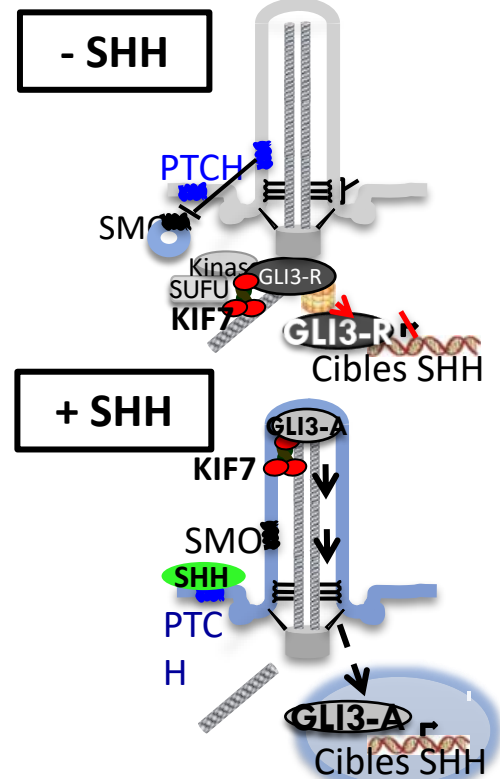
Roessler et al, Muenke
Nature Genet 1996

SHH : holoprosencéphalie

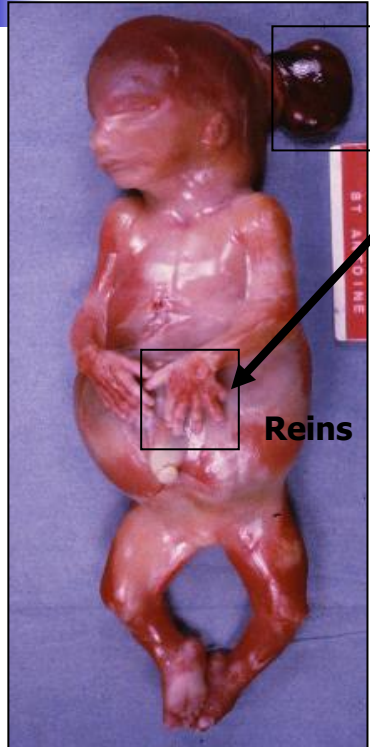
Anomalie de la ligne médiane



Régions régulatrices de SHH
Polydactylie



Le Syndrome de Meckel



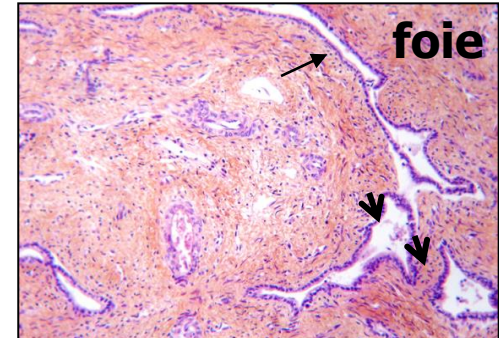
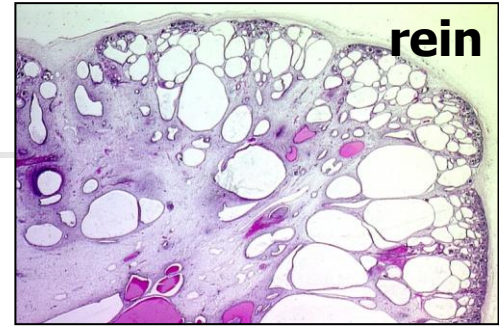
Malformations cérébrales
Encéphalocèle Occipitale

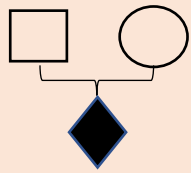
Polydactylie Post-axiale

Reins kystiques

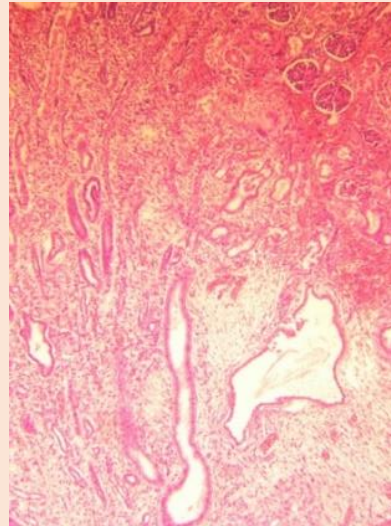
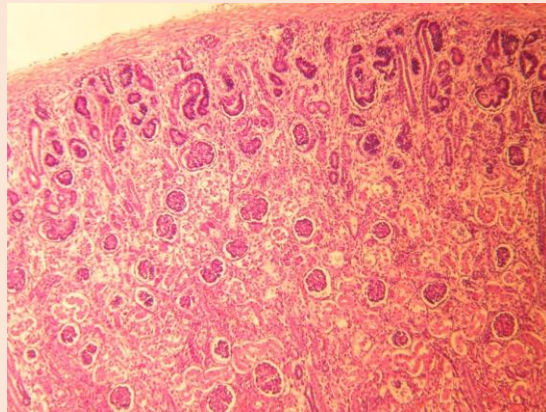
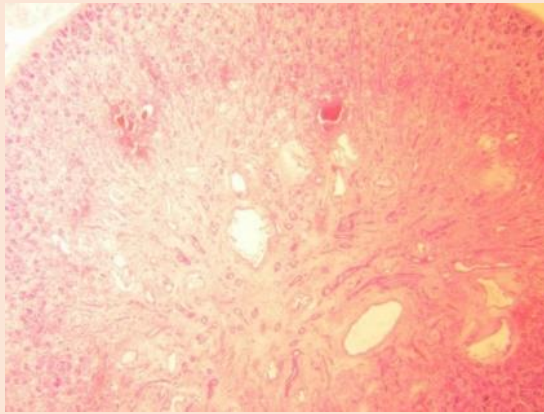
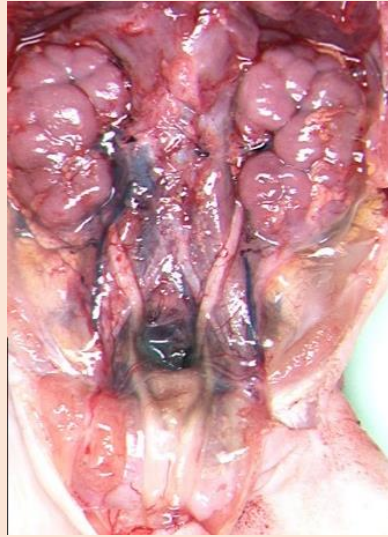
Prolifération des canaux biliaires

- Kystes épидидymaires
- Kystes pancréatiques
- Fentes labiales/palatines
- Malformations cardiaques
- *Situs inversus*
- Microphthalmie
- Anomalies osseuses





IMG 27SA pour encéphalocèle occipitale et dilatation ventriculaire, gros reins



Syndrome de Joubert (JS)

MIM213300

- Ataxie
- Hypotonie
- Retard de développement
- Anomalies mouvements oculaires
- Anomalie du rythme respiratoire
- Hypoplasie / agénésie vermis

**JS related disorders (JSRD) ou
CORS (cerebello-oculo-renal syndrome)**

-> **Signes additionnels rares**

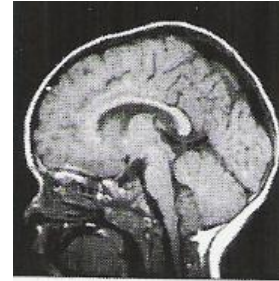
- Polydactylie
- Dystrophie rétinienne
- Reins kystiques / NPH
- Encéphalocèle occipitale
- Fibrose hépatique

1- Hypoplasie / agénésie du vermis

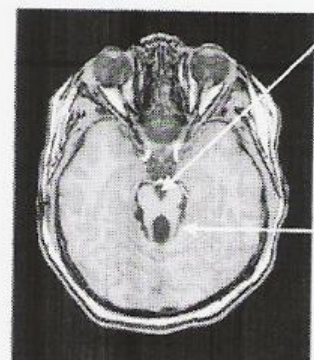
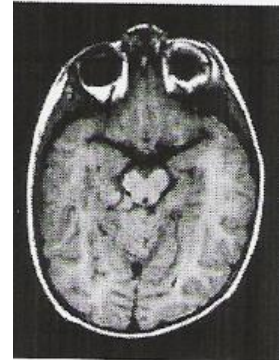
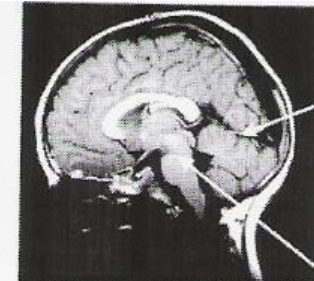
2- Fossé interpédonculaire élargi

3- Pédoncules cérébelleux élargis et allongés

Témoin



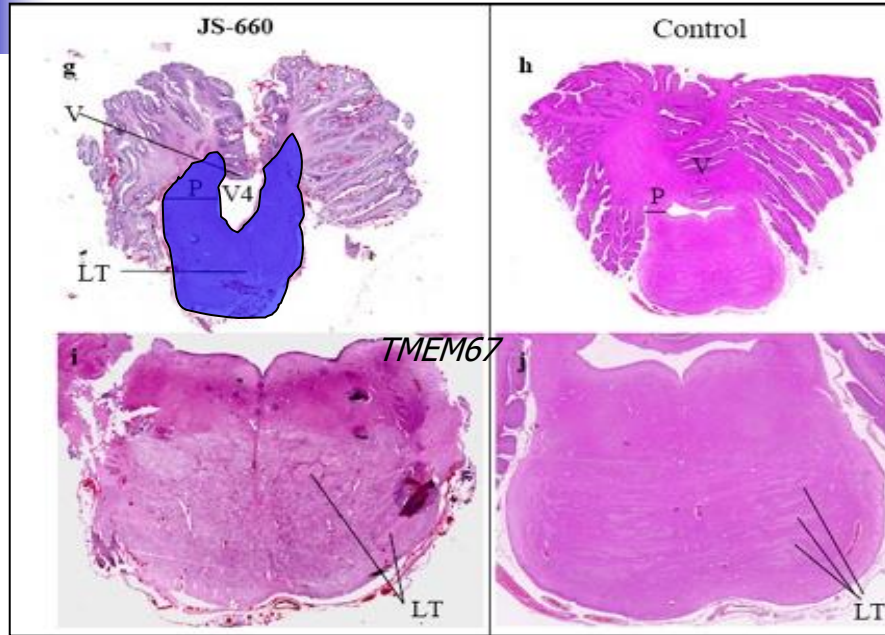
Joubert



**"molar tooth sign" (MTS)
Signe de la dent molaire**

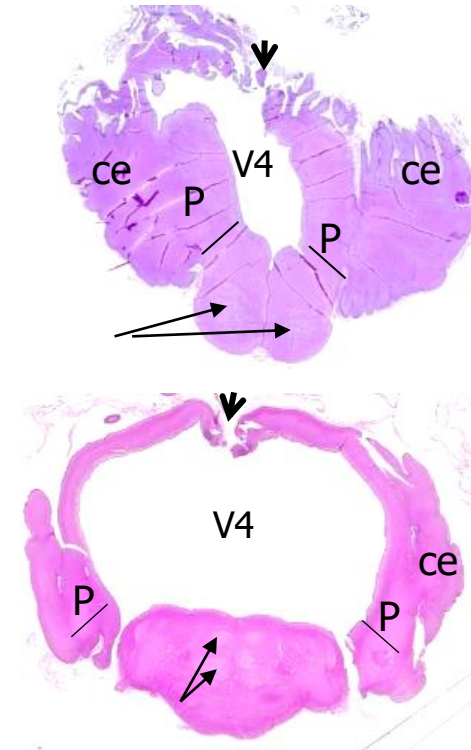
Syndrome de Joubert en foetopathologie

MIM213300



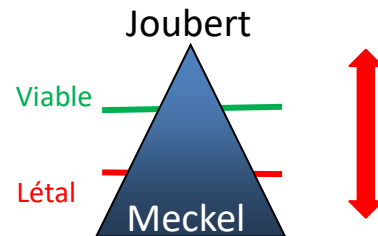
**Aspect de « dent molaire »
Sur coupe transversale pédoncules
cérébelleux supérieurs**

Agénésie du Vermis « Dandy-Walker »



Meckel : extrême phénotype du Joubert

INPP5E	9q34.3	JBS1		
TMEM216	11q13.1	JBS2	MKS2	
AHI1	6q23.3	JBS3		
NPHP1	2q13	JBS4		NPHP1
CEP290	12q21.32	JBS5	MKS4	NPHP6, BBS14
TMEM67	8q22.1	JBS6	MKS3	NPHP11
RPGRIPI1L	16q12.2	JBS7	MKS5	NPHP8
ARL13B	3q11.1	JBS8		
CC2D2A	4p15.32	JBS9	MKS6	
OFD1	Xp22.2	JBS10		OFD1
TTC21B	2q24.3	? JBS11		SRTD4 NPHP12
KIF7	15q26.1	JBS12		HYLS2
TCTN1	12q24.11	JBS13		
TMEM237	2q33	JBS14		
CEP41	7q32	JBS15		
TMEM138	11q12.2	JBS16		
CPLANE1	5p13	JBS17		
TCTN3	10q24.1	JBS18		OFDIV
ZNF423	16q12.1	JBS19		NPHP14
TMEM231	16q23.1	JBS20	MKS11	
CSPP1	8q13.2	JBS21		
PDE6D	2q37.1	JBS22		
KIAA0586	14q23.1	JBS23		
TCTN2	12q24.31	JBS24	MKS8	
CEP104	1p36.32	JBS25		
KATNIP	16p12.1	JBS26		
B9D1	17p11.2	JBS27	MKS9	
MKS1	17q22	JBS28	MKS1	
TMEM107	17p13.1	JBS29		
ARMC9	2q37.1	JBS30		
CEP120	5q23.2	JBS31		
SUFU	10q24.32	JBS32		
PIBF1	13q21.33-q22.1	JBS33		
B9D2	19q13.2	JBS34	MKS10	
ARL3	10q24.32	JBS35		
FAM149B1	10q22.2	JBS36		
TOGARAM1	14q21.2	JBS37		
KIAA0753	17p13.1	JBS38		
TMEM218	11q24.2	JBS39		
IFT74	9p21.2	JBS40		
NPHP3	3q22.1		MKS7	NPHP3
TMEM107	17p13.1		MKS13	
TXNDC15	5q31.1		MKS14	



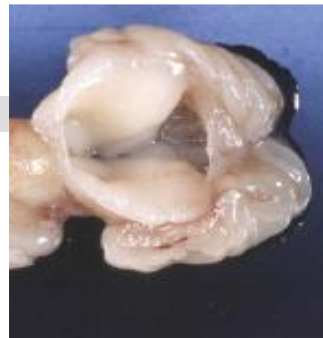
Pathologies Rares
Hétérogénéité génétique
Autosomiques récessifs
sauf *OFD1* (récessif lié à l'X -> Joubert)
**Syndrome de Meckel : phénotype extrême
du syndrome de Joubert**

Corrélations phénotype-génotype ?

- Effet prédictif des variants (Hypomorphe / Perte de fonction complète)
- « Charge mutationnelle » ?
- Gènes modificateurs ? (Effet additifs de variants)

Le Syndrome Hydrolethalus

- **Hydrocéphalie** parfois **anencéphalie**
 - defect os occipital en arrière du f. magnum « en trou de serrure »
 - Autres anomalies cérébrales
- **Dysmorphie faciale**
 - Micrognathie, Fente labio-palatine
- **Polydactylie:**
 - post-axiale au niveau des MS
 - pré-axiale au niveau des MI (duplication de l'hallux)
- **Hydramnios**
- **Reins et foie normaux**



Syndrome de Bardet-Biedl (BBS)

MIM209900

Beales et al, J Med Genet 1999
PNDS 2019

AR, 1/120 000 (x10 Bédouins, New Foundland)

Critères majeurs

4 dont un des 2 premiers

- Rétinite pigmentaire
- Polydactylie postaxiale
- Obésité
- Hypogonadisme
- DI/Troubles comportement
- Atteinte rénale

Critères secondaires

- Retard de langage
- Polyuro-polydipsie / Diabète insipide
- Signes neurologiques
- Anomalies dentaires
- Diabète
- Fibrose hépatique
- Cardiopathie

Syndrome de Bardet-Biedl (BBS)

MIM209900

*Beales et al, J Med Genet 1999
PNDS 2019*

AR, 1/120 000 (x10 Bédouins, New Foundland)

Critères majeurs

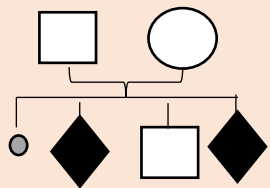
4 dont un des 2 premiers

- Rétinite pigmentaire
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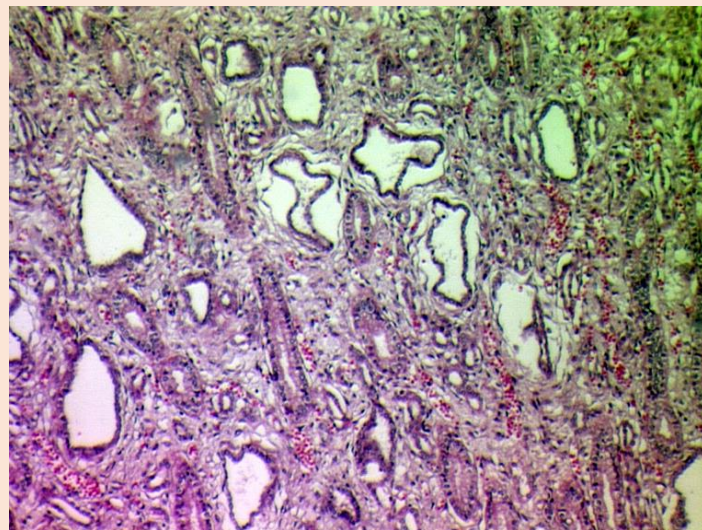
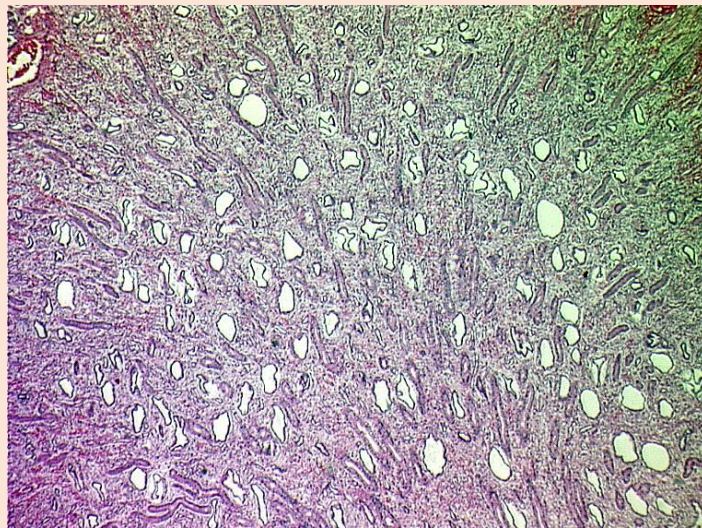
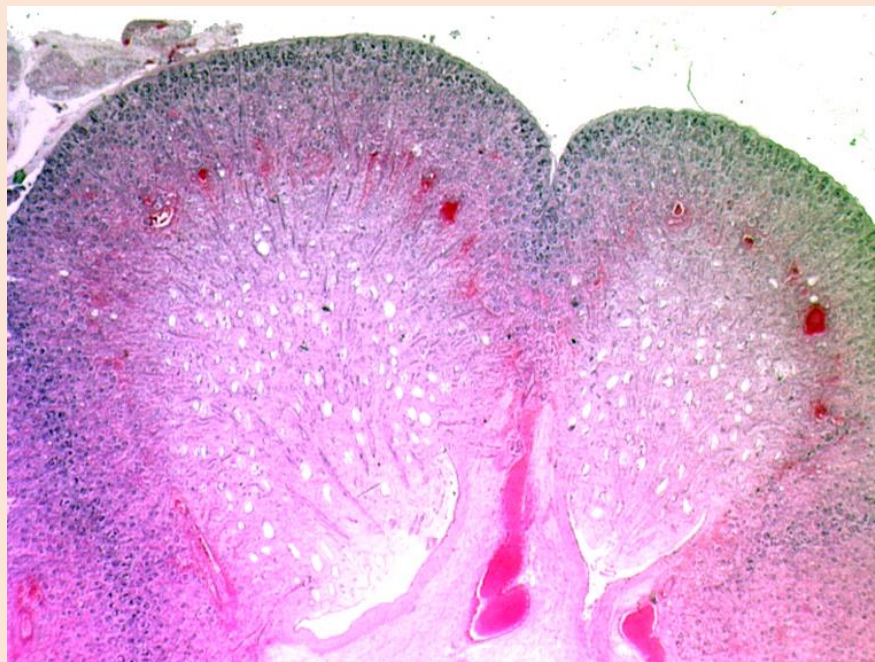
Critères secondaires

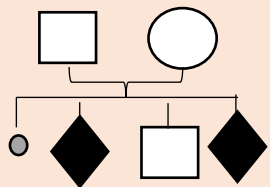
- Retard de langage
- Polyuro-polydipsie / Diabète insipide
- Signes neurologiques
- Anomalies dentaires
- Diabète
- Fibrose hépatique
- Cardiopathie

**Formes anténatales de Bardet-Biedl
Ne peuvent répondre aux critères diagnostics**

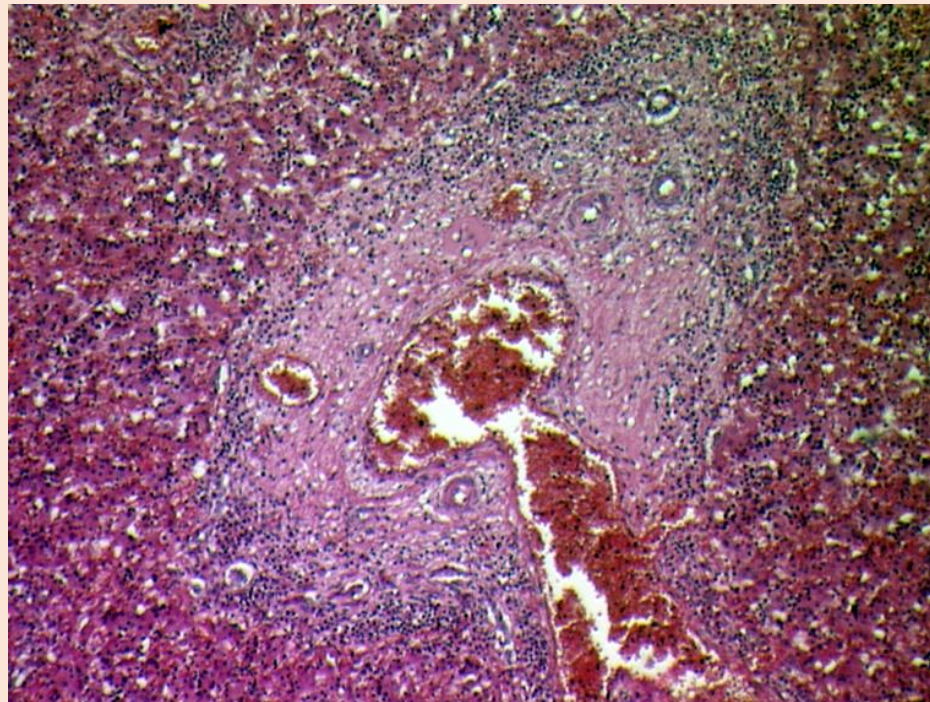
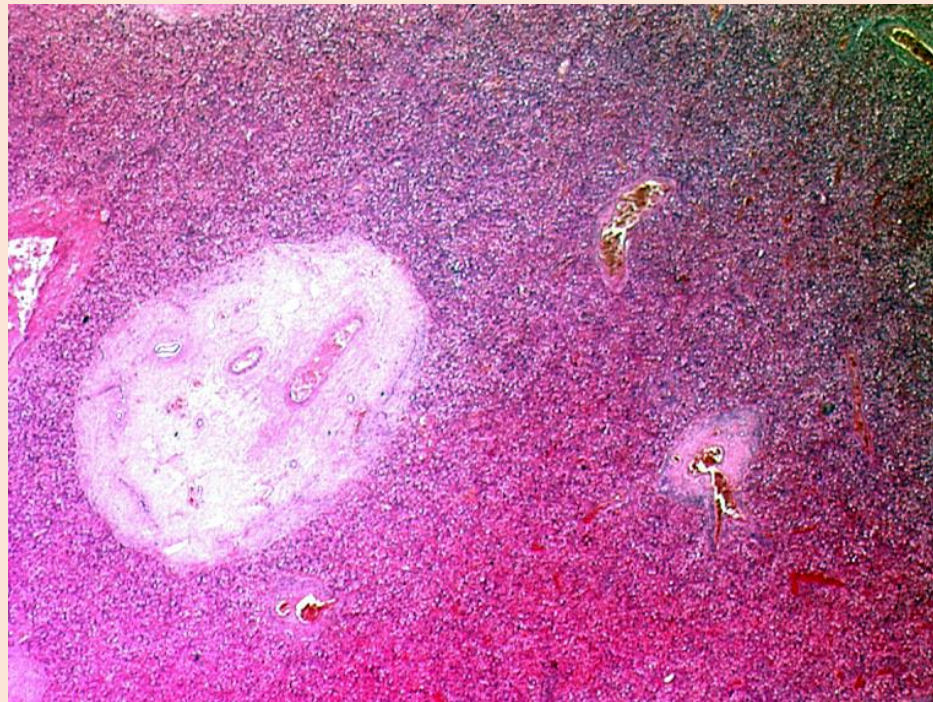


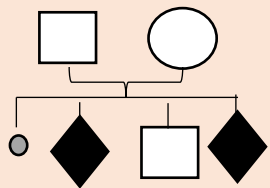
IMG 27SA pour gros reins hyperéchogènes, polydactylie



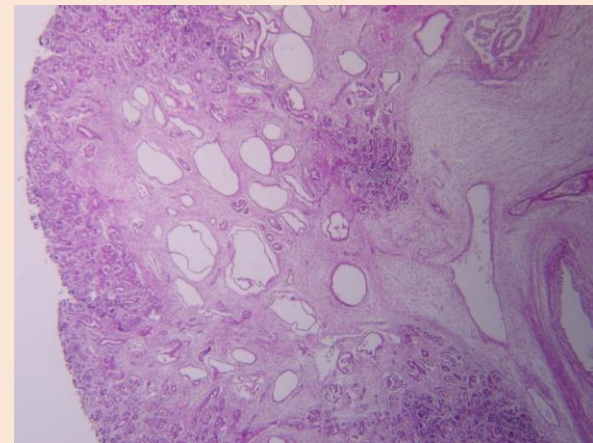
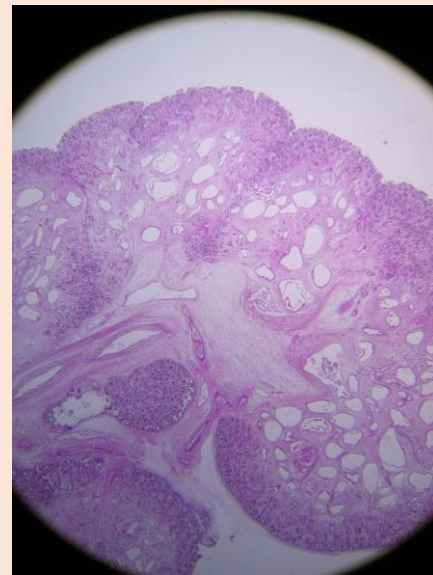
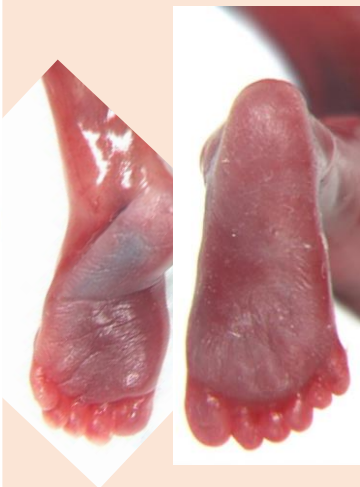


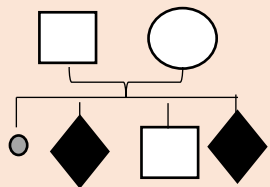
IMG 27SA pour gros reins hyperechogènes, polydactylie



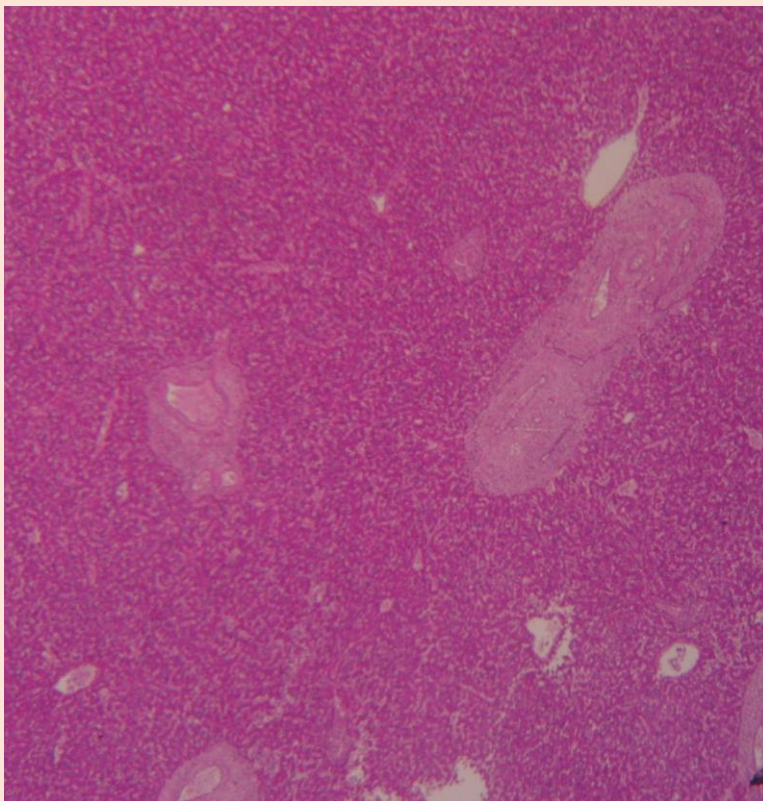


IMG 27SA pour gros reins hyperéchogènes, polydactylie
IMG 19SA pour **récidive**



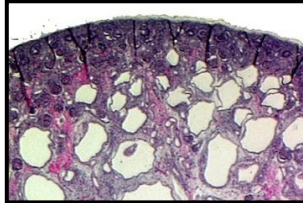


IMG 27SA pour gros reins hyperéchogènes, polydactylie
IMG 19SA pour **récidive**

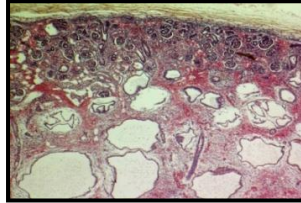


BBS et reins MKS-like

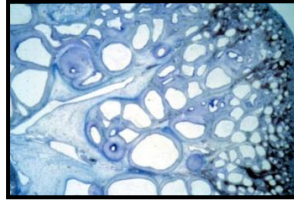
Cas 2, 22 SA



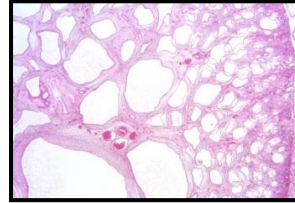
Cas 3, 26 SA



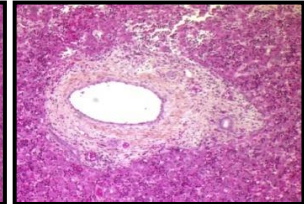
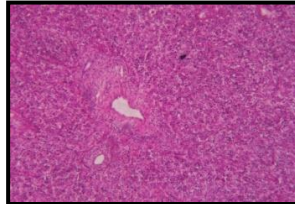
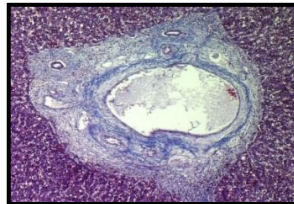
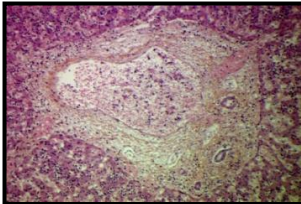
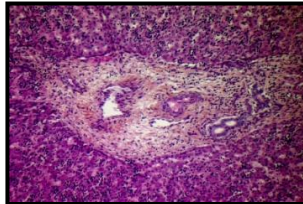
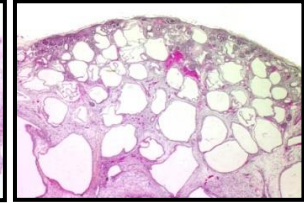
Cas 6, 24 SA



Cas 7, terme



Cas 9, 22 SA



Formes létales de syndrome de Bardet-Biedl

Situs inversus

Karmous-Benailly et al, AJHG, 2005
Putoux et al., JMG 2010

PK+ Polydactylie
Sans malformation cérébrale
Très prédictif de BBS (70%)

Reins: « Meckel like »

Foie: Pas / peu de prolifération
des canaux biliaires

Gènes responsables de syndrome de Bardet-Biedl

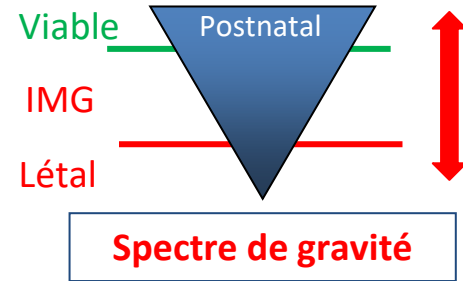
Locus	Location	%
<i>BBS1</i>	11q13	25
<i>BBS10</i>	12q21	20

Mykytyn et al, *Nat Genet* 2002

Stoetzel et al, *Nat Genet* 2006

BBS1 : *p.Met390Arg...* 0.27% population Européenne

BBS10 : *p.Cys91LeufsTer5...* 0.1 % population Européenne



Bardet-Biedl syndrome - PS209900 - 24 Entries

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
1p35.2	[Bardet-Biedl syndrome 1, modifier of]	AR, DR	3	209900	CCDC28B	610162
1q43-q44	Bardet-Biedl syndrome 16	AR	3	615993	SDCCAG8	613524
2p15	?Bardet-Biedl syndrome 15	AR	3	615992	WDPCP	613580
2q31.1	Bardet-Biedl syndrome 5	AR	3	615983	BBS5	603650
3p21.31	Bardet-Biedl syndrome 17	AR	3	615994	LZTFL1	606568
3q11.2	Bardet-Biedl syndrome 3	AR	3	600151	ARL6	608845
3q11.2	[Bardet-Biedl syndrome 1, modifier of]	AR, DR	3	209900	ARL6	608845
4q27	Bardet-Biedl syndrome 7	AR	3	615984	BBS7	607590
4q27	Bardet-Biedl syndrome 12	AR	3	615989	BBS12	610683
7p14.3	Bardet-Biedl syndrome 9	AR	3	615986	PTHB1	607968
8q22.1	[Bardet-Biedl syndrome 14, modifier of]	AR	3	615991	TMEM47	609884
8q22.1	Bardet-Biedl syndrome 21	AR	3	617406	C8orf37	614477
9p21.2	?Bardet-Biedl syndrome 20	AR	3	617119	IFT74	608040
9q33.1	?Bardet-Biedl syndrome 11	AR	3	615988	TRIM32	602290
10q25.2	?Bardet-Biedl syndrome 18	AR	3	615995	BBIPI1	613605
11q13.2	Bardet-Biedl syndrome 1	AR, DR	3	209900	BBS1	209901
12q21.2	Bardet-Biedl syndrome 10	AR	3	615987	BBS10	610148
12q21.32	?Bardet-Biedl syndrome 14	AR	3	615991	CEP290	610142
14q31.3	Bardet-Biedl syndrome 8	AR	3	615985	TTCS	606132
15q24.1	Bardet-Biedl syndrome 4	AR	3	615982	BBS4	600374
16q13	Bardet-Biedl syndrome 2	AR	3	615981	BBS2	606151
17q22	Bardet-Biedl syndrome 13	AR	3	615990	MKS1	609883
20p12.2	Bardet-Biedl syndrome 6	AR	3	605231	MKKS	604896
22q12.3	?Bardet-Biedl syndrome 19	AR	3	615996	IFT27	615870

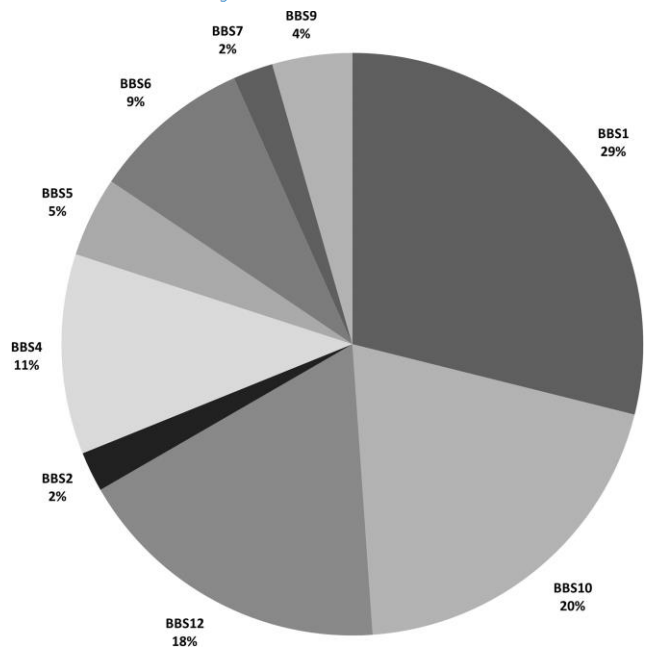
Pathologies Rares
 Autosomiques récessives
 Hétérogénéité génétique, 2 gènes majeurs
BBS en prénatal: phénotype incomplet mais possiblement létal

Bardet-Biedl syndrome: Antenatal presentation of forty-five fetuses with biallelic pathogenic variants in known Bardet-Biedl syndrome genes

Laura Mary^{1,2}, Kirsley Chennen^{2,3}, Corinne Stoetzel², Manuela Antin¹, Anne Leuvre¹, Elsa Nourisson¹, Elisabeth Alanio-Detton⁴, Maria C Antal^{5,6}, Tania Attié-Bitach^{7,8}, Patrice Bouvagnet⁹, Raymonde Bouvier¹⁰, Annie Buenerd¹⁰, Alix Clémenson¹¹, Louise Devisme¹², Bernard Gasser¹³, Brigitte Gilbert-Dussardier^{14,15}, Fabien Guimiot¹⁶, Philippe Khau Van Kien¹⁷, Brigitte Leroy¹⁸, Philippe Loget¹⁹, Jelena Martinovic²⁰, Fanny Pelluard^{21,22}, Marie-Josée Perez²³, Florence Petit²⁴, Lucile Pinson²⁵, Caroline Rooryck-Thambo²⁶, Olivier Poch³, Héléne Dollfus^{2,27,28}, Elise Schaefer^{2,27}, Jean Muller^{1,2}

Affiliations + expand

PMID: 30614526 DOI: 10.1111/cge.13500



52% Rein + PD
25% Reins hyperechogènes / kystiques isolées
6 oligoamnios (13%)

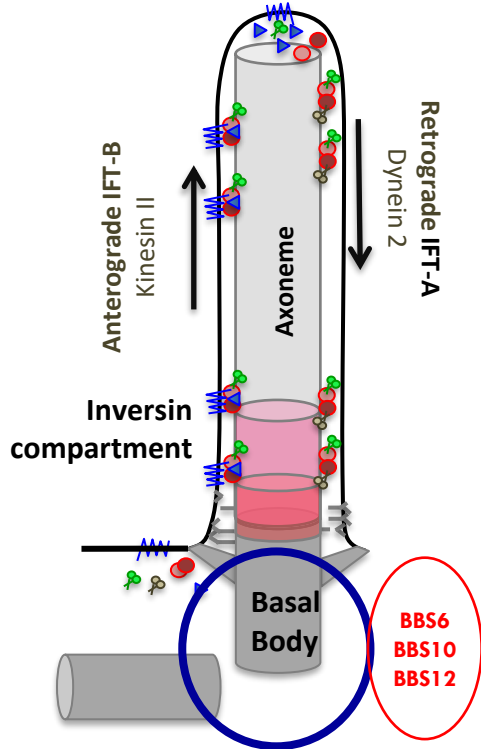
Table 2. Frequencies of the main clinical signs found in our cohort of samples with 2 pathogenic variations in BBS genes depending on the examination

Clinical signs	BBS fetuses (n = 45) (%)		Alive BBS patients (%)
	US (n = 36)	Autopsy (n = 35)	Prenatal US (n = 59)
Polydactyly	56	89	47
Renal anomalies.	94	94	64
Nephromegaly	72	69	17
Renal cysts	33	86	7
Hydrometrocolpos	6	6	0
Hepatic anomalies	3	31	2
Urogenital anomalies	6	17	5
CNS anomalies	8	6	3

Overgrowth : 4

Prolifération modérée de la plaque ductale ou retard de maturation : 5

Le BBSome



7 protéines BBS (BBS1, 2,4,5,7,8,9)
complexe impliqué dans le transport des protéines ciliaires

Nachury et al., Cell 2007

BBS6, BBS10 and BBS12
protéines chaperones
complexe impliquée dans l'assemblage du BBSome

Seo et al., PNAS, 2010

Non requis pour la ciliogenèse

Ciliopathies squelettiques

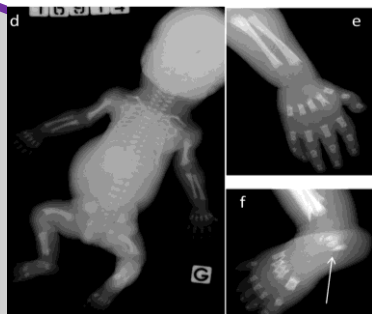
severe



SRPII

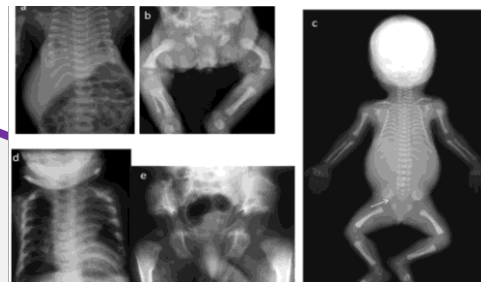
Thiel, AJHG, 2012

Sévérité variable



SRPIII

Cavalcanti, JMG, 2009



Jeune

Ciliopathies squelettiques non létales

Jeune (ATD)

Thorax étroit, RC, micromélie +/- RP, rein, foie

Mainzer-Saldino

Dystrophie rétinienne précoce, NPHP +/- RC thorax étroit

Sensenbrenner

Dysplasie cranioectodermique / craniosténose / dentaires

Ellis Van Creveld (EVC)

Cardiopathie (CAV 2/3), anomalie bucco-dentaires, PD

Chondrodysplasies létales Côtes courtes - polydactylie

I - Saldino-Noonan

▪ Côtes très courtes

III- Verma-Naumoff

▪ Micromélie

II- Majewski

▪ Os longs courts

IV- Beemer-Langer

▪ Aspect de trident au niveau du bassin

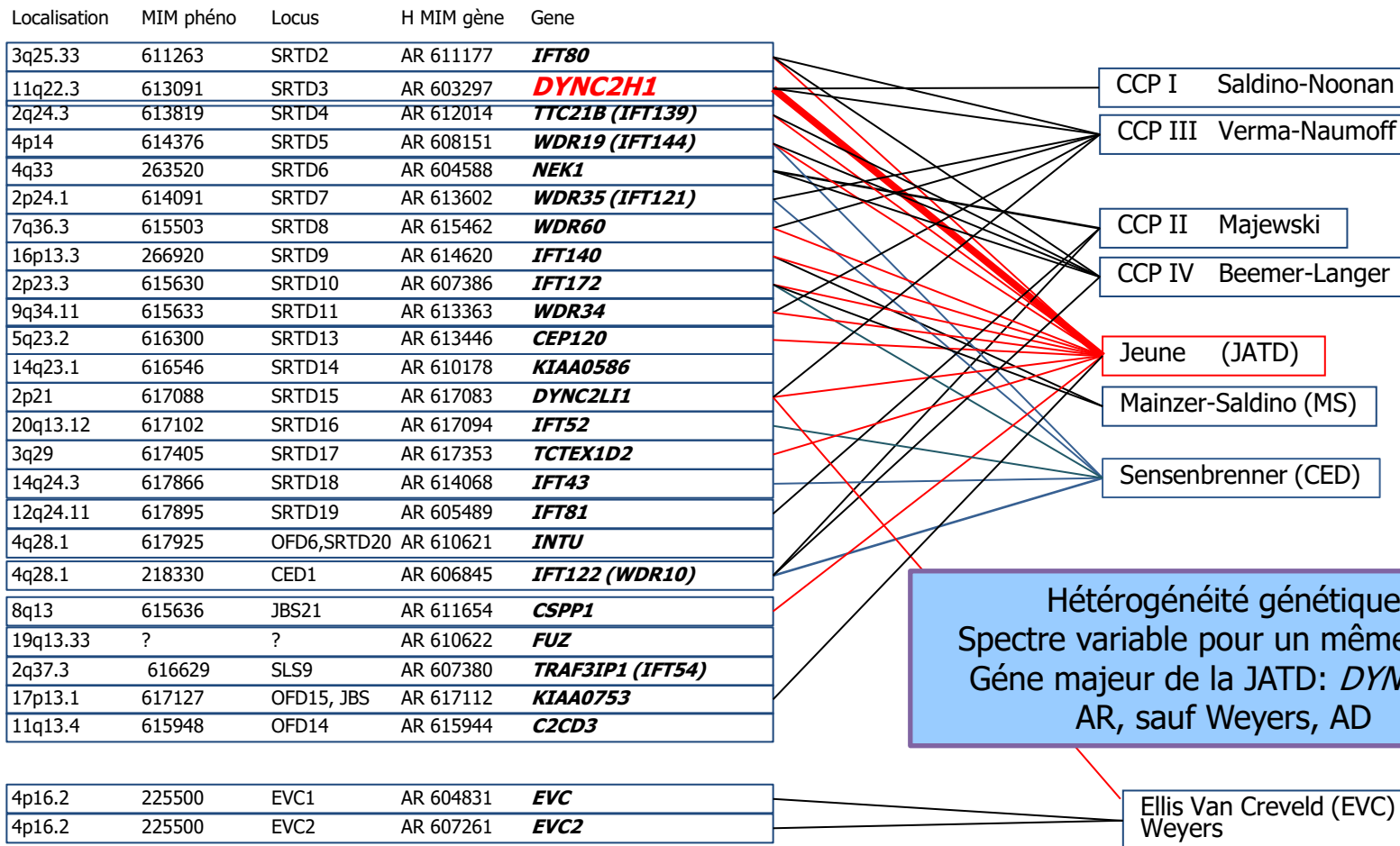
▪ +/- polydactylie

▪ +/- malformations viscérales (cardiaques, agénésie/hypoplasie rénale urogénitales, digestives, anale)

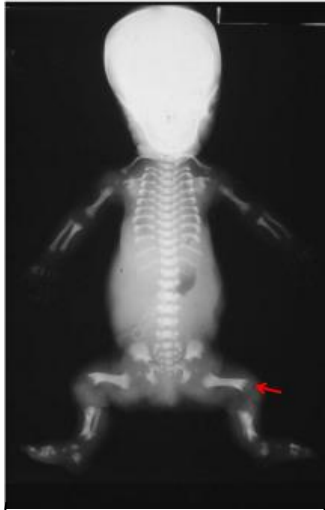
▪ +/-malformations cérébrales

Short-rib thoracic dysplasia (SRTD) – OMIM 2019- 22 entrées

Mars 2020



Côtes courtes - polydactylies

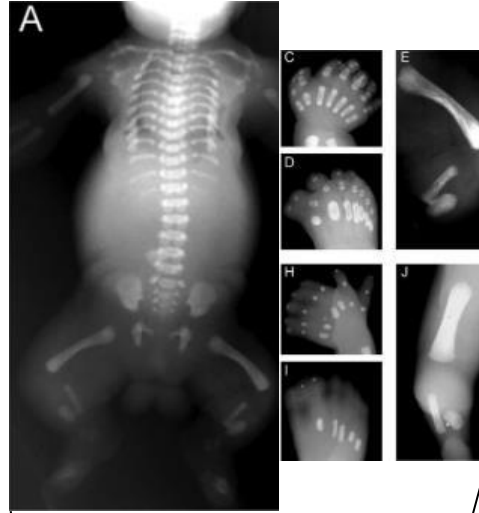


CCP – III

Verma-Naumoff

Proche du Jeune radiologiquement mais + sévère :

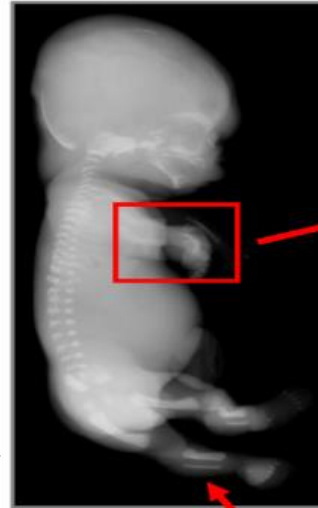
- **Spicules métaphysaires**
- Polydactylie
- Hypoplasie cérébelleuse



CCP – II

Majewski

- **Agénésie tibiale**
- **Anomalies orofaciales** (fentes labiales, anomalies de la langue, une rétrognathie)
- Polydactylie pré et **postaxiale**
- **Malformations cérébrales** (holoprosencéphalie, agénésie du corps calleux, polymicrogyrie)



CCP – IV

Beemer - Langer

- Proche du type II mais présence d'un tibia, et polydactylie inconstante
- **Métaphyses rondes**
 - **Tibia trapu plus long que le péroné**
 - **Incurvation os avant-bras**
 - Platyspondylie modérée
 - Atteinte cérébrale fréquente

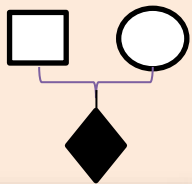


CCP – I

Saldino-Noonan

- Le plus sévère
- Micromélie extrême
 - **Anasarque**
 - **Métaphyses en flammèches**
 - Défauts osseux (crâne, vertèbres pelvis, omoplates)
 - Polydactylie
 - Malformations viscérales

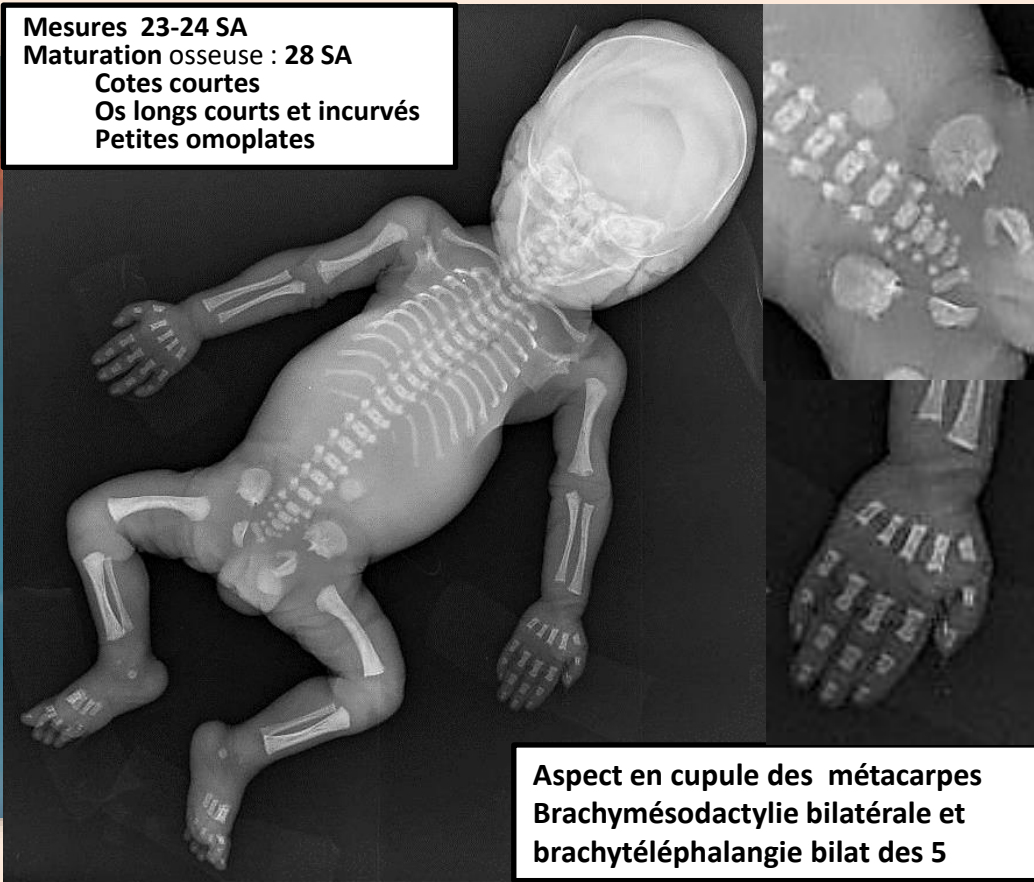
- **Côtes très courtes, Micromélie, Os longs courts, Aspect de trident au niveau du bassin**
- +/- malformations viscérales (cardiaques, agénésie/hypoplasie rénale, atteinte rénale et hépatiques urogénitales, digestives, anale)



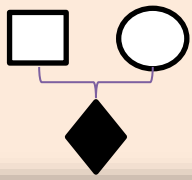
IMG 27SA pour os long courts et incurvés, côtes
courtes, hypoplasie pulmonaire
FGFR3 : Pas de mutation CGH normale



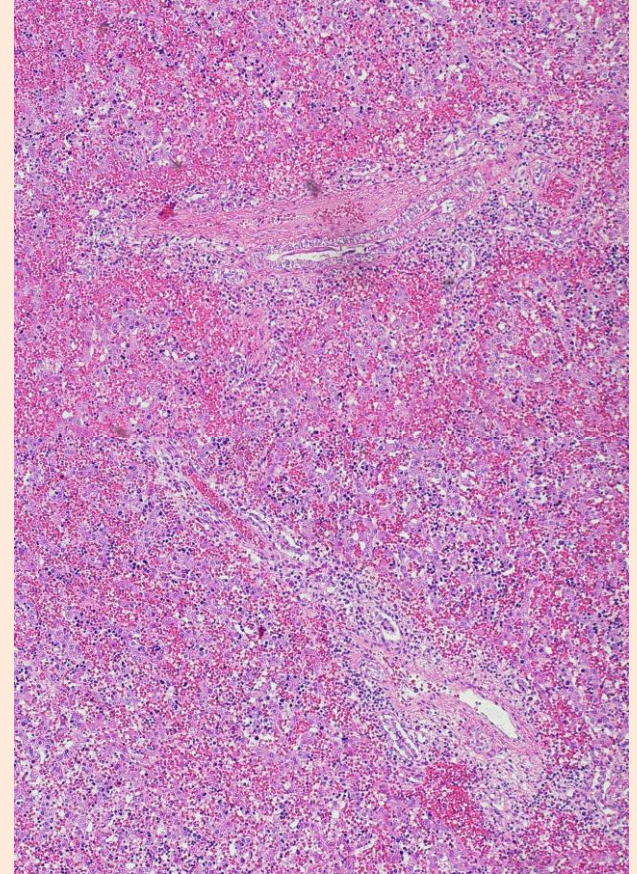
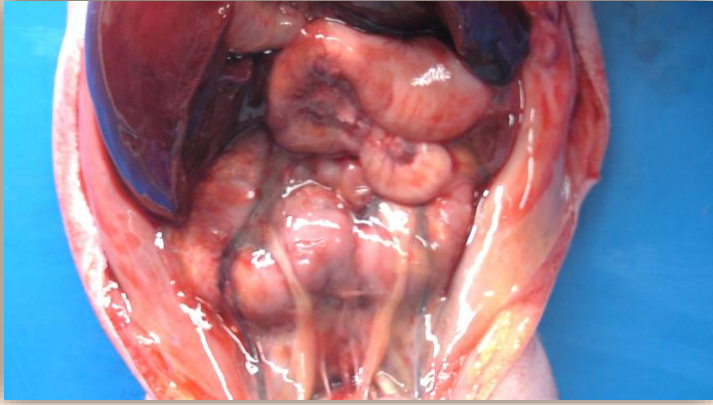
Mesures 23-24 SA
Maturation osseuse : 28 SA
Cotes courtes
Os longs courts et incurvés
Petites omoplates



Aspect en cupule des métacarpes
Brachymésodactylie bilatérale et
brachytéléphalangie bilat des 5

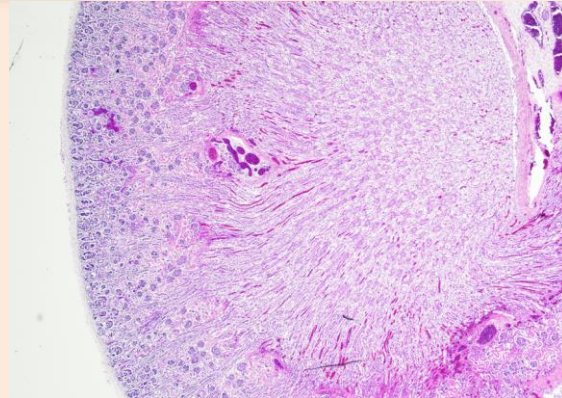


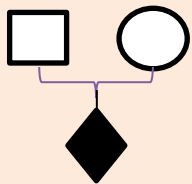
IMG 27SA pour os long courts et incurvés, côtes
courtes, hypoplasie pulmonaire
FGFR3 : Pas de mutation CGH normale



Rein enfer à cheval
Histologie normale
Foie: Prolifération canaliculaire

-> DTJ
DYNC2H1

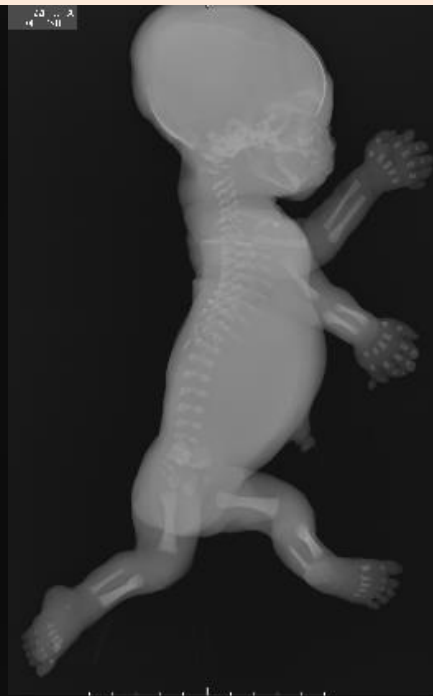
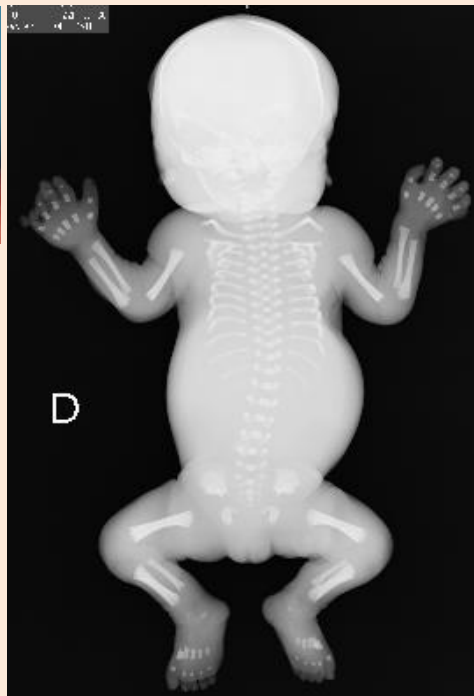




IMG 25,1SA pour micromélie, thorax étroit, hexadactylie

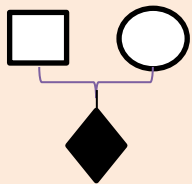


pas de fente palatine,
gencives normales

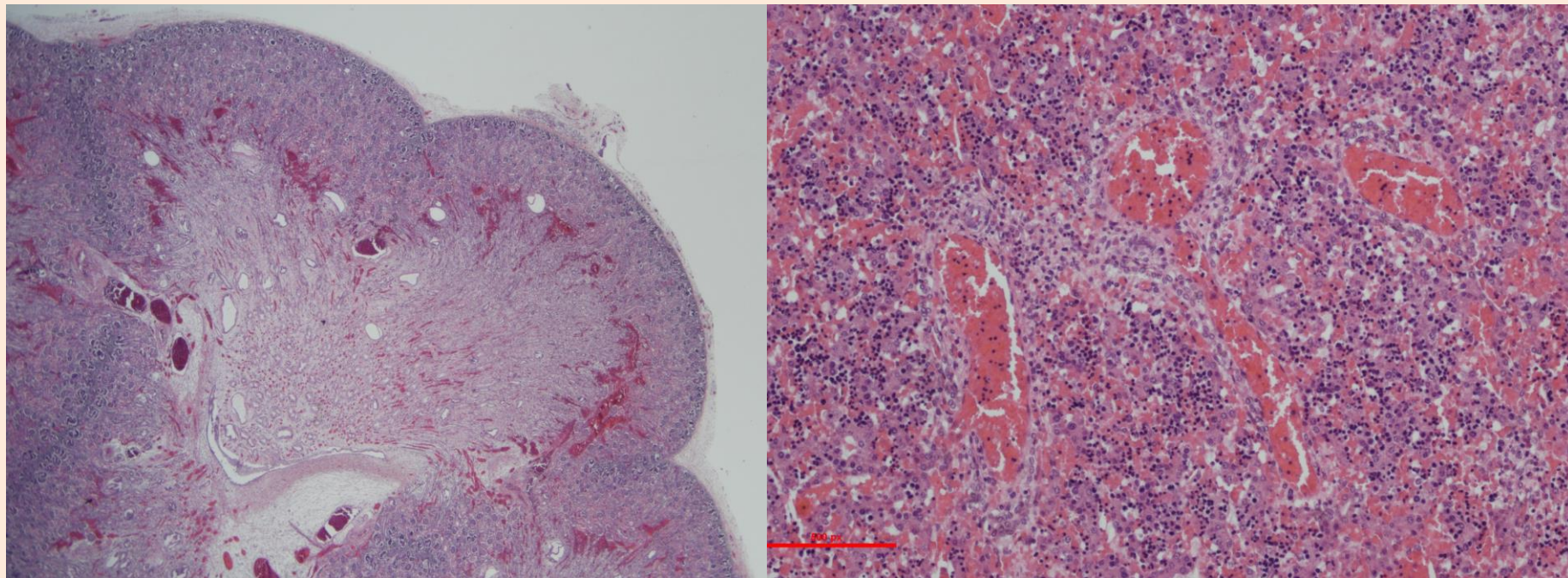


Tibia: métaphyse
cornet de glace

	mesure	percentile	Médiane terme
Poids	695 g	30 p	24,5
VC	20,5 cm	10 p	23
VT	30 cm	5 p	23
Pied	37 mm	< 5 p	22 sa
PC	22 cm	30 p	24



IMG 25,1SA pour micromélie, thorax étroit, hexadactylie



Microkystes rénaux, collecteurs

22NF00136, E Spaggiari

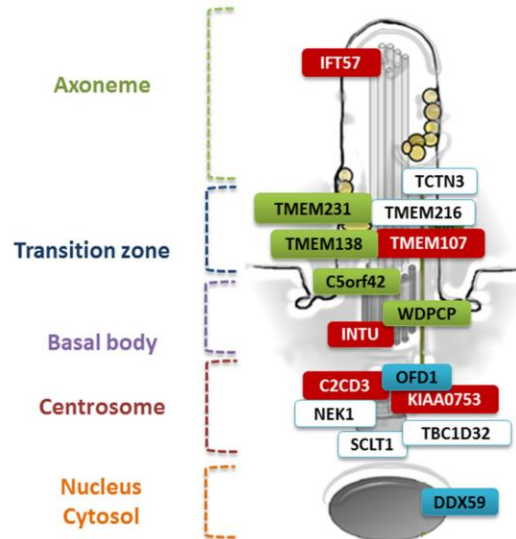
Table 1 Classified OFDS

OFD subtypes	MIM#	Altern SYMB	Aliases	Gene	REF*/Notes
OFDI	311200	OFDSI; OFD1	Orofaciodigital type I; Oral-facial-digital type I; Papillon-Leage/Psaume syndrome	<i>OFD1</i>	[7, 13]
OFDII	252100	OFDSII; OFD2	Orofaciodigital type II; Oral-facial-digital type II; Mohr syndrome	–	[3]
OFDIII	258850	OFDSIII; OFD3	Orofaciodigital type III; Oral-facial-digital type III: Sugarman syndrome	<i>TMEM231</i>	[29]
OFD IV	258860	OFDSIV; OFD4	Orofaciodigital type IV; Oral-facial-digital type IV; Mohr-Majewski Baraitser syndrome	<i>TCTN3</i>	[32]
OFDV	174300	OFDSV; OFD5	Orofaciodigital type V; Oral-facial-digital type V Thurston syndrome	–	[3] /Indian origin
OFDVI	277170	OFDSVI; OFD6	Orofaciodigital type VI; Oral-facial-digital type VI Varadi syndrome	<i>TMEM216 OFD1, C5ORF42 TMEM107</i>	[24, 34–37]
OFDVII	608518	OFDSVII; OFD7	Orofaciodigital type VII; Oral-facial-digital type VII	–	[3]
OFDVIII	300484	OFDSVIII; OFD8	Orofaciodigital type VIII; Oral-facial-digital type VIII; Edwards syndrome	–	[3]
OFDIX	258865	OFDSIX; OFD9	Orofaciodigital type IX; Oral-facial-digital type IX	<i>TBC1D32 SCLT1</i>	[41]
OFDX		OFDSX; OFD10	Orofaciodigital type X; Oral-facial-digital type X; Figuera syndrome	–	[3]
OFDXI		OFDXI; OFD11	Orofaciodigital type XI; Oral-facial-digital type XI; Gabrielli syndrome	–	[3]
OFDXII		OFDXII; OFD12	Orofaciodigital type XII; Oral-facial-digital type XII; Moran Barroso Syndrome	–	[3]
OFDXIII		OFD XIII; OFD13	Orofaciodigital type XIII; Oral-facial-digital type XIII; Degner syndrome	–	[3]
OFDXIV	615948	OFDXIV; OFD14	Orofaciodigital type XIV; Oral-facial-digital type XIV;	<i>C2CD3</i>	[43]
Unclassified OFD				<i>WDPCP</i>	[44]
Unclassified OFD				<i>DDX59</i>	[47]

* References for disease gene identification and/or review discussing the main features of the disease

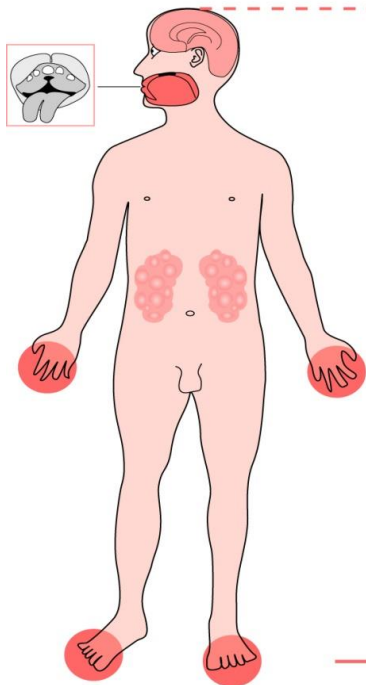
Table 3 Novel classification of oral–facial–digital (OFD) syndrome based on associated clinical feature and molecular basis. MTS, molar tooth sign.

OFD subtype	Clinical data	Genes
OFDI	Polycystic kidney disease, corpus callosum agenesis	<i>OFD1</i>
OFDIV	Tibial dysplasia	<i>TCTN3</i>
OFDVI	Molar tooth sign	<i>TMEM216, TMEM231, TMEM138, C5orf42, TMEM107, KIAA0753</i>
Classification based on the genotype for other patients	Median cleft of the upper lip Cardiac defects Retinopathy Severe microcephaly Chondrodysplasia	<i>DDX59, NEK1, INTU, WDPCP, SCLT1, TBC1D32/C7orf170, C2CD3, IFT57</i>



Syndrome orofaciodigitaux

OFDS : de 13 sous-types...à 3 reconnaissables



Type	Signes cliniques caractéristiques	Hérédité	Gènes
OFD I Papillon-Psaume-Léage	Atteinte SNC Reins kystiques (postnatal)	DLX	<i>OFDI</i>
OFD IV Mohr-Majewski	Dysplasie squelettique Dysplasie tibiale	AR	<i>TCTN3</i>
OFD VI Varadi-Papp	Polydactylie centrale (métacarpe en Y) Hamartome hypothalamique Anomalies du vermis	AR	<i>CPLANE1</i> <i>TMEM216</i> <i>TMEM231</i> <i>TMEM138</i> <i>TMEM107</i> <i>KIAA0753</i>

Syndrome orofaciadigital IV (Mohr-Majewski)



OF Anomalies
Polydactyly x4

OFD
« Mohr »

« Majewski »
Skeletal dysplasia

Short ribs

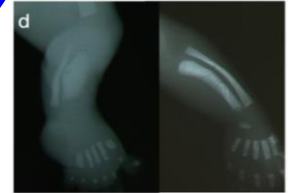
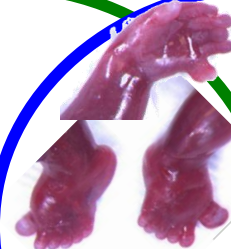
Tibia Anomalies
Pelvic Anomalies

OFD IV

Meckel

Occipital Encephalocele
Vermian hypoplasia, CCA
Cystic kidneys
Bile duct proliferation

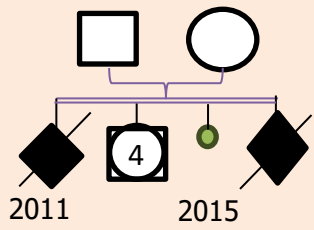
TCTN3



Indian J Pediatr (August 2011) 78(8):1023-1024



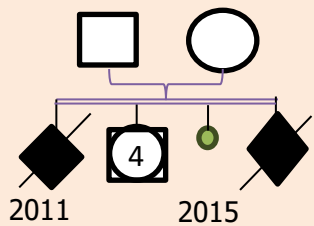
Fig. 4 X-ray of the lower limbs showing markedly shortened tibial bones



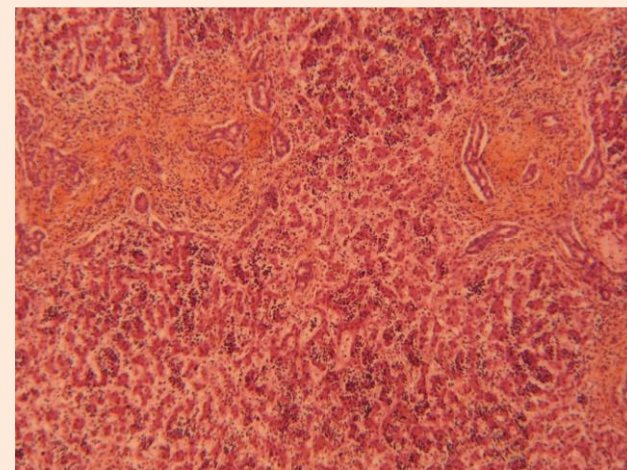
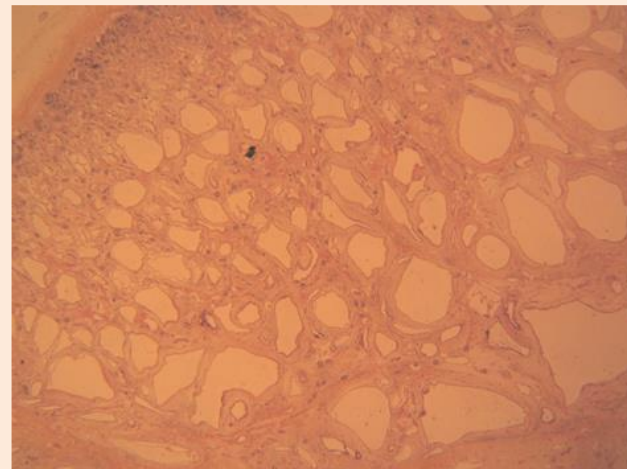
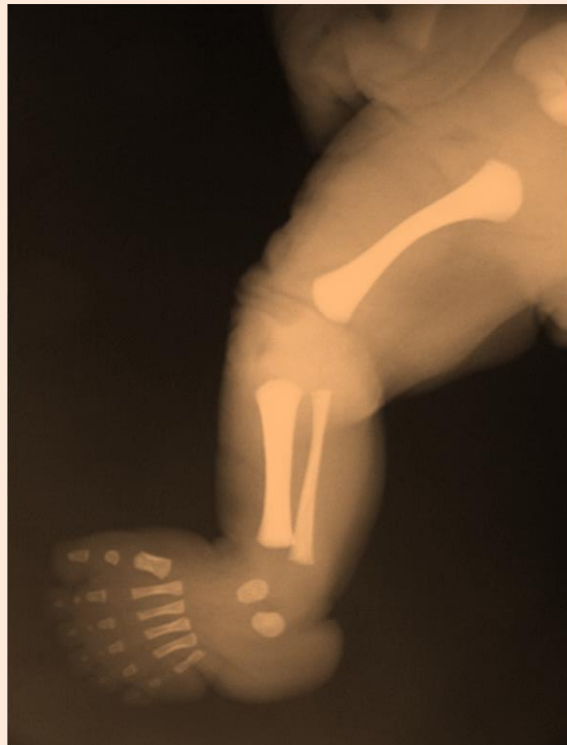
Patiente G7P4, couple apparenté.
 Patiente 7^e geste, 4^e pare. Couple apparenté.
**IMG en 2011 31SA pour syndrome de
 Meckel atypique**

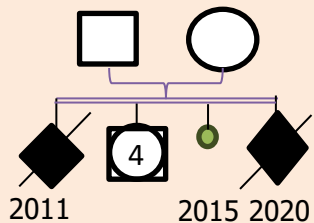


EFP1100385, Bessières



Patiente G7P4, couple apparenté.
 Patiente 7^e geste, 4^e pare. Couple apparenté.
IMG en 2011 31SA pour syndrome de Meckel atypique



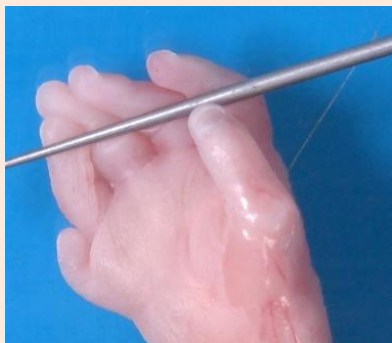


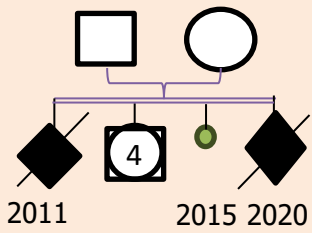
Patiente G7P4, couple apparenté.

Patiente 7^e geste, 4^e pare. Couple apparenté.

IMG en 2011 31SA pour syndrome de Meckel atypique

IMG en 2020 à 22SA méningoencéphalocèle, reins dysplasiques, anamnios, membres courts et incurvés



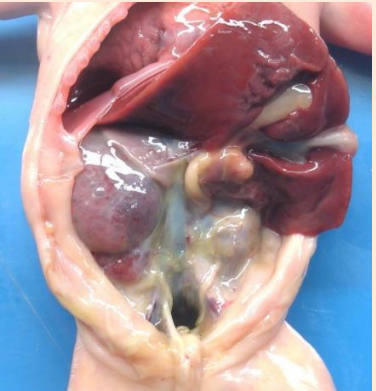
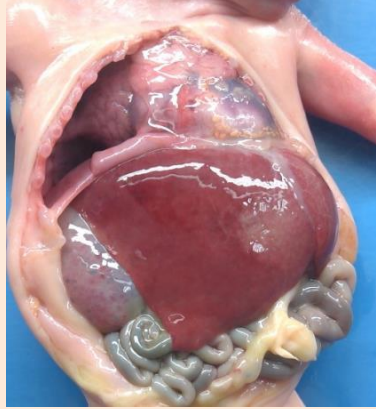


Patiente G7P4, couple apparenté.

Patiente 7^e geste, 4^e pare. Couple apparenté.

IMG en 2011 31SA pour syndrome de Meckel atypique

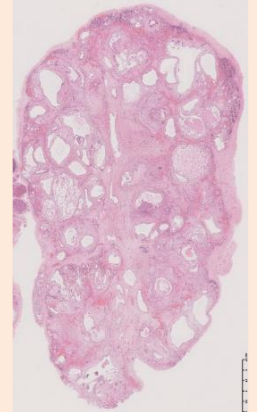
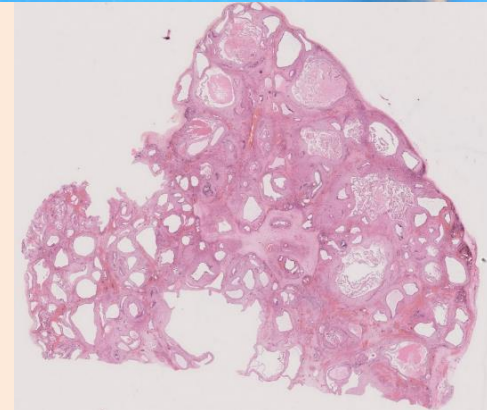
IMG en 2020 à 22SA méningoencéphalocèle, reins dysplasiques, anamnios, membres courts et incurvés



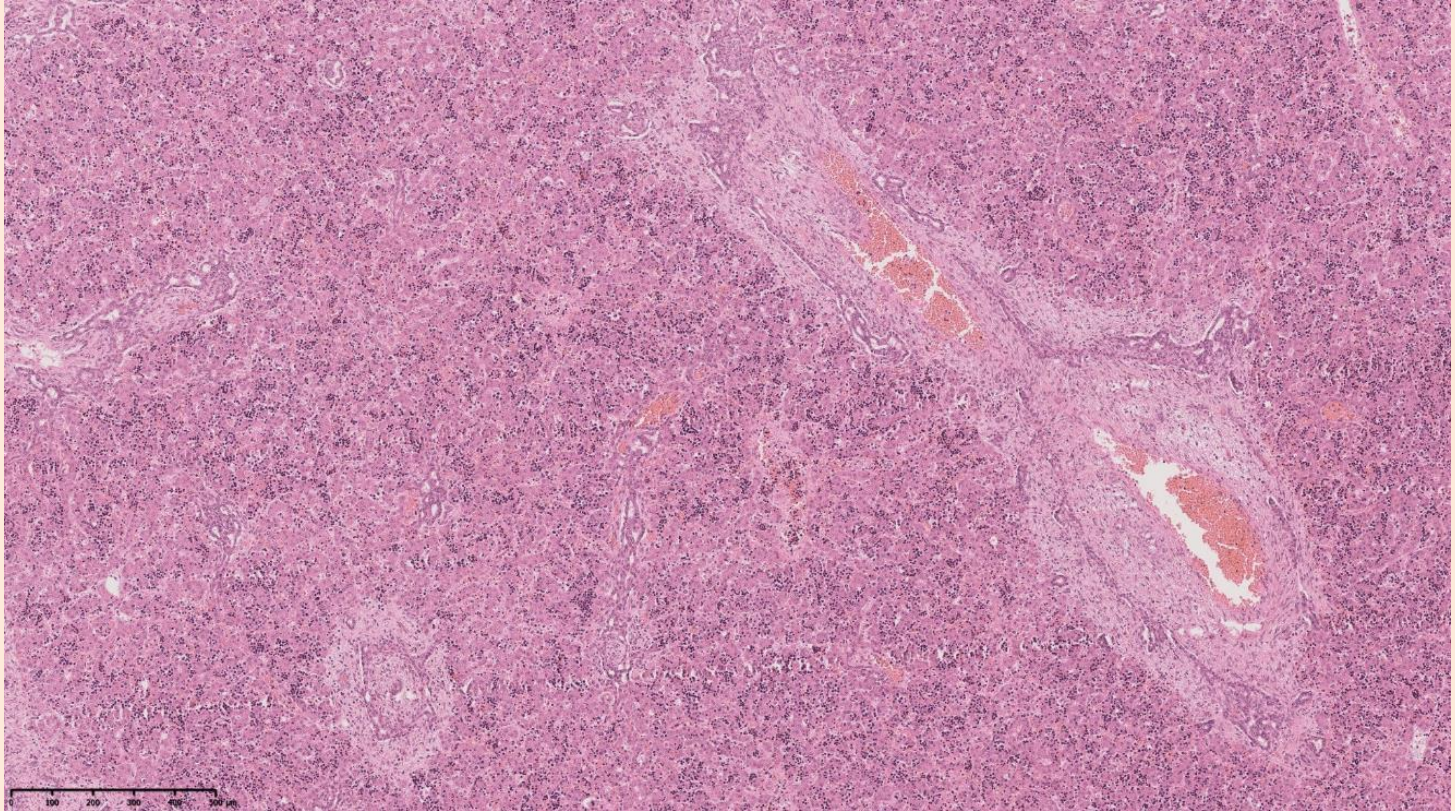
Rein D: 10,3 g > 95^e p (+20DS)

Rein G: 2,12 g < 95^e p

Foie de poids normal
(22g / 24 SA)



20NF00279 L Loeuillet



The Primary Cilium

Ciliary sensory functions

Chemosensation
Mechanosensation
Osmosensation
Light perception

Signaling pathways

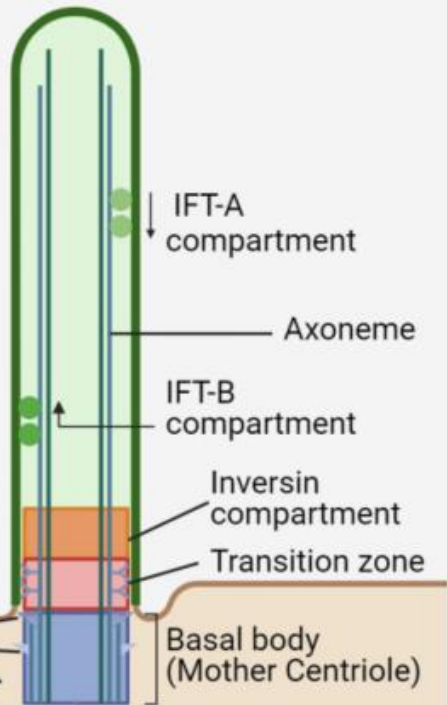
Hedgehog, Wnt, Hippo,
PCP, Notch, GPCR,
PDGF, TGF β , BMP,
mTOR

Distal and subdistal
appendages

BBSome



CPLANE

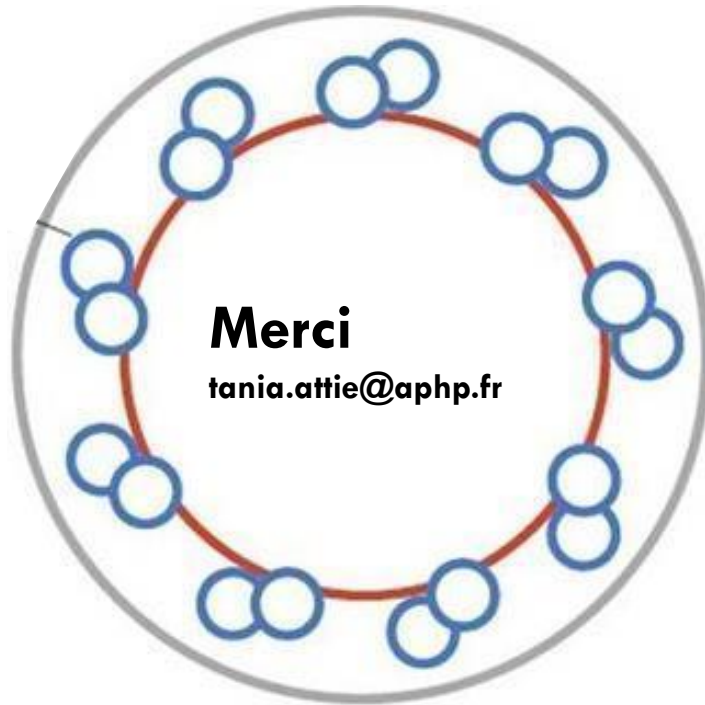


Renal Ciliopathy Proteins

Ciliary Compartment	Genes	Phenotype(s)
Ciliary Axoneme	<i>GLIS2</i> <i>DCDC2</i>	NPHP NPHP
IFT compartments	<i>IFT43</i> <i>IFT122</i> <i>IFT140</i> <i>IFT172</i> <i>TRAF3IP1</i> <i>TTC21B</i> <i>WDR19</i> <i>WDR35</i>	SRTD CED RP, SRTD NPHP, BBS, RP SLS SRTD NPHP, SLS, SRTD CED, SRTD
Inversin compartment	<i>INVS</i> <i>NPHP3</i> <i>ANK3</i> <i>ANKS6</i>	NPHP NPHP, MKS, RHPD NPHP, RHPD NPHP
Transition Zone NPHP module	<i>NPHP1</i> <i>NPHP4</i> <i>RPGRIP1L</i>	NPHP, JS, SLS NPHP, SLS JS, MKS
Transition Zone CEP290 module	<i>IQCB1</i> <i>CEP290</i>	SLS JS, SLS, MKS, LCA
Transition Zone MKS module	<i>MKS1</i> <i>BBD1-2</i> <i>TCTN1-3</i> <i>CC2D2A</i> <i>TMEM67</i> <i>TMEM107</i> <i>TMEM138</i> <i>TMEM216</i> <i>TMEM231</i> <i>TMEM237</i>	BBS, JS, MKS JS, MKS JS, OFD, MKS JS, MKS, RP NPHP, JS, MKS MKS, OFD JS JS, MKS JS, MKS JS
Centrosome	<i>C2CD3</i> <i>CEP83</i> <i>CEP104</i> <i>CEP120</i> <i>CEP164</i> <i>SDCCAG8</i>	OFD NPHP JS JS, SRTD NPHP BBS, SLS
CPLANE Complex	<i>CPLANE1</i> <i>INTU</i> <i>WDPCP</i> <i>FUZZY</i>	OFD, JS OFD, SRPS BBS SRPS
BBSome	<i>BBS1</i> <i>BBS2</i> <i>ARL6</i> <i>BBS4</i> <i>BBS5</i> <i>MKKS</i> <i>BBS7</i> <i>TTC8</i> <i>PTHB1</i> <i>BBS10</i> <i>TRIM32</i> <i>BBS12</i> <i>LZTFL1</i>	BBS BBS, RP BBS, RP BBS BBS BBS BBS BBS BBS BBS BBS BBS

Ciliopathies rénales anténatales

DIAGNOSTIC	Reins	Polydactylie	Cerveau	Orales	Os
Bardet -Biedl	+++	++			
Joubert / Meckel	+ / +++	++	Vermis / Encéphalocèle	+/-	+/-
Orofaciodigital IV	+++	+/-	Variable ++	+++	+
Cotes courtes - PD	+/-	++	+	+	++ +
Hydrolethalus		+ préaxiale MI	Hydrocéphalie Anencéphalie	+	



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Juliette Nectoux
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LA PLATEFORME GÉNOMIQUE
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Merci pour votre attention

