COLLÈGE NATIONAL
HOSPITALIER ET UNIVERSITAIRE
DE CHIRURGIE PÉDIATRIQUE

Tumeurs et malformations

Sabine Sarnacki, MD, Ph.D

Université de Paris Cité & Hôpital Necker Enfants-Malades
Imagine Institute

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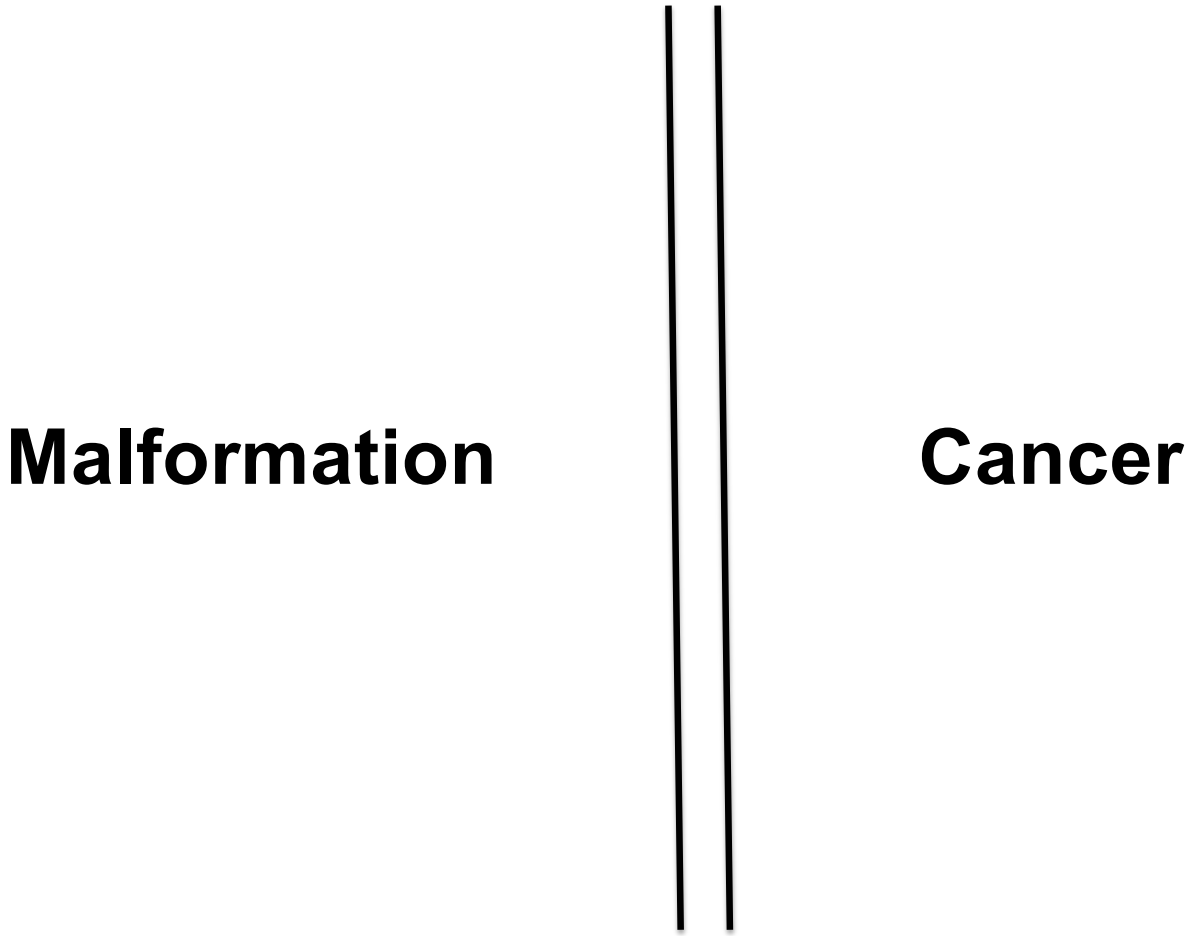
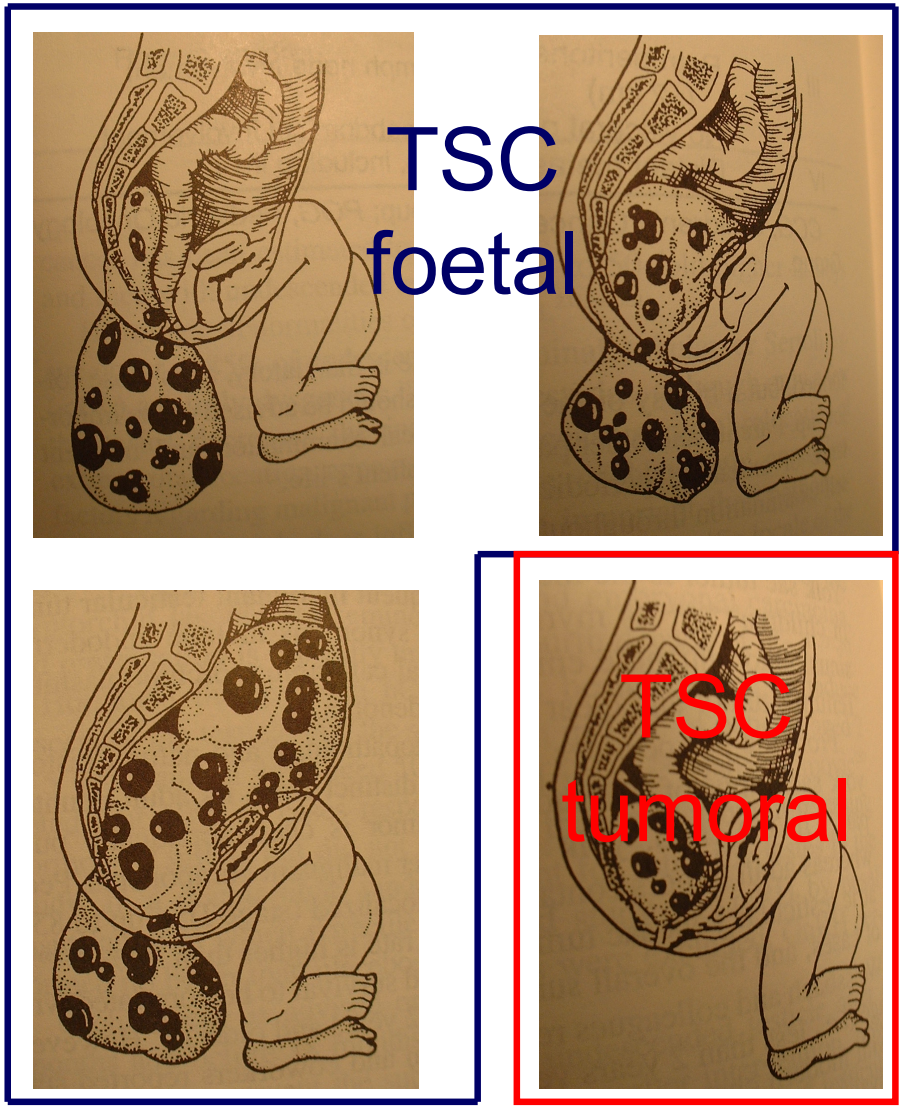
imagine
INSTITUT DES MALADIES GÉNÉTIQUES

Université Paris Cité

Necker
ENFANTS MALADES


Malformation
Cancer



Type I
(47%)

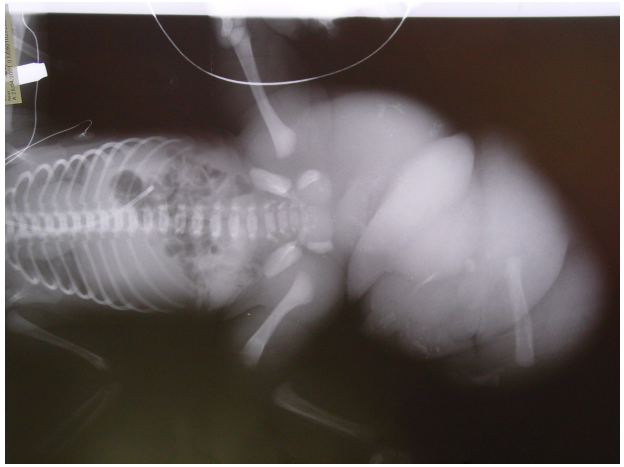
Type II
(34%)

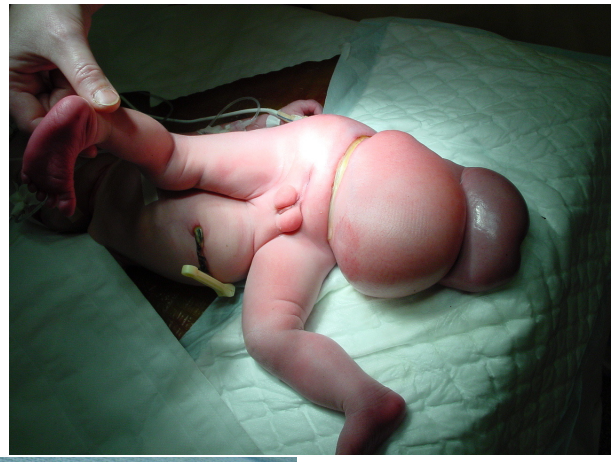
Type III
(9%)

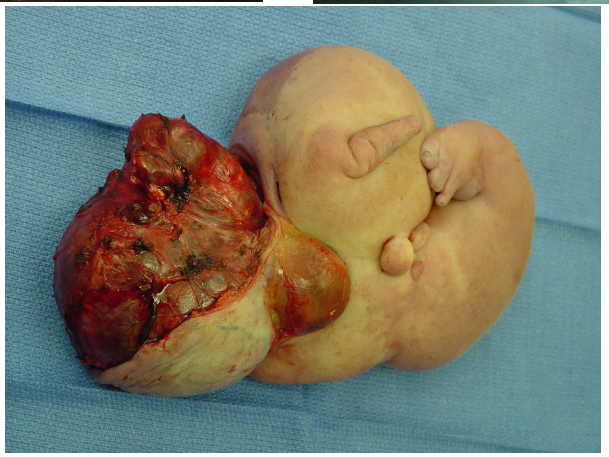
Type IV
(10%)

TSC: La malformation

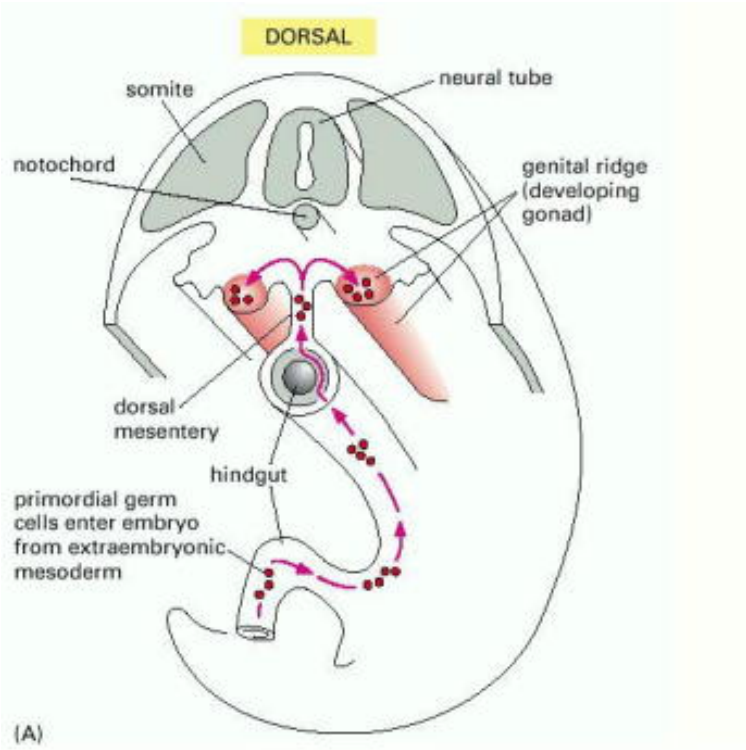
Tératome mature foetal

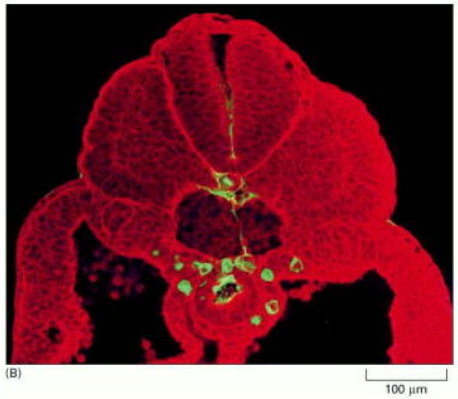


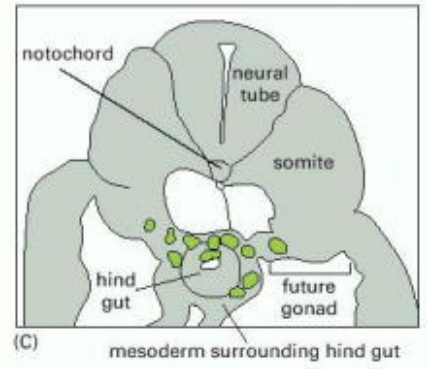




Migration of primordial germ cells

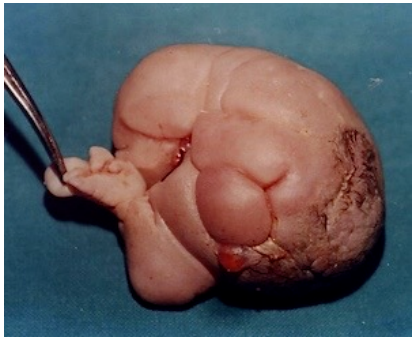




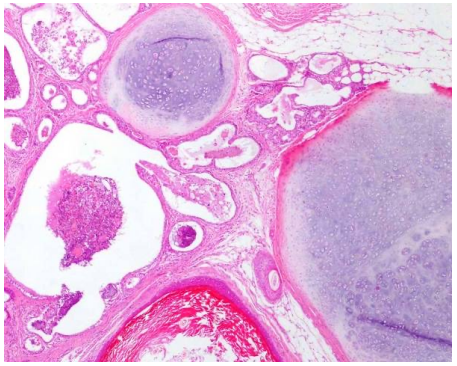


from Molecular Biology of the Cell, 4th edition

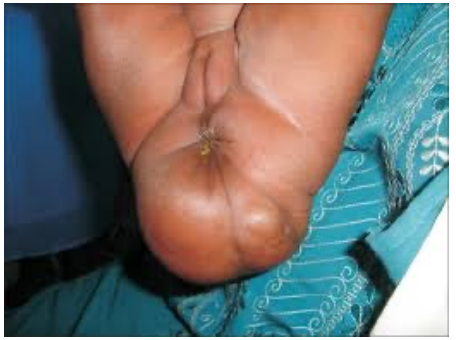
Tératome mature



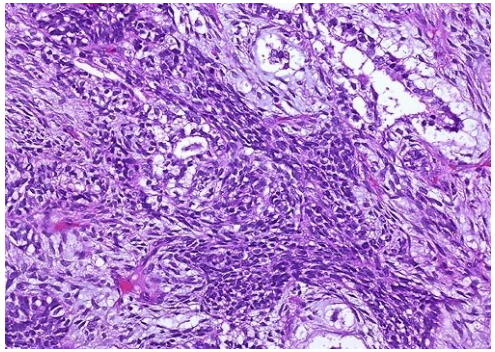
Malformation



Tératome immature



Cancer

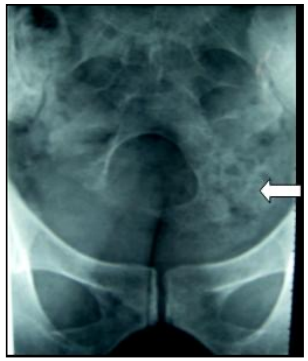


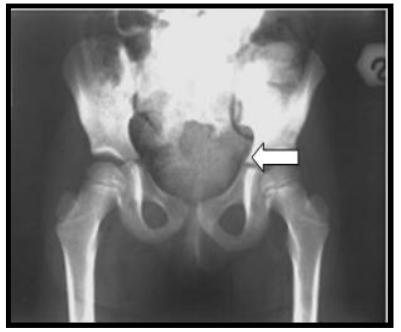
Âge ?

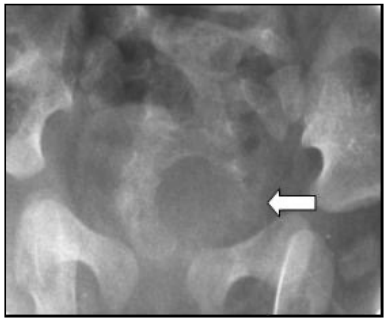
Une forme syndromique de TSC: le syndrome de Currarino, 1981

3 signes cliniques majeurs

1. Agénésie partielle du sacrum en cimeterre
2. Malformation de l' intestin terminal
3. Tumeur pré-sacrée
4. Anomalies médullaires
5. Duplication Müllerienne







1 / 100 000 naissances

Pediatric Blood & Cancer

LETTER TO THE EDITOR

Malignant transformation of presacral mass in Currarino syndrome

Julien Rod ✉, Celia Cretolle, Laurence Faivre, Caroline Jacquot, Ossama Yacoub, Philippe Ravasse, Nicolas Cheynel, Sabine Sarnacki

First published: 10 February 2019 | https://doi.org/10.1002/pbc.27659

13 cas de dégénérescences malignes sur plus de 300 cas rapportés: 8 adultes et 5 enfants

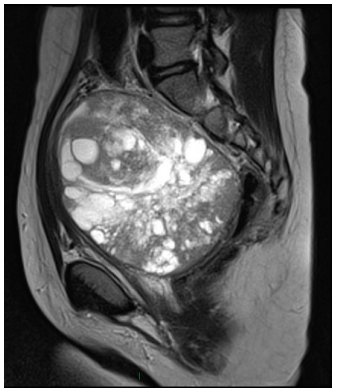
- 6 TGM
- 1 tumeur neuroectodermique
- 3 tumeur neuroendocrine
- 1 léiomyosarcome
- 1 nephroblastome présacré
- 1 PNET

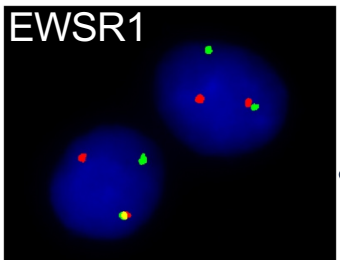
Relation étroite entre

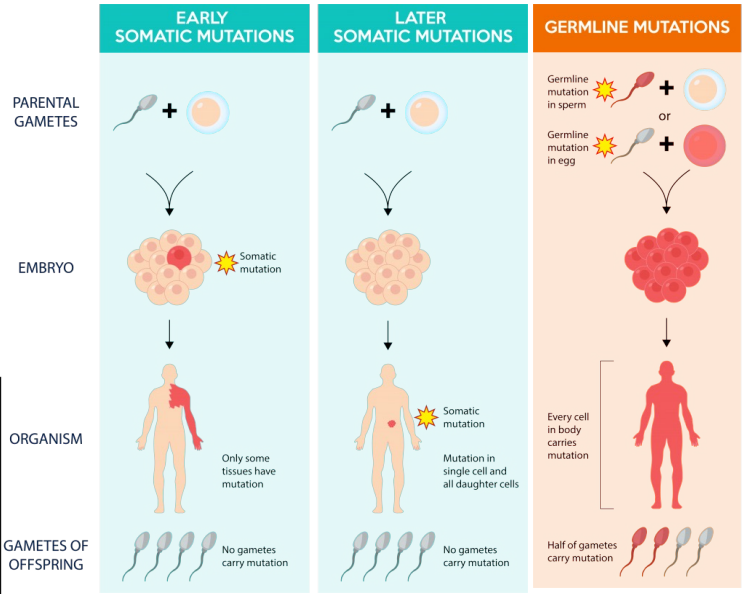
une anomalie du développement normal

et la prolifération tumorale de cellules embryonnaires

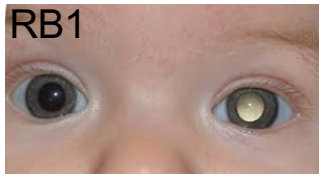
Pediatric cancer and genetics

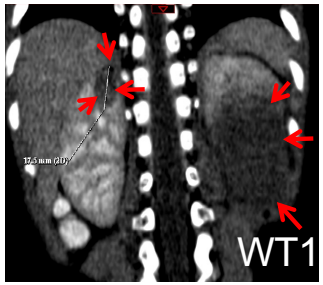


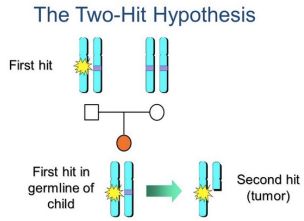




Somatic



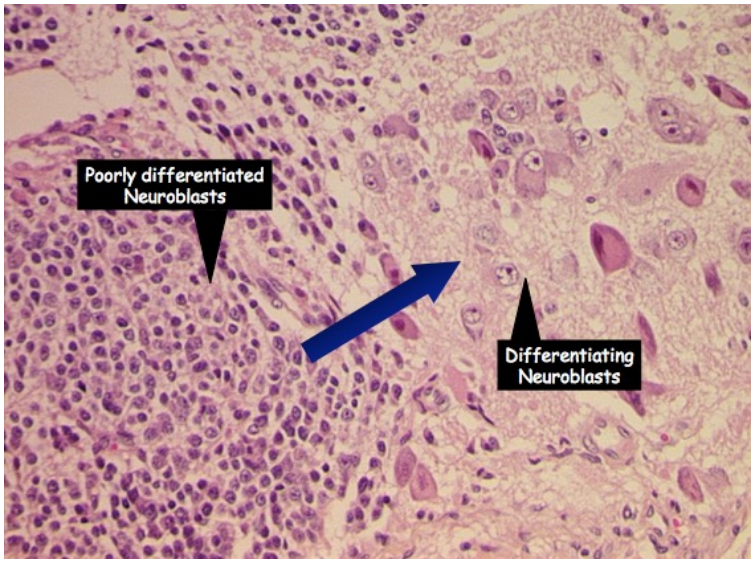


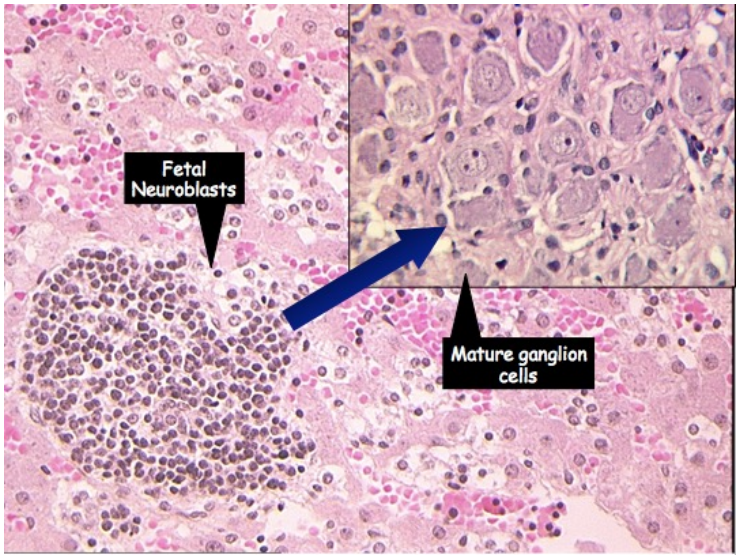


Constitutional

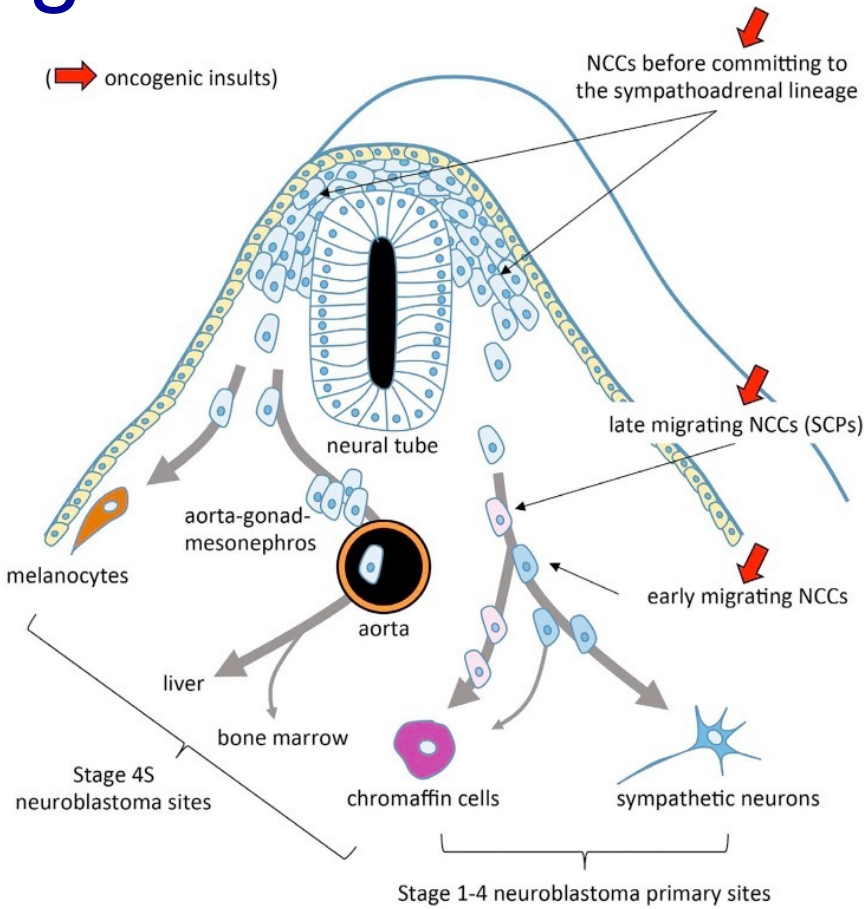
Rational #1

Pediatric cancers often arise from immature cell type (blastoma)





Origins of neuroblastoma

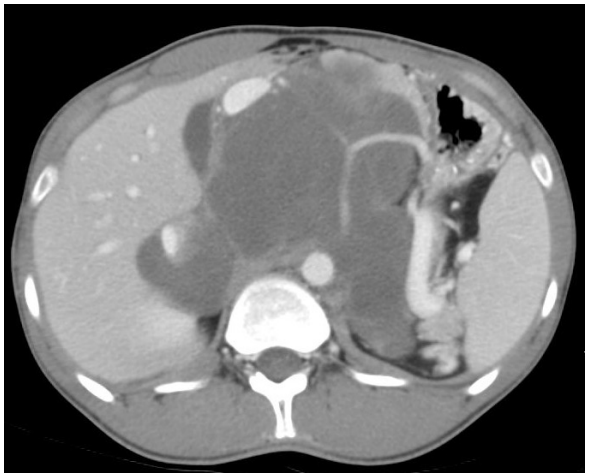


S.Tsubota & K.Kadomatsu, Oncosciences 2017

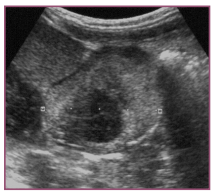
Le neuroblastome

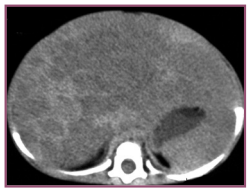
1. **Le neuroblastome congénital**: possibilité d'involution spontanée ou de différentiation

2. Les neuroblastomes syndromiques



The wait and see strategy





Fœtal NBL	Ms Neuroblastoma
- Prenatal - Neonatal < 3 months - L1, Size < 5 cm - No LTS	- < 6 months - Liver, BM, SC mets - No bone mets - No LTS

72- 81% are cured without any treatment

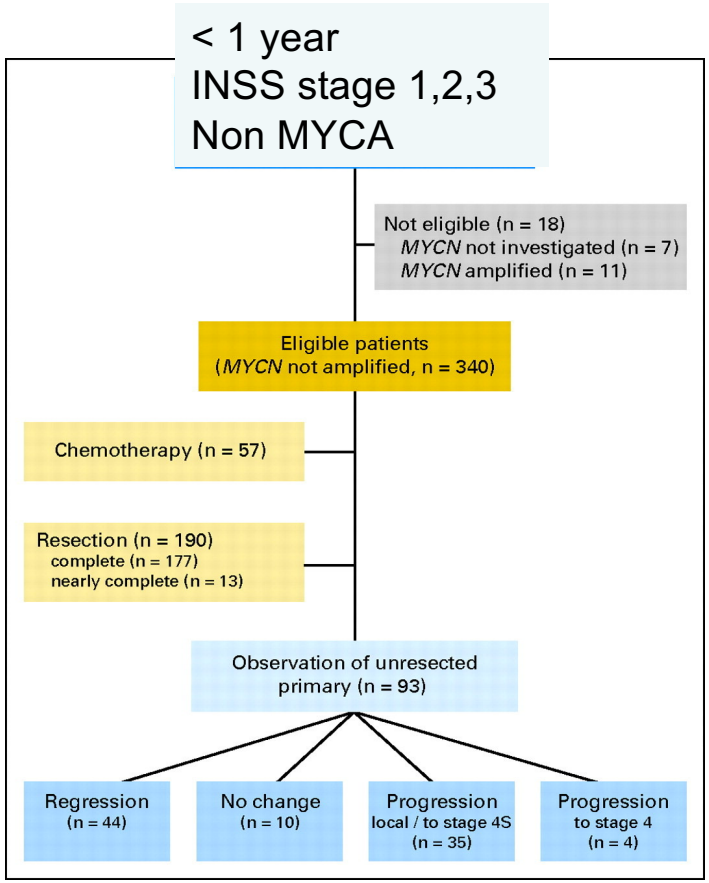
Beckwith JB and Perrin EV, Am J Pathol 1963

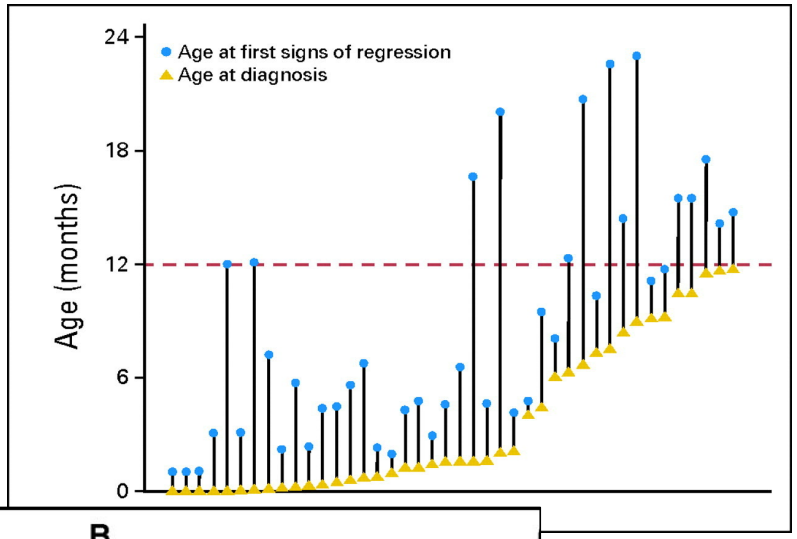
Nutchern JG et al, Ann Surg 2012

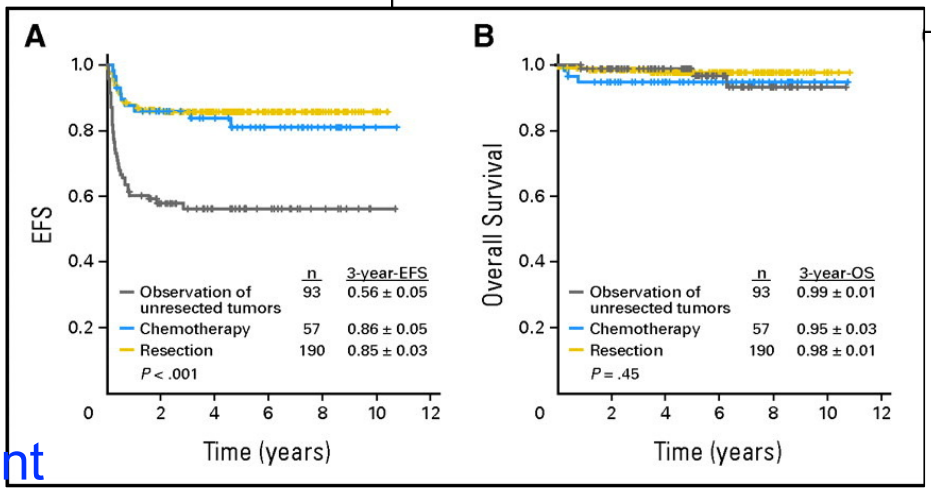
SIOPEN communication, 2020

Vassilios Papadakis et al, Cancers 2022

Wait and See strategy: GPOH experience



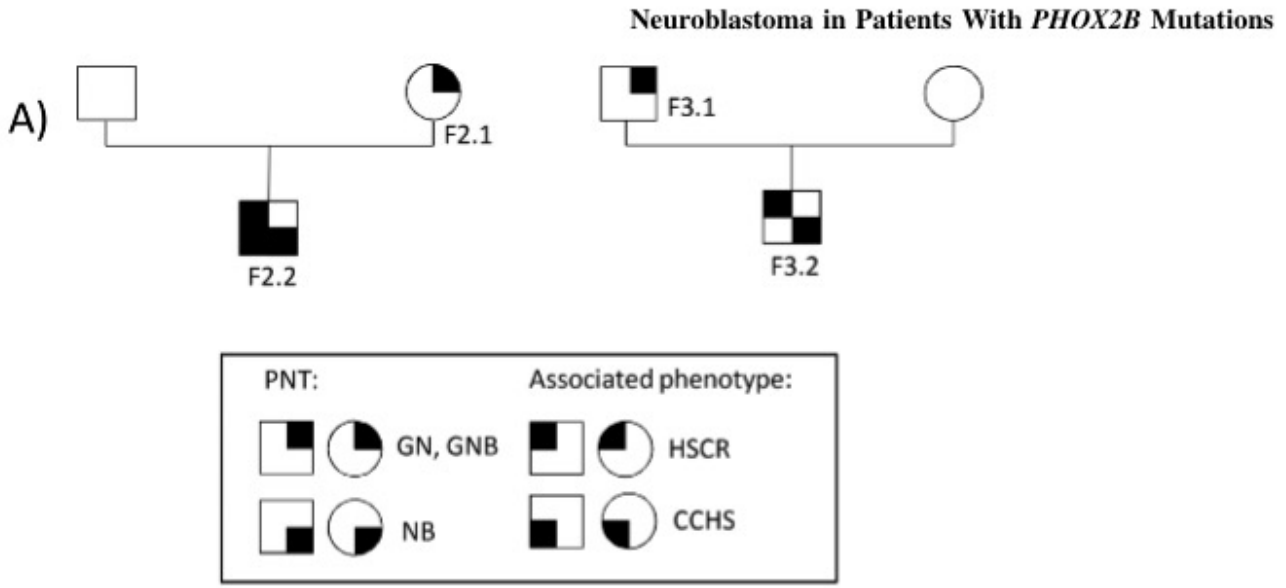




B.Hero et al, JCO 2008

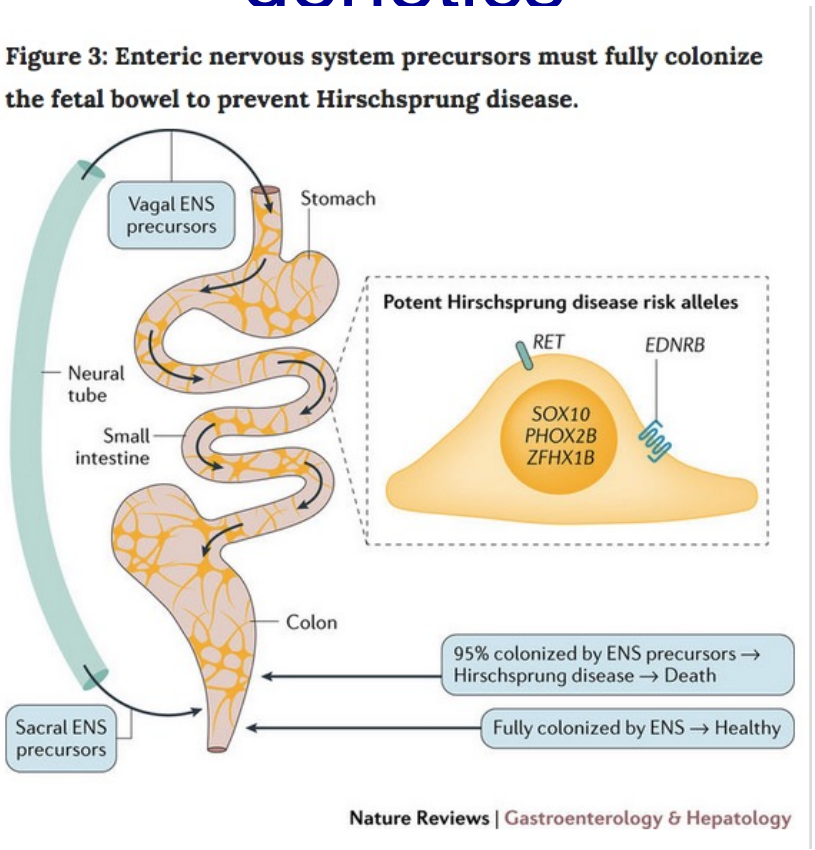
60% are cured without any treatment

Fox2b: a molecular link between Hirschsprung and neuroectodermic tumours



Amiel J et al, Nature 2003
Trochet D et al, Am J Hum Genet 2004
Heide S et al, PBC 2016

Human Hirschsprung disease genetics



Heuckeroth, R. O. (2018) Hirschsprung disease — integrating basic science and clinical medicine to improve outcomes *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2017.149

Les neuroblastomes syndromiques

- Neurocristopathies
  - Sd d'Ondine
  - Sd d'hypoventilation avec dysfinction hypothalamique (début tardif)
  - Sd de Goldenhar
  - Cardiopathies (conotroncales-défaut de fermeture septale)
  - Sd de Di-George
- Syndromes avec excès de croissance:
  - Sd de Wiedemann-Beckwith
  - Sd de Weaver
  - Sd de Simpson-Golabi-Behmel
  - Sd de Sotos
  - Sd de Cowden
- Remaniements chromosomiques germinaux (Turner, Klinefelter, T21, T13…)

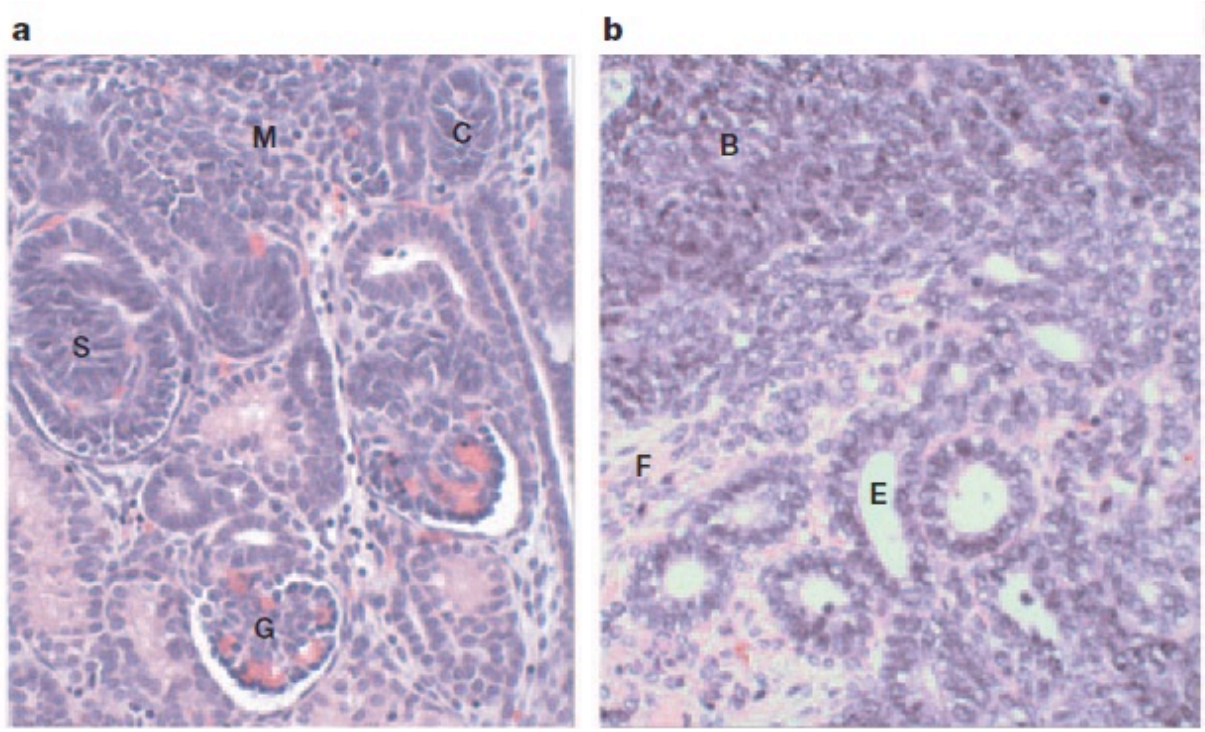
Rational #2

Many pediatric cancer are linked to predisposition syndromes involving defects in normal development

Childhood solid tumours*	Genes disrupted in sporadic tumours	Associated syndromes (genetic defect)
Wilms' tumour	*WT1*, *WT2* (including *IGF2*)	WAGR syndrome (*WT1* deletion); Denys–Drash syndrome (*WT1* mutation); Perlman syndrome (chromosome 11p deletion); Beckwith–Weidemann syndrome (altered imprinting on chromosome 11p1.5); Sympson–Golabi–Behmel syndrome (mutation in *GPC3*); Soto syndrome (mutations in *NSD1*)
Medulloblastoma	*PTCH*, *SMO* and *SUFU* (encoding components of the SHH pathway); β-catenin	Gorlin's syndrome/nevoid basal cell carcinoma syndrome (mutations in *PTCH*); Familial adenomatosis polyposis/Turcot's syndrome (mutations in *APC*)
Neuroblastoma	*MYCN*, *PHOX2B*	Sympson–Golabi–Behmel syndrome (mutations in *GPC3*); Congenital central hypoventilation syndrome (mutations in *PHOX2B*)
Hepatoblastoma	β-Catenin	Beckwith–Weidemann syndrome (altered imprinting on chromosome 11p1.5); Sympson–Golabi–Behmel syndrome (mutations in *GPC3*); familial adenomatosis polyposis/Gardner syndrome (mutations in *APC*)

Paul J. Scotting, David A. Walker and Giorgio Perilongo, Nature Reviews 2005

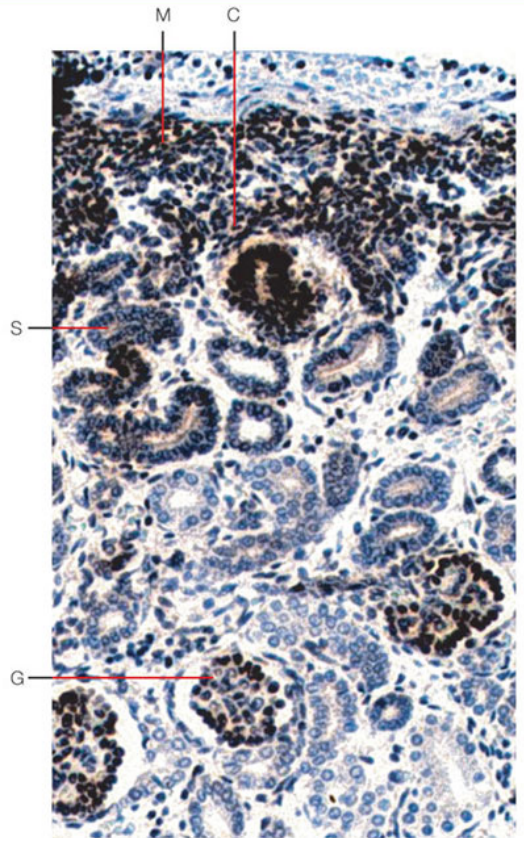
WILMS' TUMOUR: CONNECTING TUMORIGENESIS AND ORGAN DEVELOPMENT IN THE KIDNEY

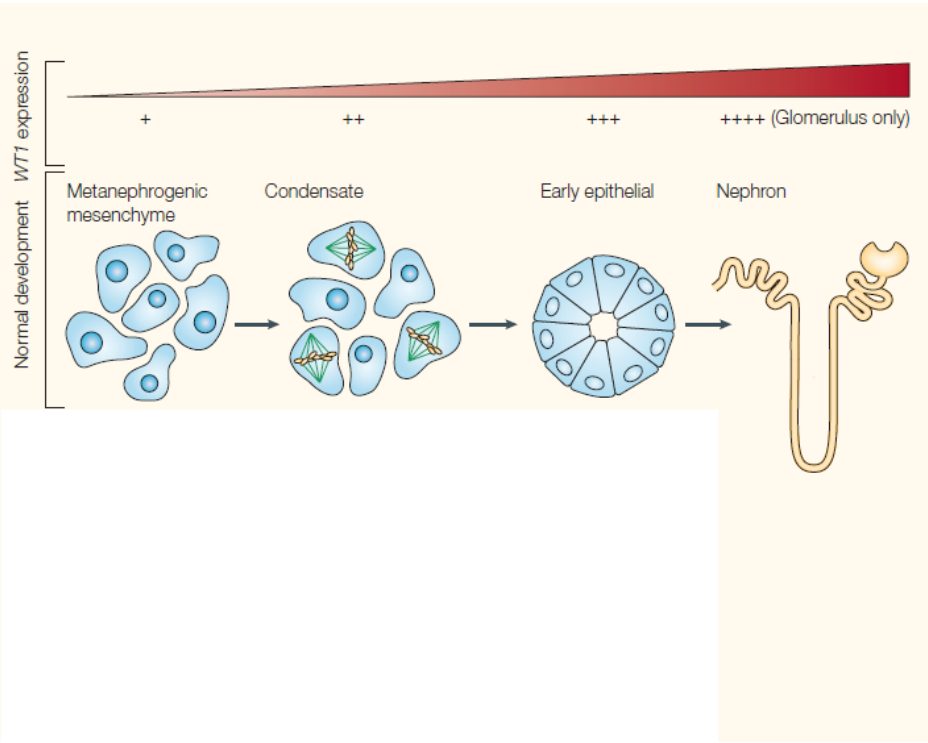


Implication des gènes du développement: WT1

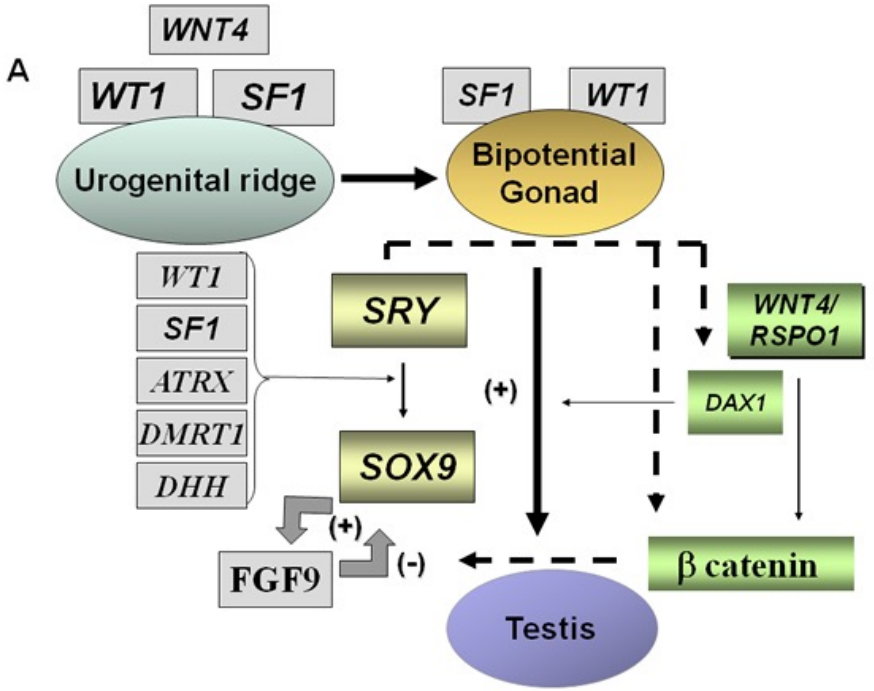
Nat Rev Cancer, 2008

WT1, gène du développement rénal

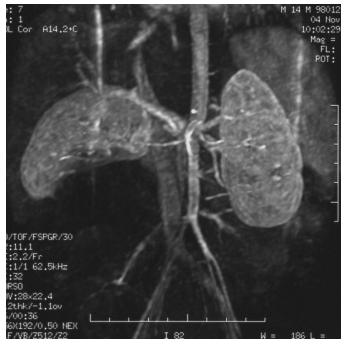




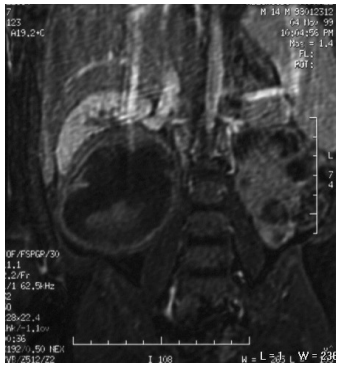
WT1, gène du développement gonadique



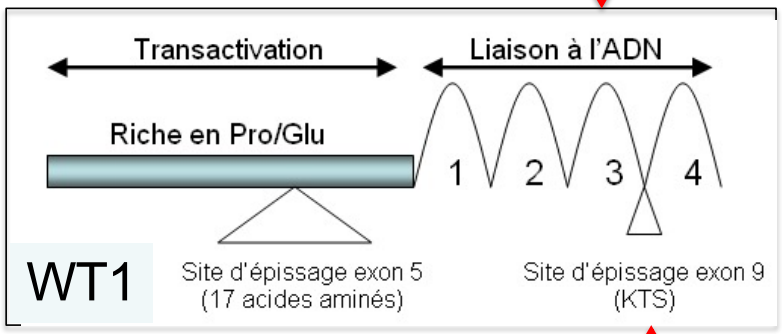
WT1 related Wilms predisposition syndromes



WAGR syndrome, 20 years FU
normal renal function



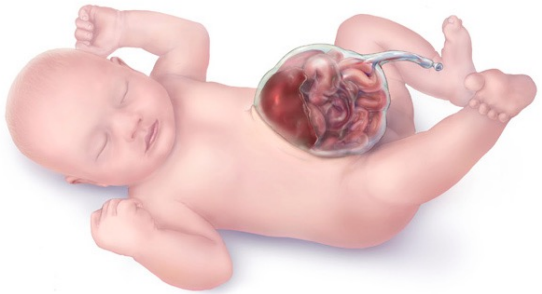
Denys Drash

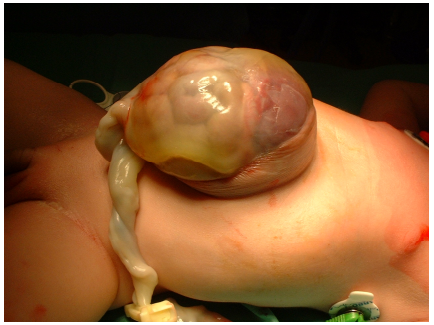


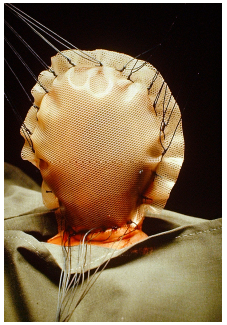
Frasier

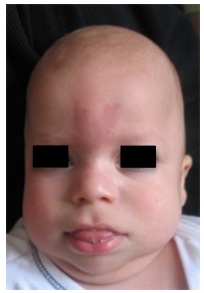
WAGR syndrome

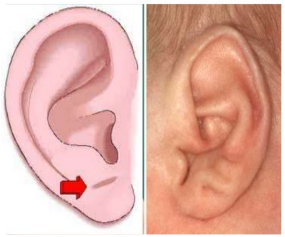
Charlotte, twin, BW:3800g



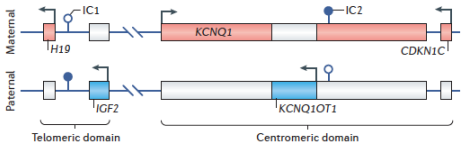






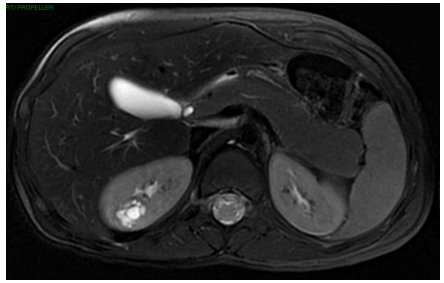


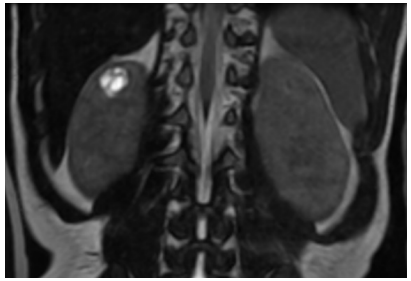
Wiedemann-Beckwith syndrome (11p1.5)

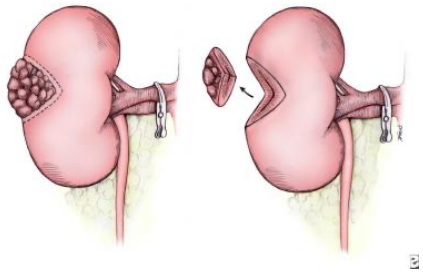


Maternal expression antiproliferative

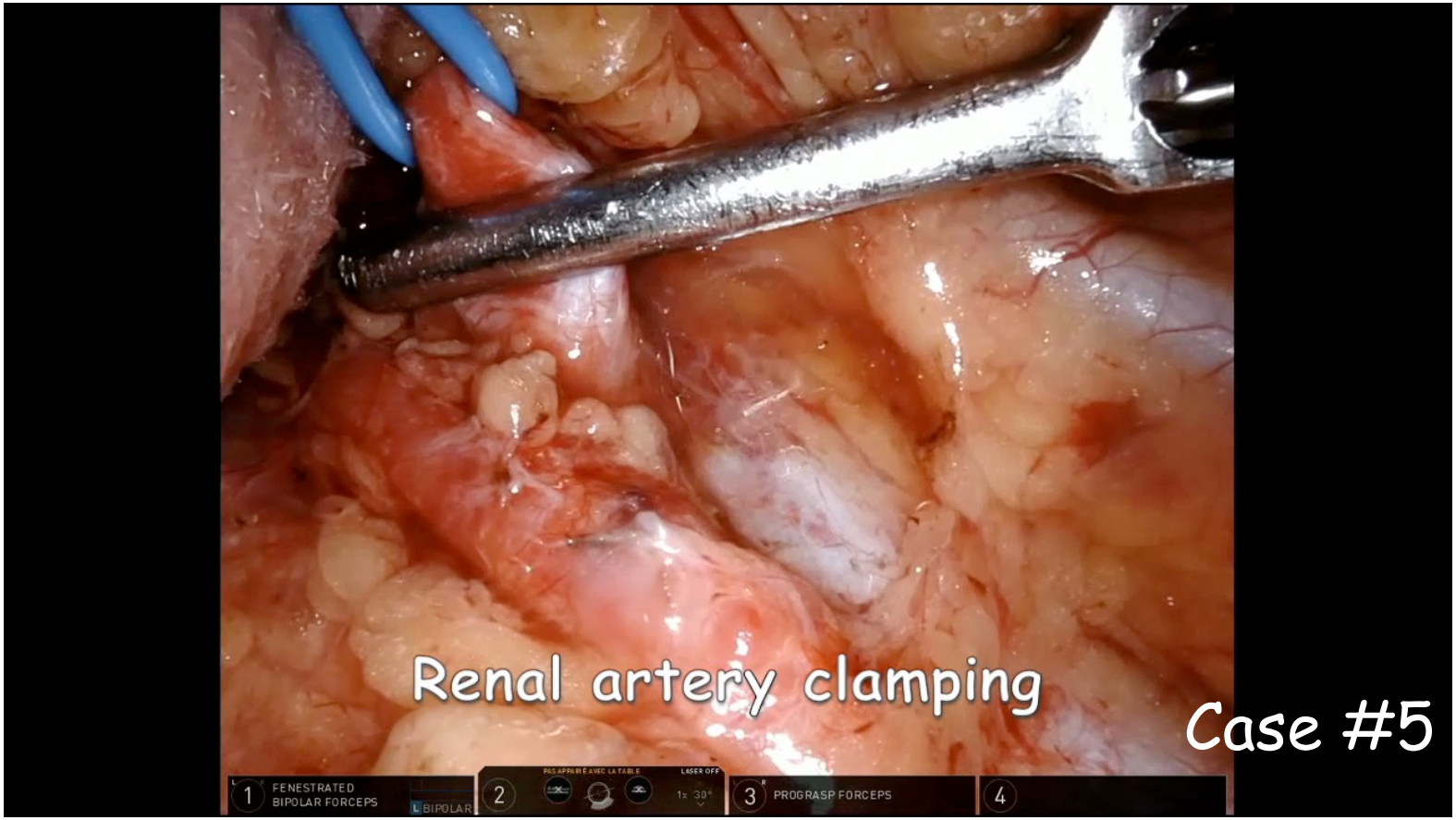
Paternal expression: proliferative







Retroperitoneal partial nephrectomy (T.Blanc)

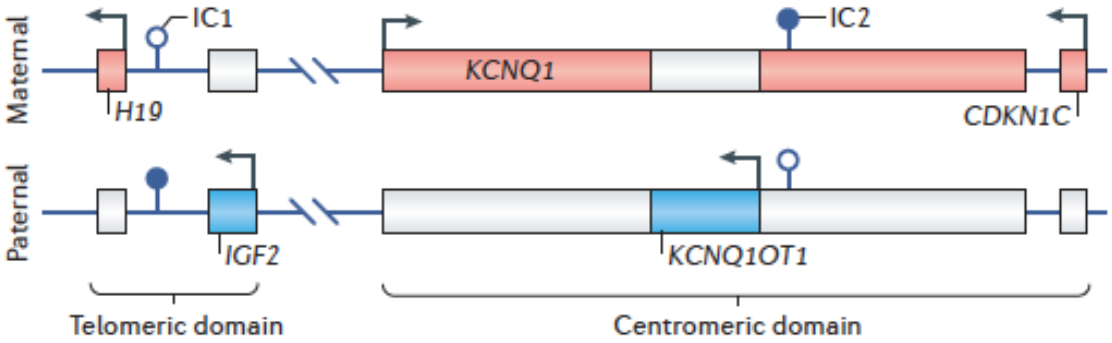


Wiedemann-Beckwith syndrome

Altereted imprinting in the 11p1.5 region

Maternal expression : antiproliferative function

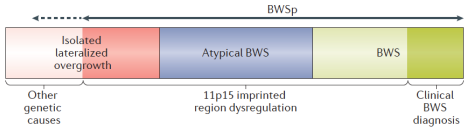
Paternal expression: proliferative function



Increased cancer risk

- 5 à 10% before 15 years old (vs 0,014%)
- 11% before 4 years for Wilms (RR: 800-1000)
- Wilms , hepatoblastoma, adrenocortical carcinoma…
- Phenotype correlation (hémihypertrophie, organomégalie)
- Cancer risk linked to genetic type anomaly

The Beckwith-Wiedemann spectrum



Cardinal features
(2 points/feature)

- Macroglossia
- Exomphalos
- Lateralized overgrowth
- Multifocal and/or bilateral Wilms T or nephroblastomatosis
- Hypersinsulinism (> 1 week, requiring treatment)
- Pathology findings: adrenal cortex cytomegaly..

Suggestive features
(1 points/feature)

- Birth weight > 2DS above in the mean
- Facial naevus simplex
- Polyhydramnios and/or placentomegaly
- Ear creases and/or pits
- Transient hypoglycaemia (lasting <1 week)
- Typical BWSp tumours (NBL, RMS, unilateral WT, hepatoblastoma, adrenocortical carcinoma or phaeochromocytoma)
- Nephromegaly and/or hepatomegaly

asis recti

Classical BWS: score $\geq$ 4
If score $\geq$ 2: genetic testing is lawful
If score < 2: genetic testing is not indicated

Brioude et al, Nature Reviews Endocrinology 2018

Tumour surveillance strategy recommendations

BWSp and embryonal tumours		
56	Screening should be stratified according to the genotype	A+++
57	Abdominal USS for BWSp-related tumours every 3 months until age 7 years is recommended for all patients with BWSp except patients with isolated IC2 LOM	A++
58	For patients with BWSp and upd(11)pat, abdominal USS for Wilms tumour and hepatoblastoma every 3 months until age 7 years is recommended	A+++
59	For patients with BWSp and IC1 GOM, abdominal USS for Wilms tumour every 3 months until age 7 years is recommended	A+++
60	For patients with BWSp and IC2 LOM, no tumour surveillance is recommended	*A/B+
61	For patients with BWSp and a *CDKN1C* mutation, abdominal USS for neuroblastoma every 3 months until age 7 years is recommended	A+
62	For patients with BWSp and an 11p15 duplication, abdominal USS for Wilms tumour every 3 months until age 7 years is recommended	A+++
63	For patients with classical BWS without a molecular defect, abdominal USS every 3 months until age 7 years is recommended	A++
64	α-Fetoprotein (AFP) screening is not recommended for patients with BWSp	A+
65	Catecholamine screening is not recommended for patients with BWSp	A+++
66	There should be a lower threshold for investigation in cases of possible tumour-related symptoms or in response to parental concerns	A+++
67	Treatment of tumours in patients with BWSp might be different from treatment of patients with sporadic diseases and should be discussed with respective study groups unless specific BWSp recommendations are given in the relevant tumour treatment protocols	A+++

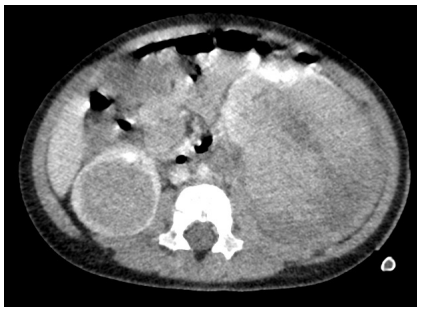
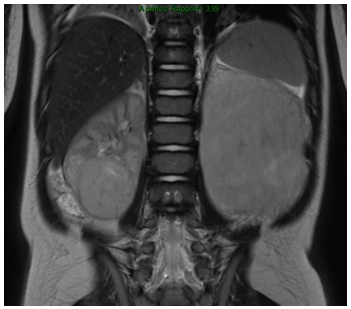
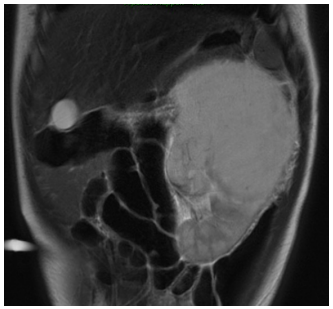
Brioude et al, Nature Reviews Endocrinology 2018

DDS: a frequent misdiagnosed genetic syndrome predisposing to cancer

- Male patient
- Prenatally: Suspiscion of posterior hypospadias, karyotype : 46,XY
- At birth: Confirmation of a posterior hypospadias + bilateral ectopia
  - CGH: normal, renal US: normal
  - Androgenic stimulation
- 1 year old: Surgical correction of the hypospadias

Proteinuria +

Two weeks later: urethral fistula – renal US – bilateral renal tumor

- L partial nephrectomy: R1
- Completion of L nephrectomy and R nephrectomy
- Patient on dialysis, kidney transplant planned in one year

Overgrowth syndromes predisposing to cancer

Table 3
Overgrowth syndromes predisposing to cancer.

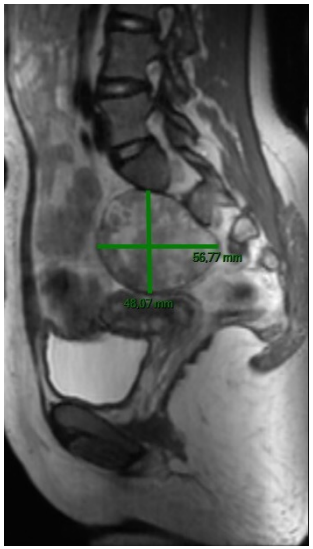
Syndrome	Malignancies reported	Ref.
Generalized overgrowth syndromes		
Beckwith Wiedemann syndrome	Wilms tumor, hepatoblastoma, adrenocortical carcinoma, neuroblastoma, rhabdomyosarcoma	(Rump et al., 2005)
Sotos syndrome	Leukemia, lymphoma, Wilm's tumor, sacrococcygeal teratoma, neuroblastoma	(Tatton-Brown and Rahman, 2007)
Simpson Golabi Behmel syndrome	Wilms tumor, hepatoblastoma, neuroblastoma, gonadoblastoma, hepatocellular carcinoma	(Lapunzina et al., 1998)
Perlman syndrome	Wilms tumor	(Alessandri et al., 2008)
Weaver syndrome	Neuroblastoma	(Basel-Vanagaite, 2010)
Partial overgrowth syndromes		
Isolated Hemihyperplasia	Wilms tumor, hepatoblastoma, adrenocortical carcinoma	(Bliek et al., 2008; Clericuzio and Martin, 2009)
Macrocephaly-capillary malformation syndrome	Leukemia, meningioma, retinoblastoma, Wilms tumor	(Lapunzina et al., 2004)
Proteus syndrome	Various, but rare	(Gordon et al., 1995)
PIK3CA-Related Segmental Overgrowth	Wilms tumor, meningeoma	(Mirzaa et al., 2013)
Macrocephaly syndromes		
PTEN hamartoma tumor syndrome	Cerebellar gangliocytoma, thyroid cancer, breast cancer, endometrial cancer, colon cancer	(Nieuwenhuis et al., 2014)
Neurofibromatosis type 1	Optic pathway glioma, leukemia, malignant peripheral nerve sheath tumor	(Walker et al., 2006)
Costello syndrome	Rhabdomyosarcoma, neuroblastoma, bladder cancer	(Kratz et al., 2011; Gripp, 2005; Kratz et al., 2015)
Gorlin syndrome	Medulloblastoma, basal cell carcinoma	(Evans et al., 1991a; Jones et al., 2011)
Tall stature		
MEN 2B	Medullary thyroid carcinoma, phaeochromocytoma	(Skinner et al., 1996)

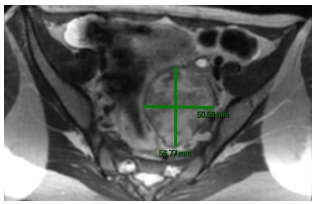
* various epigenetic and/or genetic alterations that deregulate imprinted genes on chromosome 11p15.5.

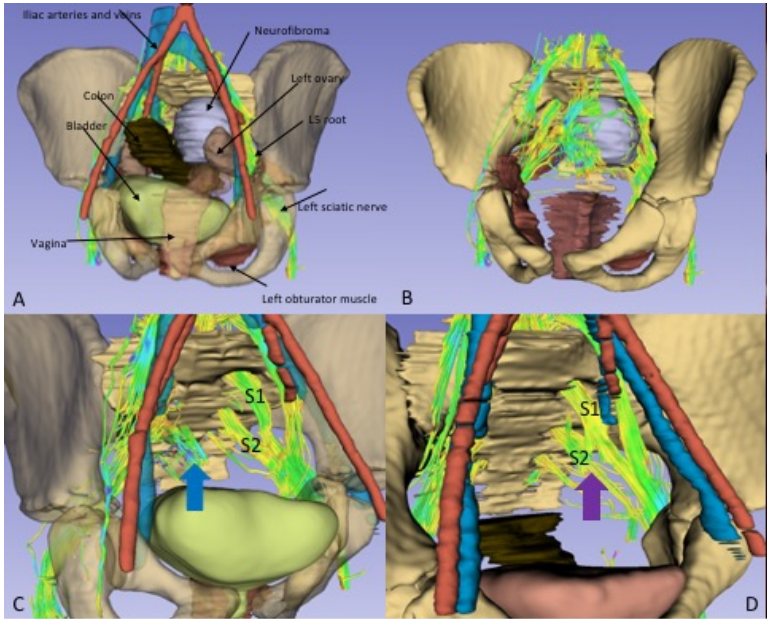
Jongmans MCJ et al, European Journal of Medical Genetics 2016

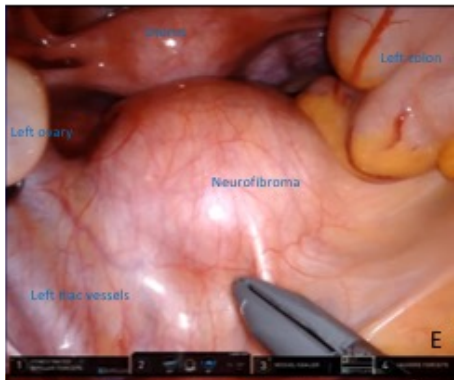
- 11 years old girl
- NF1
- PetScan: > 2 SUV max

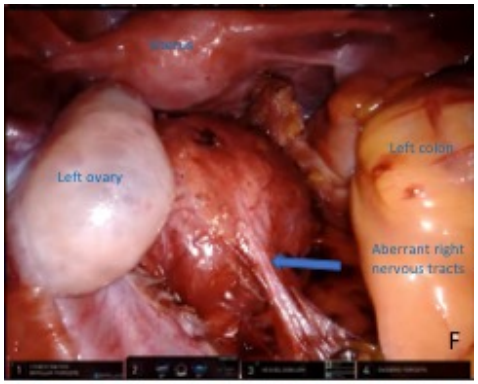
→ High MPNST risk











Growth retardation syndromes predisposing to cancer

Table 4
Growth retardation syndromes predisposing to cancer.

Growth retardation syndromes	Low birth-weight	Short stature	Micro-cephaly	Malignancies reported	Ref.
DNA repair syndromes					
Mosaic Variegated Aneuploidy	+	+	+	Wilms tumor, rhabdomyosarcoma	(Jacquemont et al., 2002)
Fanconi anemia	~5%	+	~20%	MDS, AML, ALL, squamous cell carcinomas of the head, neck and anogenital region	(Alter, 2003)
Rothmund Thomson syndrome	+	+	−	Osteosarcoma, skin cancer	(Wang et al., 2001)
Cartilage Hair Hypoplasia	+	+	−	Lymphoma, basal cell carcinoma	(Taskinen et al., 2008)
Bloom syndrome	+	+	+	AML, lymphoma, epithelial cancers	(German, 1997)
Nijmegen Breakage syndrome	+	+	+	Lymphoma, medulloblastoma, glioma, rhabdomyosarcoma	(Wegner et al., 1999)
Ras related disorders					
Cardio Facio Cutaneous syndrome	−	+/−	−	leukemia, lymphoma	(Kratz et al., 2011; Kratz et al., 2015)
Costello syndrome	−	+	−	Rhabdomyosarcoma, neuroblastoma, bladder cancer	(Kratz et al., 2011; Gripp, 2005; Kratz et al., 2015)
Noonan syndrome	−	+	−	Leukemia, neuroblastoma, rhabdomyosarcoma	(Kratz et al., 2011; Kratz et al., 2015; Jongmans et al., 2011)
Noonan syndrome with multiple lentigines	−	<50%	−	Leukemia, neuroblastoma	(Kratz et al., 2011)
Chromosomal aberrations					
Trisomy 21	+/−	+	+	Leukemia	(Khan et al., 2011)
(Mosaic) Trisomy 18	+	+	+	Hepatoblastoma	(Maruyama et al., 2001)
Turner syndrome	+	+	−	Gonadoblastoma	(Bianco et al., 2009)
Other					
Rubinstein Taybi syndrome	−	+	+	Various	(Miller and Rubinstein, 1995)
Mulibrey Nanism	+	+	−	Wilms tumor	(Karlberg et al., 2009)

Jongmans MCJ et al, European Journal of Medical Genetics 2016

Childhood cancer, indication for referral to a clinical geneticist?

If your patient fulfills one or more of the criteria mentioned below (one or more circles filled), he or she may benefit from referral to a clinical geneticist.

1. Family history of the child with cancer

- ○ ≥ 2 malignancies at childhood age (≤ 18 years of age)
- ○ a first degree relative (parent or sibling) with cancer < 45 years of age
- ○ ≥ 2 second degree relatives with cancer < 45 years of age on the same side of the family
- ○ the parents of the child with cancer are related, i.e. consangious

2. A person with one of these tumors in childhood

- ○ Adrenocortical carcinoma
- ○ Atypical teratoid rhabdoid tumor
- ○ Cerebellar gangliocytoma
- ○ Choroid plexus carcinoma
- ○ Endolymphatic sac tumors
- ○ Hemangioblastoma
- ○ Hepatoblastoma
- ○ JMML
- ○ Low hypodiploid ALL
- ○ Malignant peripheral nerve sheath tumor
- ○ Medullary thyroid carcinoma
- ○ Medulloblastoma
- ○ Optic glioma
- ○ Ovarian sertoli-leydig cell tumor
- ○ Pleuropulmonary blastoma
- ○ Pituitary blastoma
- ○ Pineoblastoma
- ○ Retinoblastoma
- ○ Schwannoma
- ○ Subependymal giant cell tumor

Or ○ A cancer of adult age, i.e. colorectal cancer, ovarian cancer, basal cell carcinoma etc.

3. ○ **A child with two malignancies** one of those with onset < 18 years of age (unless the 2nd malignancy is consistent in time and/or tissue type with these expected from their treatment regimen).

4. ○ **A child with cancer and congenital anomalies or other specific symptoms**

Sign	*Think of*
Congenital anomalies	Organs, bones, oral clefting, teeth, eyes, ears, brain, urogenital anomalies, etc.
Facial dysmorphisms	
Intellectual disability	
Aberrant growth	Length, head circumference, birth weight, asymmetric growth
Skin anomalies	Aberrant pigmentation i.e. > 2 café-au-lait spots, vascular skin changes, hypersensitivity for sunlight, multiple benign tumors of the skin
Hematological disorders	Pancytopenia, anemia, thrombocytopenia, neutropenia
Immune deficiency	

5. ○ **A child with excessive treatment toxicity**

When to reffer a pediatric cancer patient to a clinical geneticist ?

Jongmans MCJ et al, European Journal of Medical Genetics 2016

Evidence accumulated over several decades suggests positive association between birth defects and pediatric malignancy

Autor	Year	Study	V1	V2	RR
Narod *et al.* (UK)	1997	Register comparison	Incidence cancer/ congenital abnormalities	Incidence cancer/ no congenital abnormalitie	1,85
Altmann *et al.* (Australia)	1998	Register comparison	Prevalence congenital abnormalities/ cancer	Prevalence congenital abnormalities/no cancer	4,5
Nishi *et al.* (Japan)	2000	Register comparison	Incidence cancer/ congenital abnormalities	Incidence cancer/ no congenital abnormalitie	2,1
Agha et al. (Canada)	2005	Case-control	Incidence cancer/ congenital abnormalities	Incidence cancer/ no congenital abnormalitie	5,8
Merks *et al.* (Netherlands)	2008	Case-control	Prevalence congenital abnormalities/ cancer	Prevalence congenital abnormalities/no cancer	1,7

RESEARCH ARTICLE

Pediatric cancer risk in association with birth defects: A systematic review

Kimberly J. Johnson[1,2*], Jong Min Lee[1☯], Kazi Ahsan[1☯], Hannah Padda[1‡], Qianxi Feng[1‡], Sonia Partap[3], Susan A. Fowler[1], Todd E. Druley[2,4]

PlosOne, July 2017

14478 article citations identified
80 articles met inclusion criteria
Specific points:

- CNS tumors & CNS anomalies
- Rib anomalies & several cancers types

Benjamin D…..né le 30/03/05

Père : 42 ans, pilote de ligne ; Mère : 31 ans, sans emploi
Fratrie :Une demi soeur du côté maternel de 6 ans, bien portante

Anténatal: découverte à 12 SA de logettes avec hygroma
- ponction trophoblastique normale, 46 XY,
- diagnostic de kystes para-ventriculaires à l'IRM à 32 SA

Accouchement à terme
PN : 2590 g, TN : 50 cm, PCN : 33 cm
- Dysmorphie faciale associant micro-rétro-gnatisme, philtrum proéminent,
fentes palpébrales horizontales , pas d'anomalie des OGE , pas d'anomalie oculaire
- Anomalie de la luette avec luette bifide et voile court
- Echographie rénale (naissance) : taille des reins à la limite supérieure de la normale
- Embryo toxon temporal oeil droit diagnostiqué à 2 mois

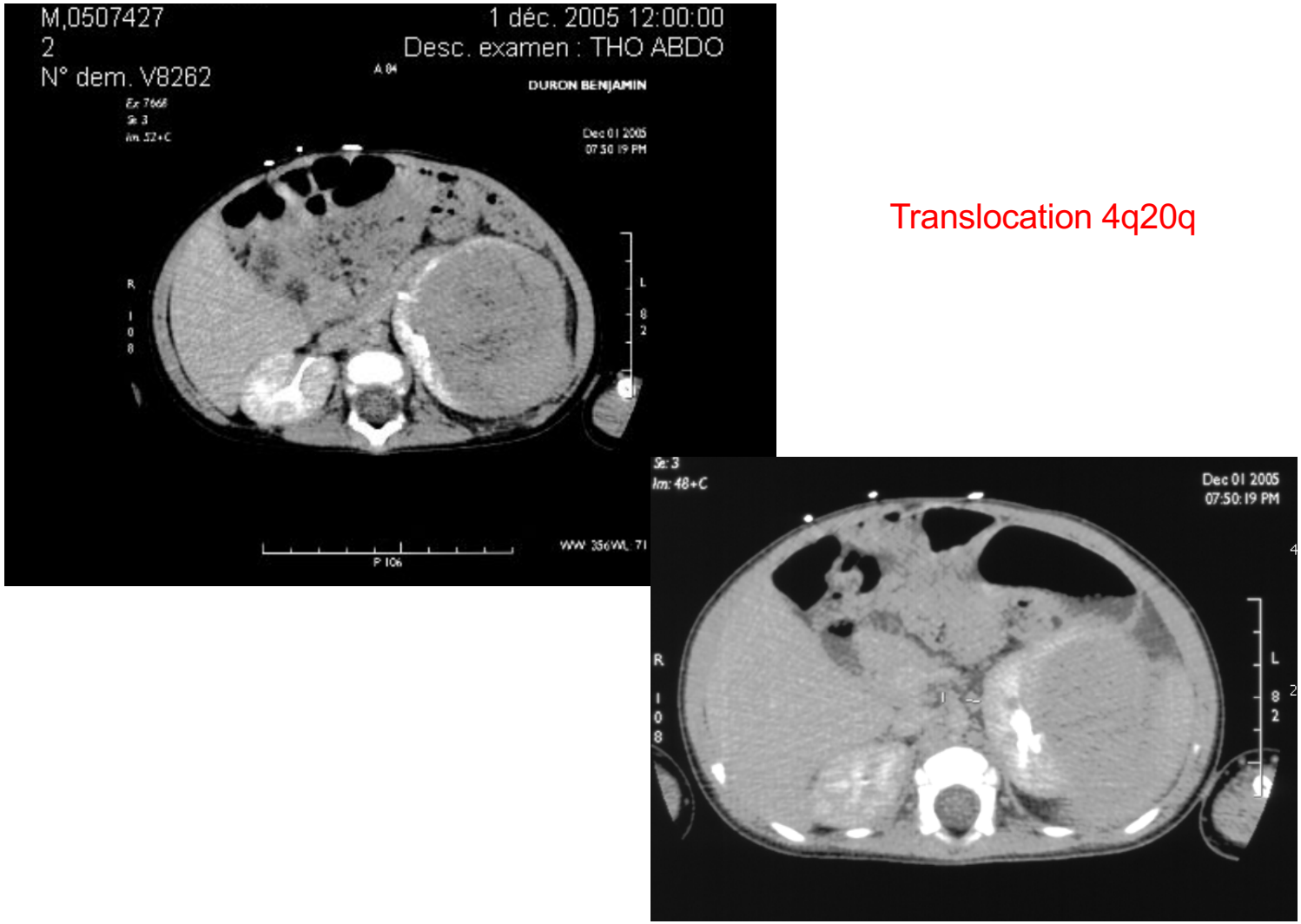
Benjamin D…..né le 30/03/05

Exploration dans le Sce du Pr Abadie pour dysfonctionnement du tronc cérébral (troubles de la succion, déglutition et cyanose pendant la tétée). Alimenté par sonde NG pendant plusieurs mois, O2 à domicile.

- Enregistrement polysomnographique (le 30/05/05) : apnées obstructive et centrale
- Potentiels évoqués auditifs seuil à 60 dB à G, retard de maturation du tronc cérébral ou dysfonctionnement? à contrôler
- Holter effectué en raison d'une hypertonie vagale pendant et après l'arrêt du Prantal : normal
- Radio de squelette complet effectué sans anomalie
-Caryotypes effectué le 26/05/05 à Béclère 46 XY, normal

Histoire tumorale:

-Découverte d' une masse de l' hypochondre gauche dans le cadre d' une consultation de neuro-pédiatrie: masse rénale gauche retrouvée à l' échographie
- HTA



Translocation 4q20q

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Pediatric Tumors and Developmental Anomalies: A French Nationwide Cohort Study

Michaela Semeraro, MD, PhD[1,2,3], Cyrielle Fouquet, MD[4], Yoann Vial, MD, PhD[2,5], Jeanne Amiel, MD, PhD[2,6], Louise Galmiche, MD[7], Célia Cretolle, MD, PhD[8], Thomas Blanc, MD, PhD[2,8], Valérie Jolaine, DNM[1], Nicolas Garcelon, PhD[9], Natacha Entz-Werle, MD, PhD[10], Isabelle Pellier, MD, PhD[11], Cécile Vérité, MD[4], Sophie Taque, MD[12], Aurore Coulomb, MD, PhD[13], Arnaud Petit, MD, PhD[14], Nadège Corradini, MD, PhD[15], Naim Bouazza, PhD[2,16], Brigitte Lacour, PhD[17,18], Jacqueline Clavel, MD, PhD[17,18], Laurence Brugières, MD[19], Franck Bourdeaut, MD, PhD[2,20], and Sabine Sarnacki, MD, PhD[2,8], the members of the TED Consortium*

J Pediatr. 2023

TED : Tumor & Development

Aim of the study

Retrospective and prospective registry of all cases,
associating
pediatric cancer & developmental anomaly,
in order to describe new predisposition syndroms,
and their molecular basis.

Methodology

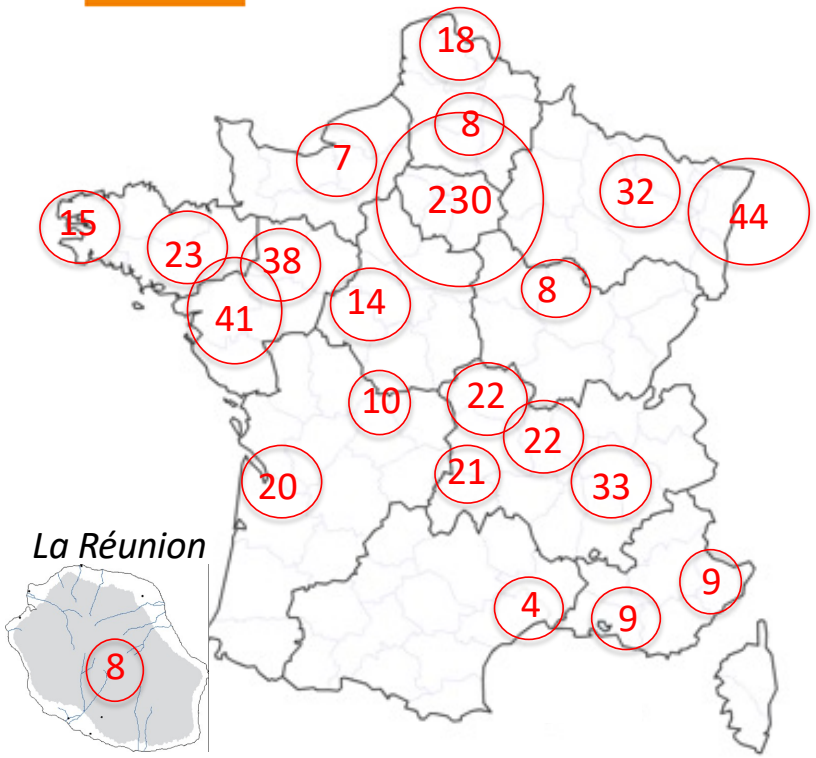
- Prospective and retrospective nationwide study
- Spontaneous declaration of cases by:
  - Pediatric oncology centers (SFCE)
  - Pediatric surgery centers (SFCP)
  - Pediatric onco-geneticists & pediatric geneticists
  - Pediatric pathologists
  - Biologists involved in tumor development
- Tumor and developmental anomalies described according the ICCC-3 and ICD10 classification respectively
- Missing datas:
  - Parents age
  - ART (assisted reproduction technology)
  - Age at diagnosis for congenital anomaly

Inclusion criteria

Age < 18 years presenting with solid tumor or hematologic malignancy + one or more developmental anomaly (ies) among:

- organ malformation familial or not
- neurosensory deficit, familial or not
- delay in psychomotor activity (before any treatment)
- epilepsy not linked to the tumor
- pathological disorder of the statural and/or weight growth and/or of the cranial perimeter
- congenital, sporadic and/or familial metabolic or endocrinological disease
- Immune deficiency, familial or not
- Signs of dysmorphology
- ≥ Café au lait spots or 1 spot >1cm or 3 hypochromic spots > 1 cm
- Inform consent from the parents and/or patient
- Patient ou parents informés de l'étude

TED : A national prospective & retrospective study



June 2013- July 2017

642 inclusions
by 27 surgical /medical centres

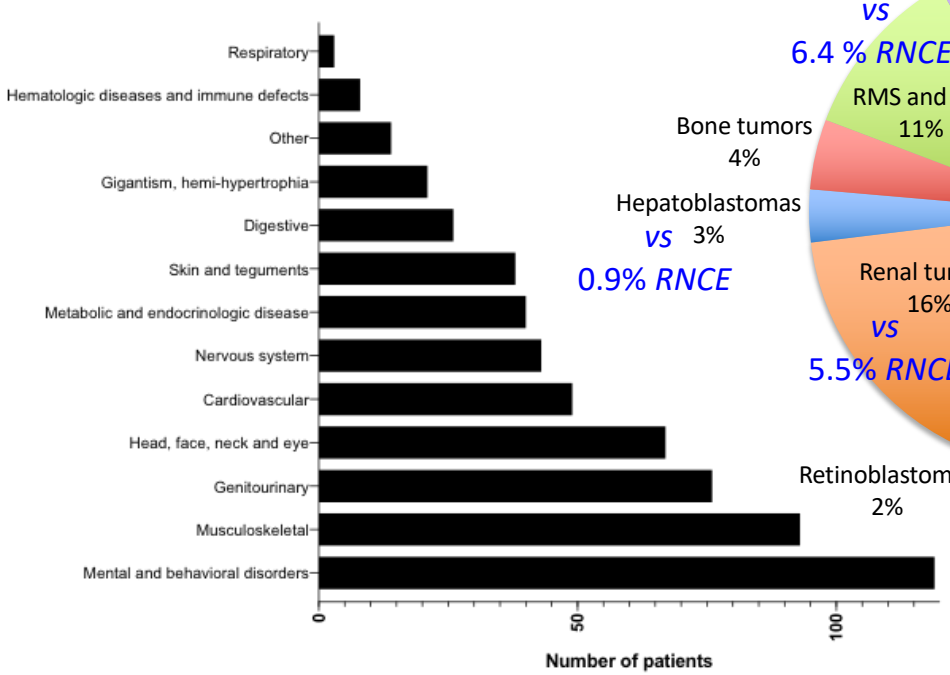
617 met the inclusion criteria

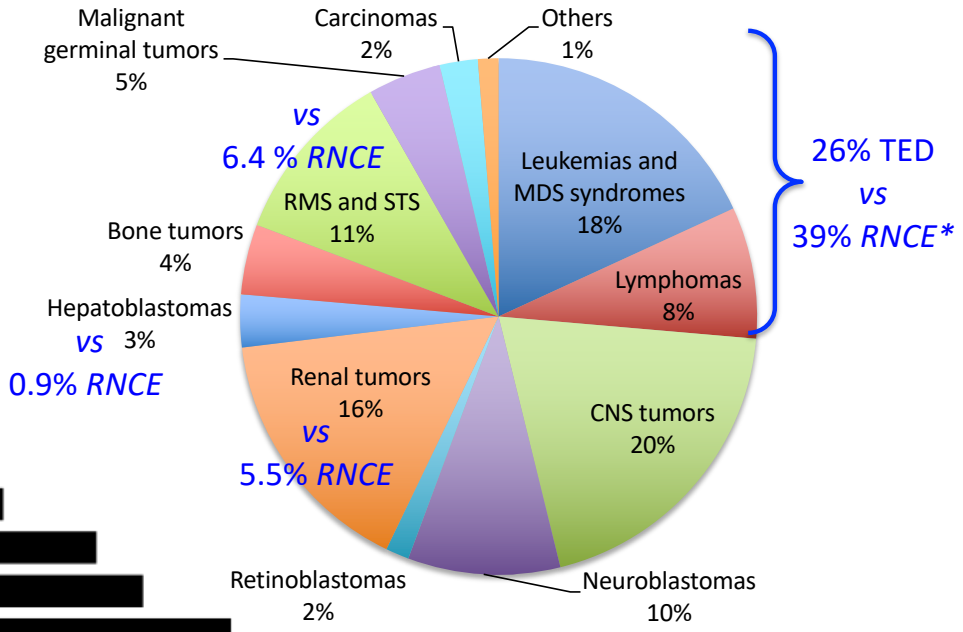
546 completelly informed

French national registry for childhood cancers & congenital abnormalities associations (TED)
N=628 patients, 855 congenital anomalies

30% Cancer Predisposition syndromes
70% Isolated congenital anomalies

* National registry of children cancers

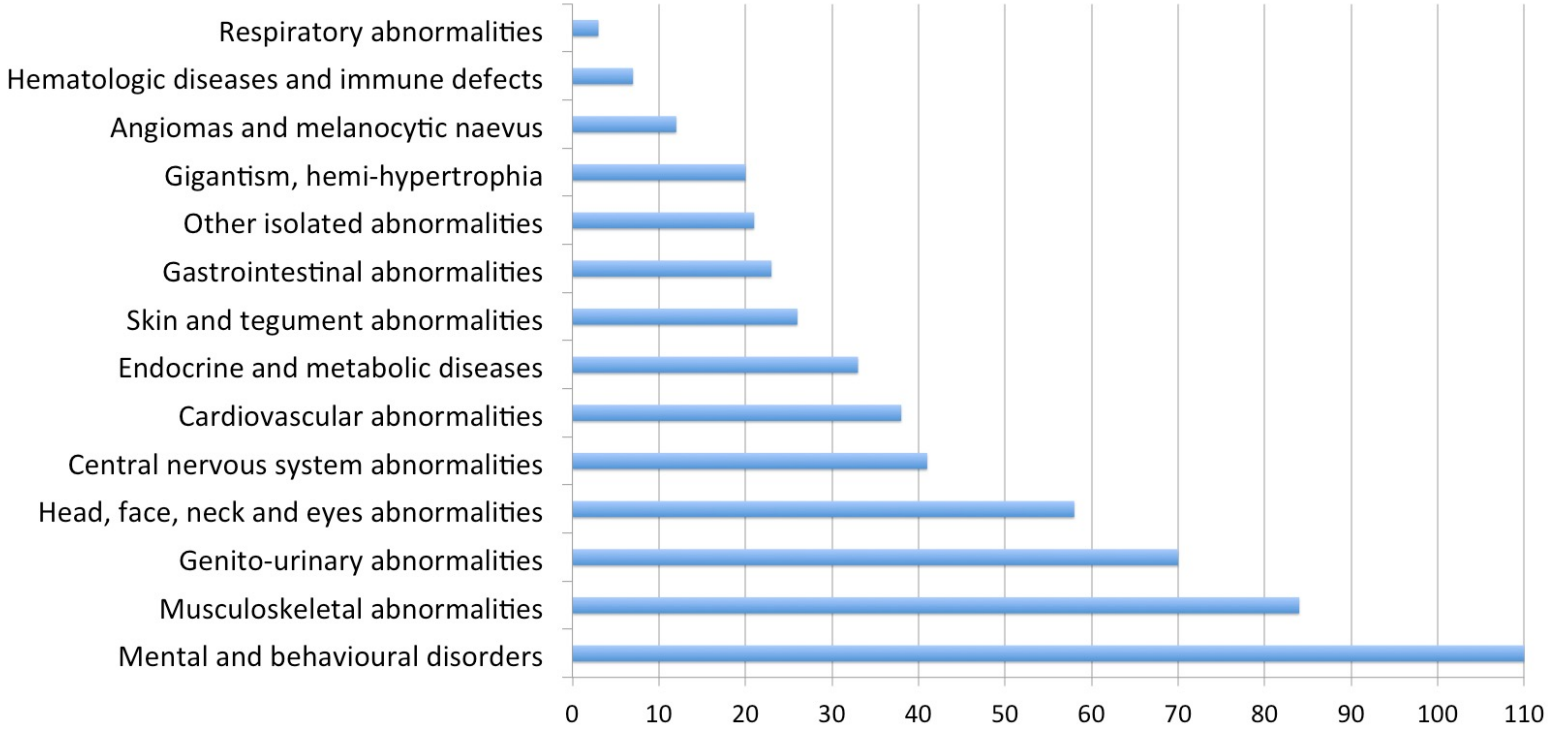


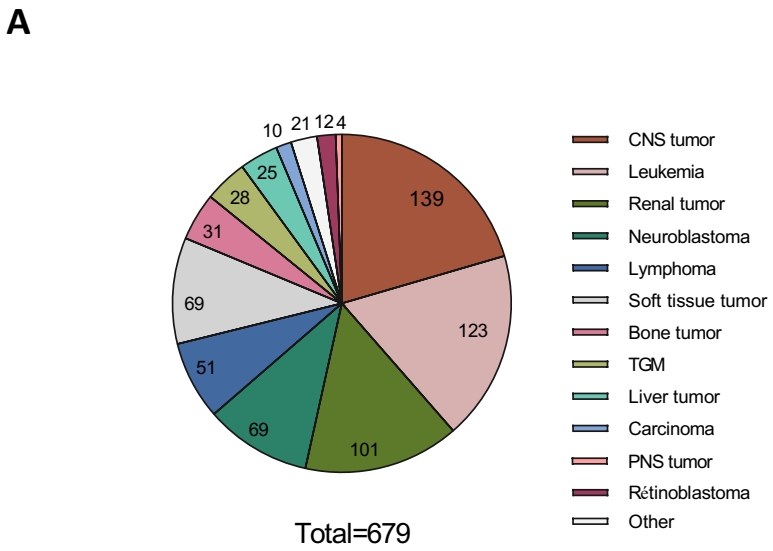


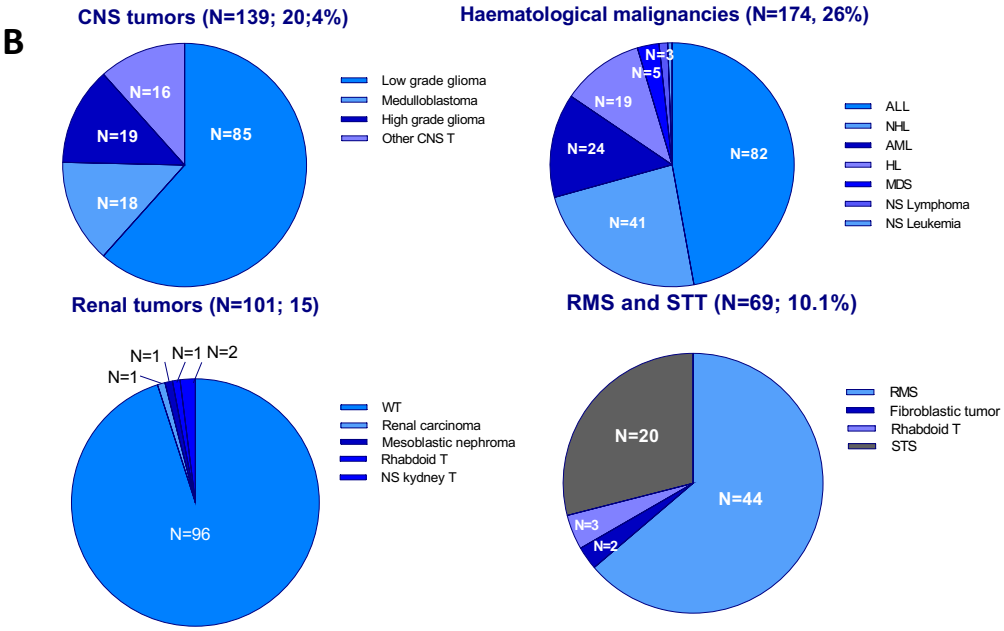
M.Semeraro et al, personal data

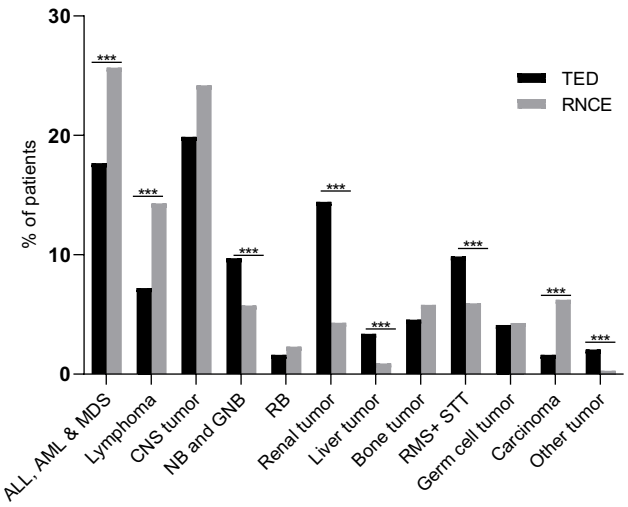
Isolated birth defect, n=546/783 (69.7%)

Median age at diagnosis (year) : 1.0 (antenatal ; 17.0)




A
10
21
12
4
139
123
101
69
51
69
31
28
25
CNS tumor
Leukemia
Renal tumor
Neuroblastoma
Lymphoma
Soft tissue tumor
Bone tumor
TGM
Liver tumor
Carcinoma
PNS tumor
Rétinoblastoma
Other
Total=679


B
CNS tumors (N=139; 20;4%)
N=16
N=19
N=85
N=18
Low grade glioma
Medulloblastoma
High grade glioma
Other CNS T
Haematological malignancies (N=174, 26%)
N=3
N=5
N=19
N=24
N=82
N=41
ALL
NHL
AML
HL
MDS
NS Lymphoma
NS Leukemia
Renal tumors (N=101; 15)
N=1
N=1
N=1
N=2
N=96
WT
Renal carcinoma
Mesoblastic nephroma
Rhabdoid T
NS kydney T
RMS and STT (N=69; 10.1%)
N=20
N=44
N=3
N=2
RMS
Fibroblastic tumor
Rhabdoid T
STS


C
30
20
10
0
% of patients
***
TED
RNCE
ALL, AML & MDS
Lymphoma
CNS tumor
NB and GNB
RB
Renal tumor
Liver tumor
Bone tumor
RMS+ STT
Germ cell tumor
Carcinoma
Other tumor

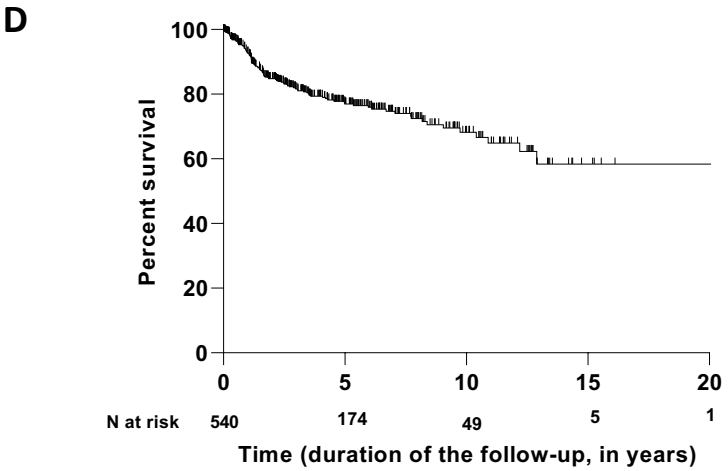
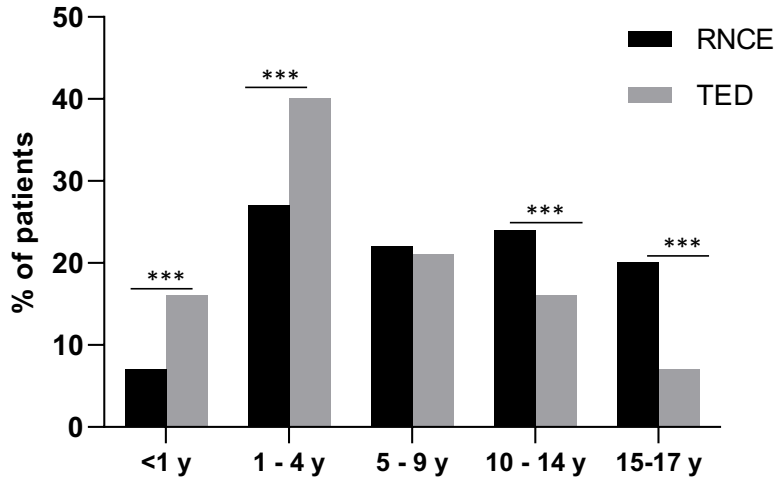

D
100
80
60
40
20
0
Percent survival
0
5
10
15
20
N at risk
540
174
49
5
1
Time (duration of the follow-up, in years)

Figure 2



Supplemental Figure 1

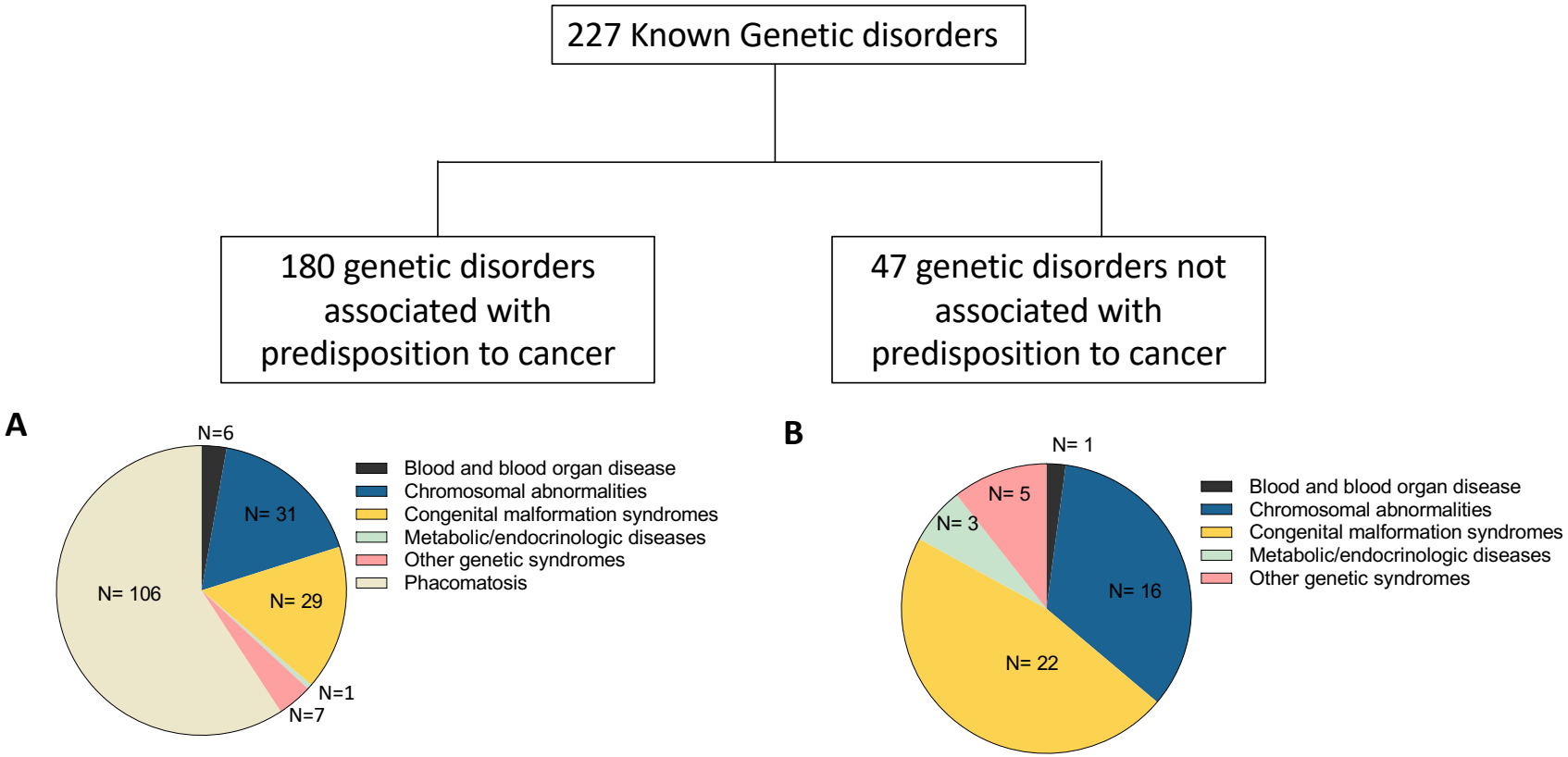

227 Known Genetic disorders
180 genetic disorders associated with predisposition to cancer
47 genetic disorders not associated with predisposition to cancer
A
N=6
N= 31
N= 106
N= 29
N=1
N=7
Blood and blood organ disease
Chromosomal abnormalities
Congenital malformation syndromes
Metabolic/endocrinologic diseases
Other genetic syndromes
Phacomatosis
B
N= 1
N= 5
N= 3
N= 16
N= 22
Blood and blood organ disease
Chromosomal abnormalities
Congenital malformation syndromes
Metabolic/endocrinologic diseases
Other genetic syndromes

Figure 3

452 isolated anomalies

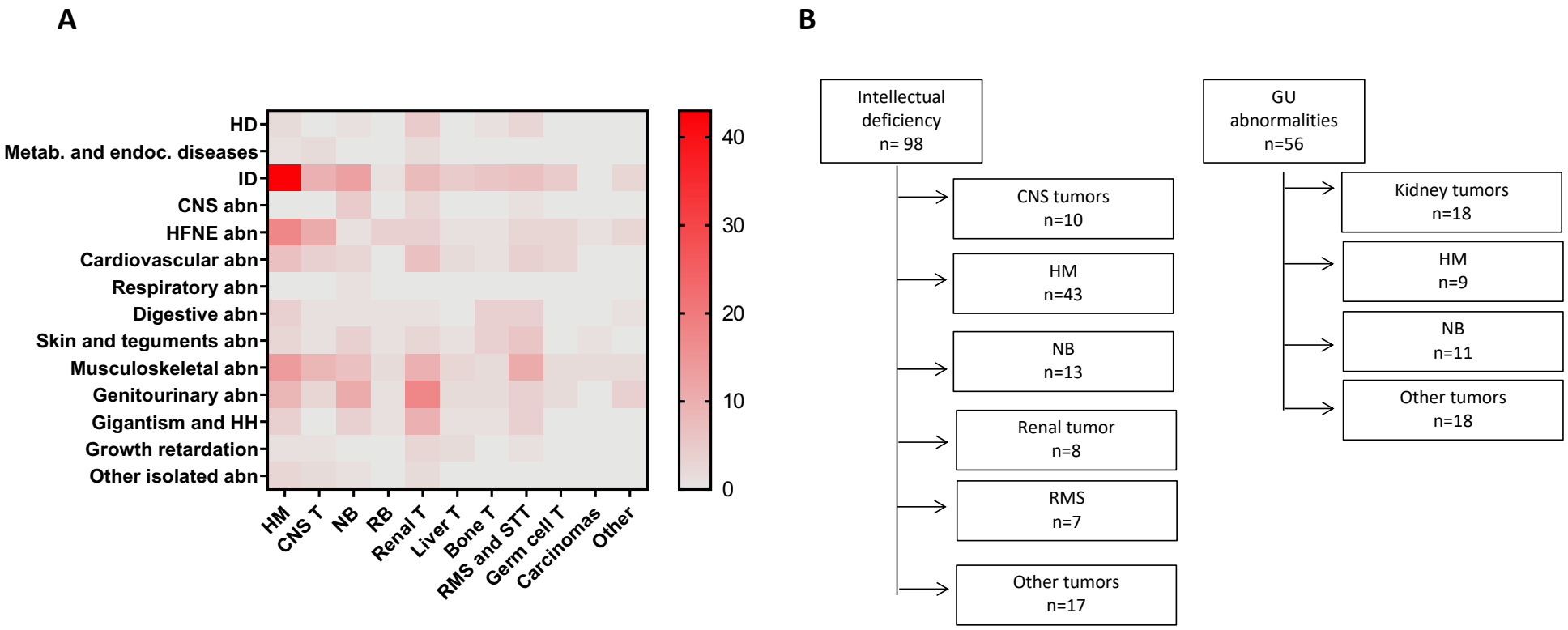
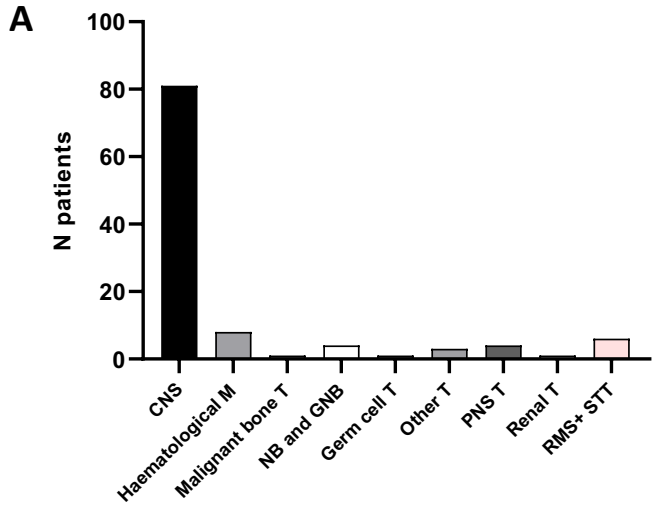
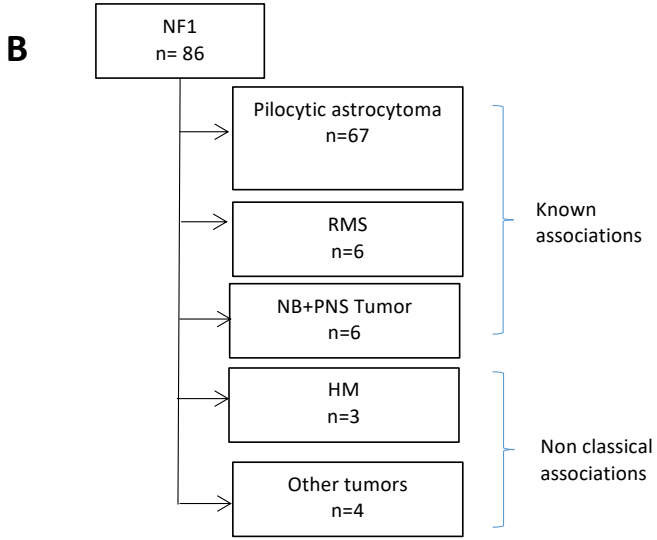
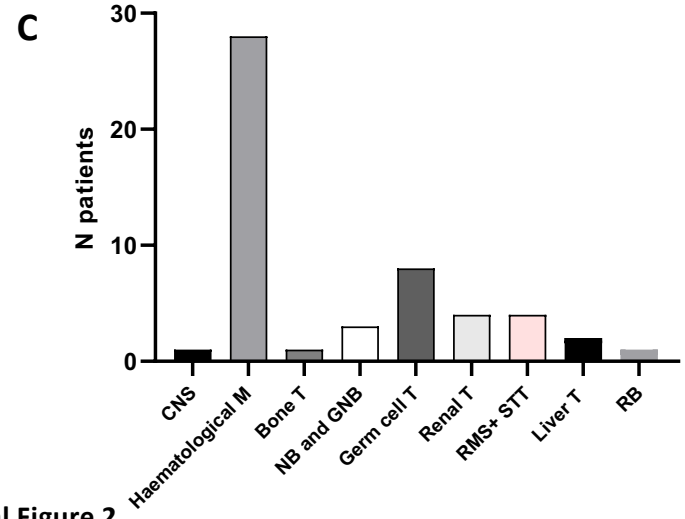
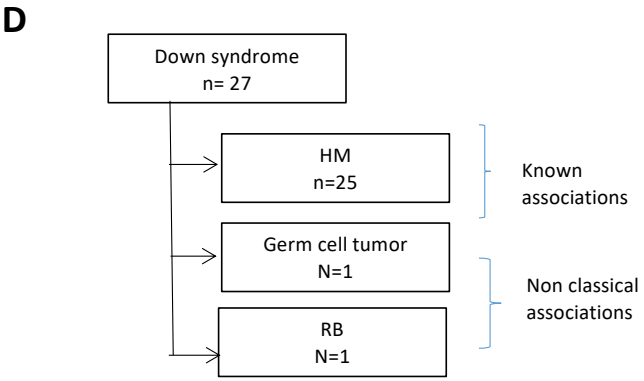


Figure 4

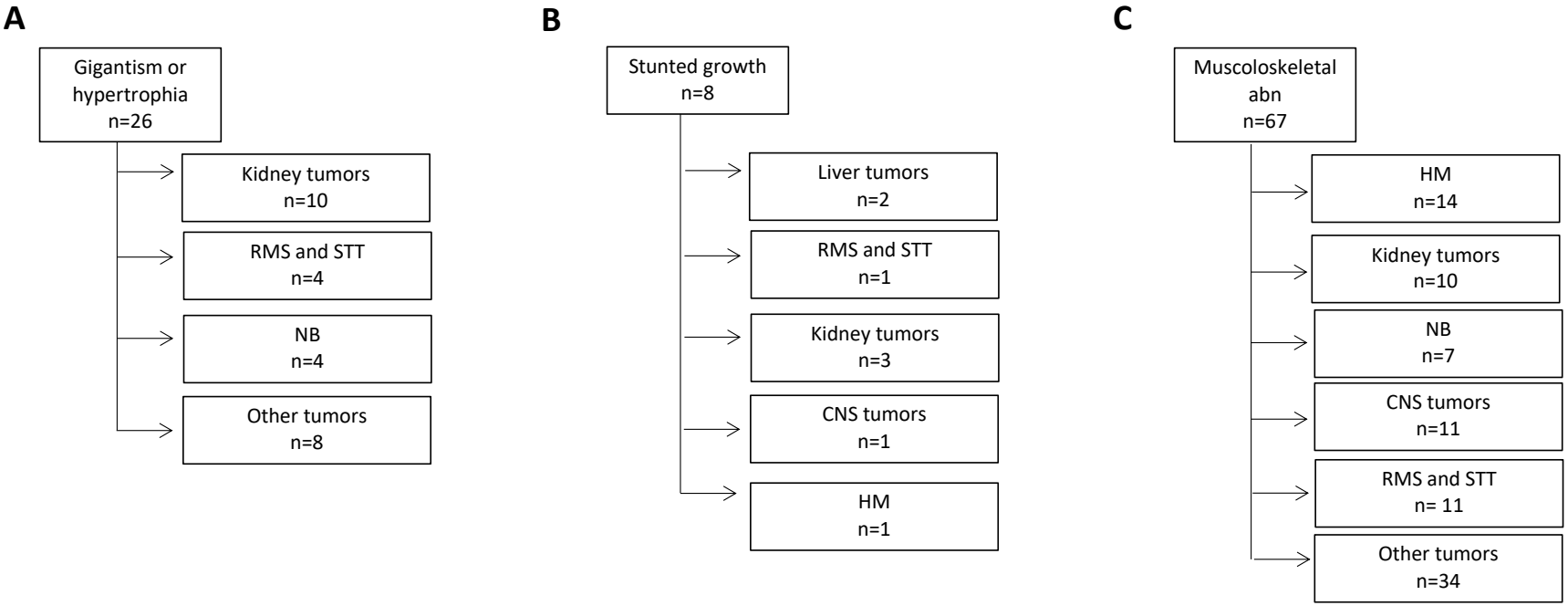








Supplemental Figure 2

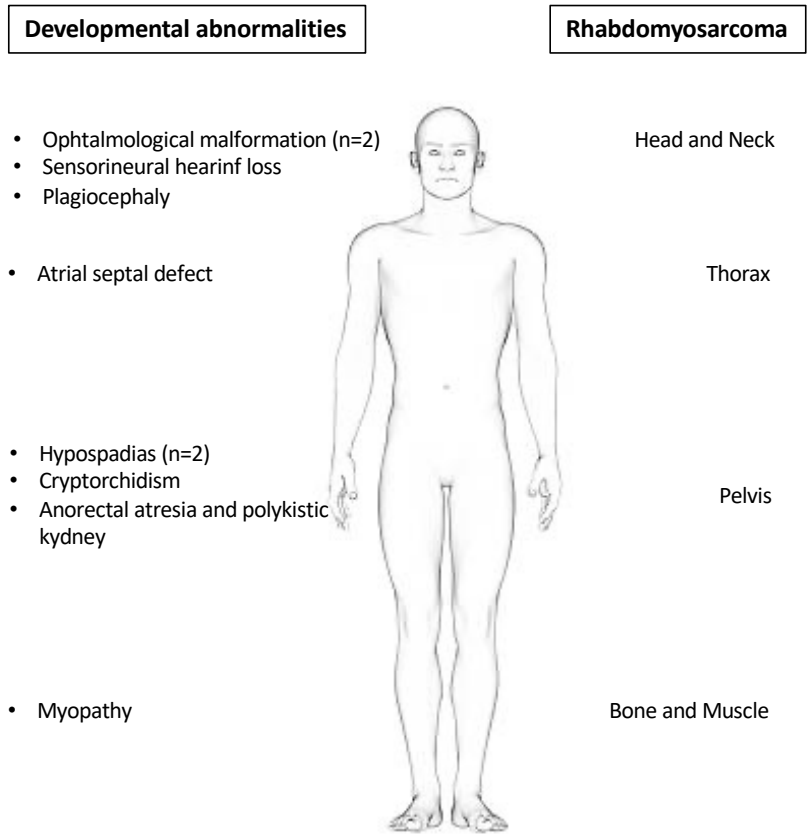


Supplemental Figure 3

A

Co-localisations		
WT	GU abnormalities	N=12
CNS tumor	Muscoloskeletal craniofacial disease	N= 11
Germ cell tumor	Genital or sacral disease	N=3
RB	Skull malformation	N=3
NB	GU abnormalities	N=9
RMS	Skull, thorax, muscle, pelvis	N=9

B



Supplemental Figure 4

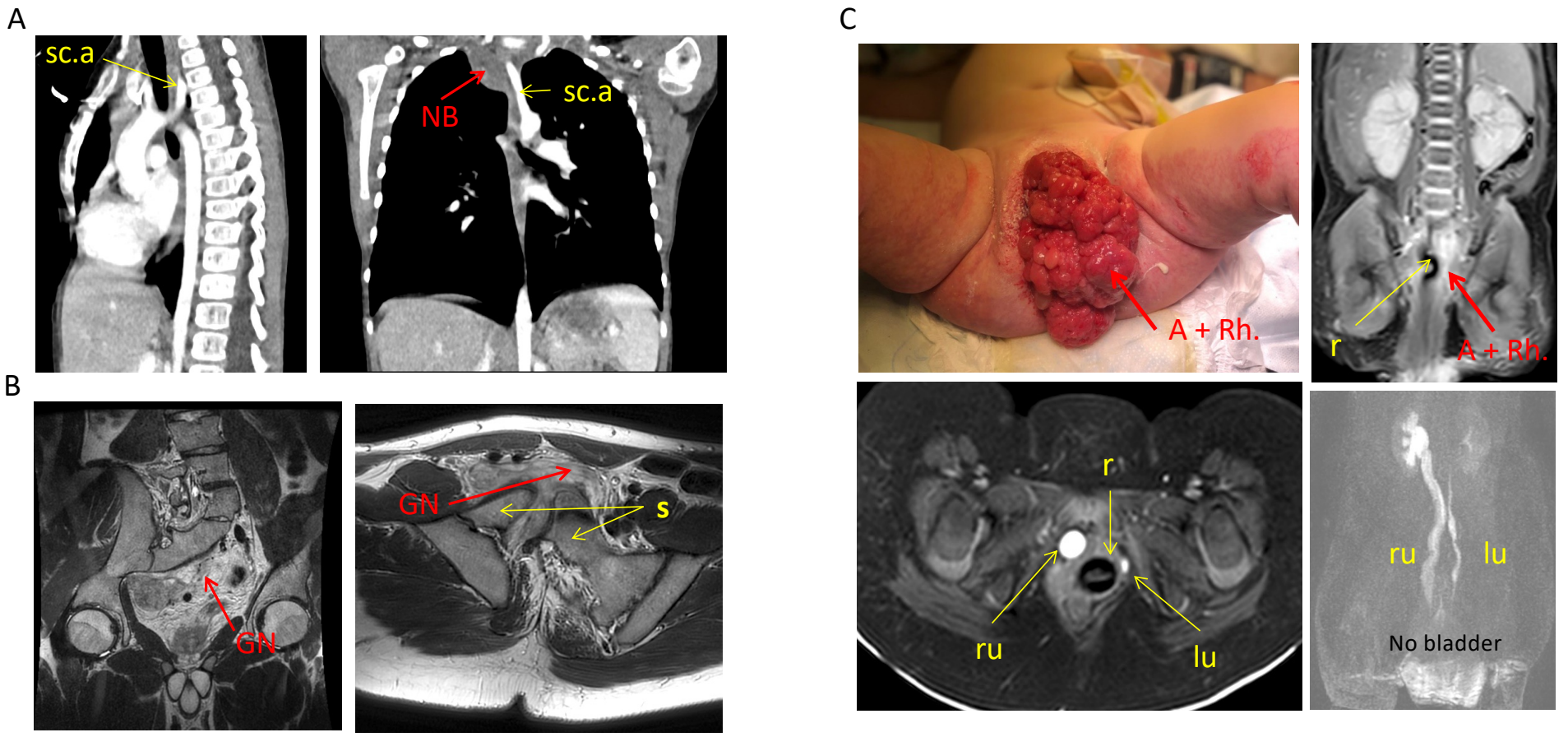


Figure 5

Conclusion and perspectives

- TED database is a unique French registry that collect children presenting cancer & developmental anomaly
- Biais do exist (nature of the collection, missing data…)
- Genetic counseling & recruitment improve during the study
- 70% of cases presented as unknown associations
- Mental and behaviour disorders & musculoskeletal anomalies appear as the most frequent reported anomalies
- In main instance colocalization of congenital anomalies and tumors
  - Genitourinary anomalies & Wilms / Neuroblastoma
  - Musculoskeletal anomalies & bone tumors / RMS
  - Hypothesis of mosaicim ?
- Future studies aim to focus on this hypothesis (EXOCARE- PREDCAP)

Why genetics may improve surgical management of pediatric cancer?

1. To identify genetic predisposition syndromes (germinal anomalies)
   - Genetic counseling
   - Specific modality treatments (risk of recurrence, others cancers, radiosensitivity…)

Tumors that should lead to suspect a genetic predisposition to cancer

Retinoblastoma	(RB1)
Wilms Tumor	(11p13,11p15…)
Adrenocortical carcinoma	(11p15, p53…)
Pancreatoblastoma	(WT1)
Pleuropneumoblastoma	(DICER1)
Sertoli-Leydig cell tumor	(DICER1)
Germinal cell Tumor	(Sd de Klinefelter, Turner…)
Neuroblastoma	(ALK, Phox2b…)
ATR/Rhabdoïd tumors	(SMARCB1/ INI1)
Medulloblastoma	(SUFU)
Medullary thyroid cancer	(RET)

……

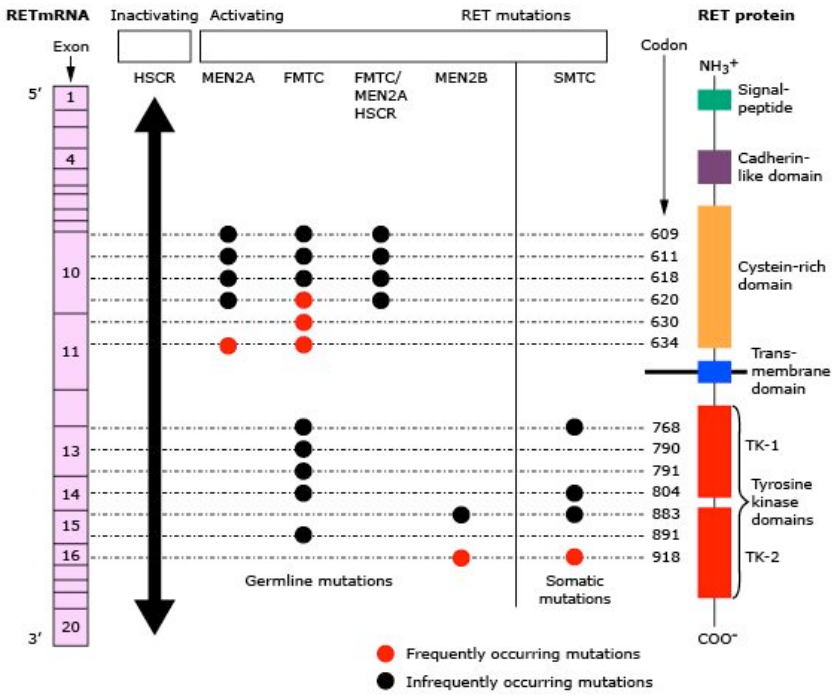
Genetic predisposition syndromes without developmental anomalies

Syndrome	Associated genes
Familial Retinoblastoma	RB1
Li-Fraumeni	TP53
Familial adenomatous polyposis	APC
Constitutional mismatch repair deficiency (CMMRD)	biallelic germline mutations of MMR genes (MLH1,MSH2,MSH6, PMS1,PMS2)
Von Hippel Lindau	VHL
Cowden	PTEN
Medullary thyroid carcinoma, Men2a	RET
DICER 1 predisposition Sd	DICER 1
Rhabdoid tumor (RT) syndrome	SMARCB1 (SMARCA4)
Medulloblastoma predisposition	SUFU

Dominantly inheredited

Medullary thyroid carcinoma genetics
RET gene mutations

- Men 2a
  - MTC (100%)
  - Pheochromocytoma (50%)
  - Primary hyperparathyroidy (5-20%)
- Men 2b
  - MTC (100%)
  - Pheochromocytoma (50%)
  - Marfanoid phenotype
  - ganglioneuromatosis
- Familiar MTC
- 50% of sporadic MTC



Genotype-phenotype correlations as a guideline for prophylactic thyroidectomy

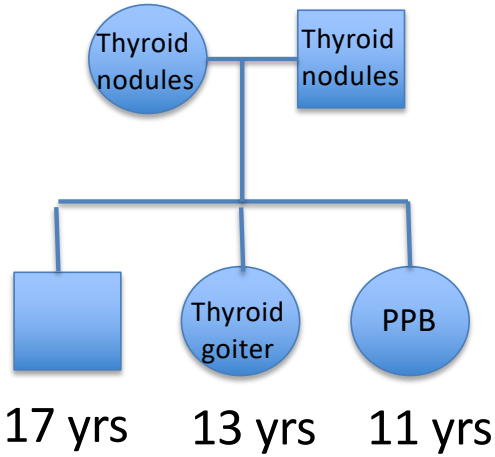
Table 2 - Management of patients with different *RET* mutations (4).

Characteristic/management	Codons 321, 515, 533, 600, 603, 606, 635, 649, 666, 768, 776, 790, 791, 804, 819, 833, 844, 861, 891, 912	Codons 609, 611, 618, 620, 630, 631	Codon 634	Codons 918, 883
ATA risk level (2009)[a]	A	B	C	D
MEN2 subtype	FMTC	FMTC/MEN2A	MEN2A	MEN2B
MTC aggressiveness	Moderate	High	Higher	Highest
MTC age of onset	Adults	5 years	Before the age of 5 years	First year of life
Timing of prophylactic thyroidectomy	When calcitonin rises/age 5 or 10 years	5 years	Before the age of 5 years	First months of life
Screening for Pheo	Start at 20 years, periodically	Start at 20 years, annually	Start at 8 years, annually	Start at 8 years, annually
Screening for HPT	Start at 20 years, periodically	Start at 20 years, periodically	Start at 8 years, annually	-

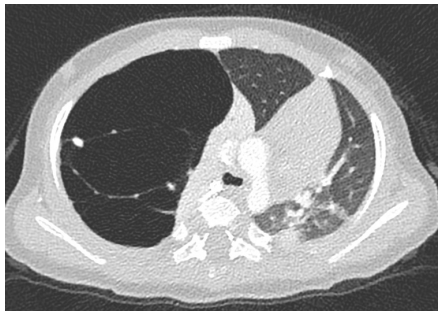
ATA: American Thyroid Association. FMTC: familial medullary thyroid carcinoma. HPT: primary hyperparathyroidism. MTC: medullary thyroid carcinoma. Pheo: pheochromocytoma.
[a]Risk for aggressive MTC; level D is the highest risk (4).

Brandi ML, J Clin Endocrinol Metab 2001
Szinnai G, Endoc Dev 2007
Raue E et al, Clinics 2012

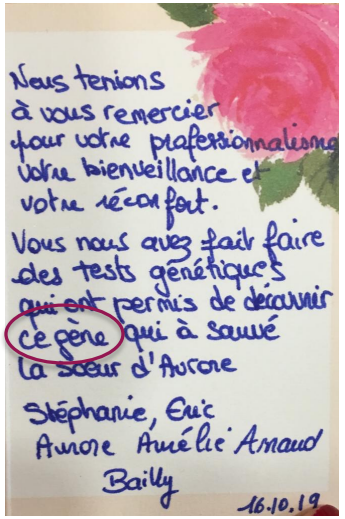
Aurore, female 13 years old
Diagnosis of huge multinodular goiter
Familial history of benign thyroid disease
Systematic screening for DICER1 mutation



Early diagnosis: conservative treatment



- Upfront surgery
- RO
- No additional treatment

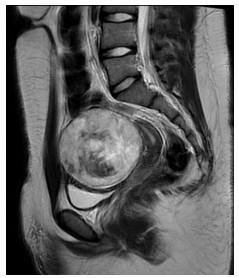


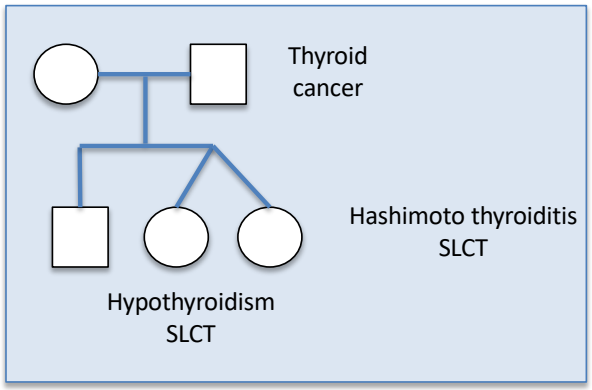
Journal of Pediatric Urology (2016) 12, 5–10

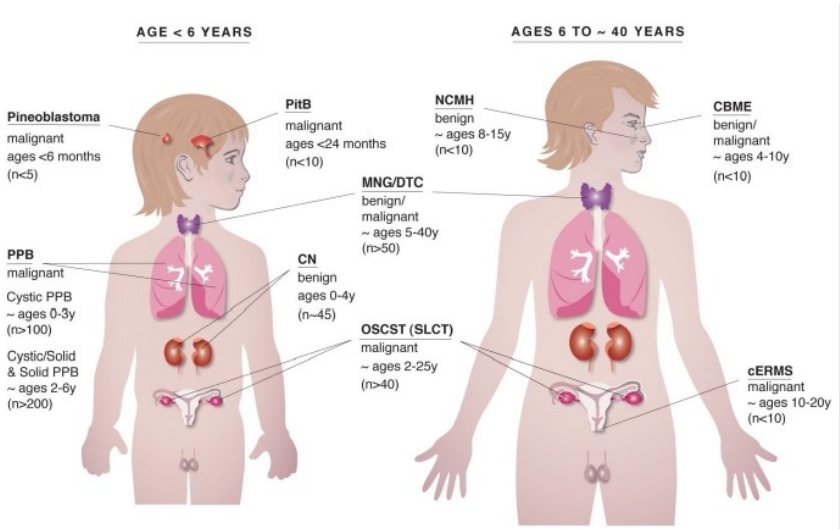
Review article

DICER1 pleuropulmonary blastoma familial tumour predisposition syndrome: What the paediatric urologist needs to know

Alice Faure [a], John Atkinson [a], Aurore Bouty [a], Mike O'Brien [a], Guillaume Levard [b], John Hutson [a,c,d], Yves Heloury [a]







Choong CS et al, Trends Mol Med, 2012

Faure A et al, J Pediatr Urol 2016
Schulte KAP et al, Clin Cancer Res, 2018

Why genetics may improve surgical management of pediatric cancer?

1. To identify genetic predisposition syndromes (germinal anomalies)
   - Genetic counseling
   - Specific modality treatments (risk of recurrence, others cancers, radiosensitivity…)
2. To identify tumoral genetic anomalies for improving
   - Diagnosis of cancer type (molecular signature)
   - Prognosis: personalized medicine
   - Treatment: targeted therapies

Pediatric cancer and genetic

somatic genetic alterations: diagnosis and prognosis

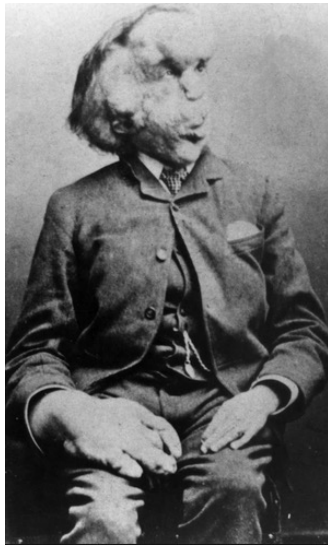
- Ewing : EWS/FL1
- Alveolar rhabdomyosarcoma: PAX3 ou PAX7/FKRH
- Synovialosarcoma: SYT/SSX1 ou SSX2 ou SSX4
- Desmoplastic Round cell Tumor (DRCT): EWS/WT1
- Infantile congenital fibrosarcoma: ETV6/NTRK3
- Myxoïd liposarcoma: TLS ou EWS/CHOP
- Myxoïd chondrosarcoma EWS ou TAF68 ou TCF12/TEC
- Soft tissue melanoma: EXS/ATF
- Anaplastic lymphoma : NPM ou TM30ou TFG ou ATIC/ALK
- Soft tissue alveolar sarcoma: ASPL/TFE3
- Middle line sarcoma (NUT): BRD4/NUT
- …….

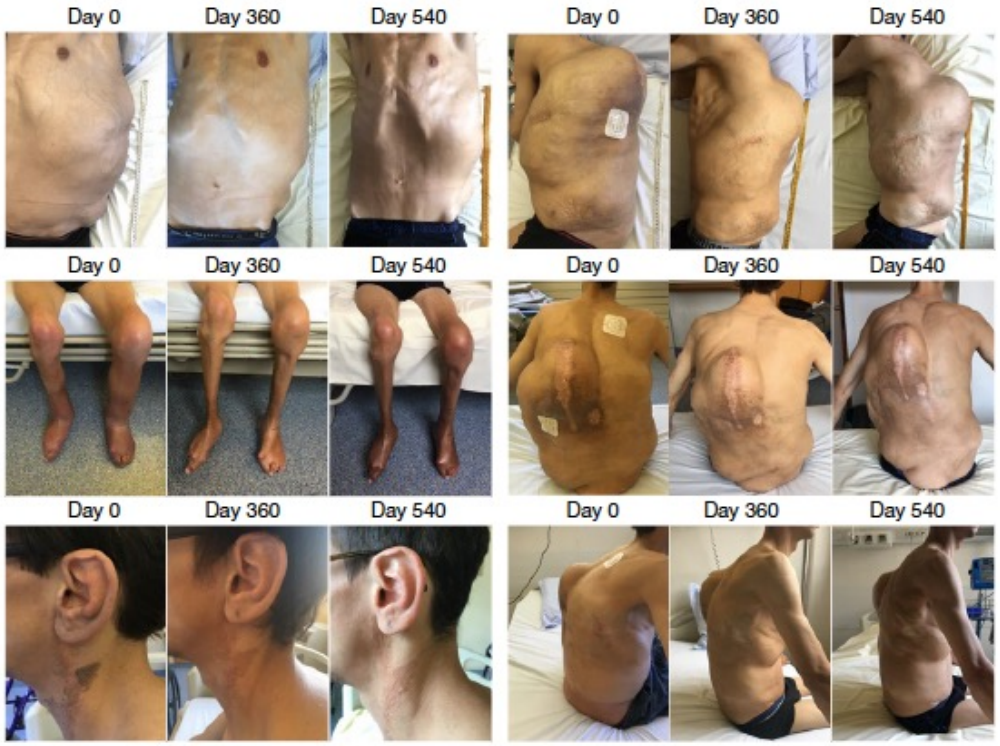
ARTICLE

https://doi.org/10.1038/s41586-018-0217-9

Targeted therapy in patients with PIK3CA–related overgrowth syndrome

Quitterie Venot[1], Thomas Blanc[1,2,3,21], Smail Hadj Rabia[2,4,5,21], Laureline Berteloot[5,6], Sophia Ladraa[1], Jean-Paul Duong[2,7], Estelle Blanc[8], Simon C. Johnson[9], Clément Hoguin[1], Olivia Boccara[4], Sabine Sarnacki[2,3], Nathalie Boddaert[2,5,6], Stephanie Pannier[2,10], Frank Martinez[11], Sato Magassa[1], Junna Yamaguchi[1], Bertrand Knebelmann[1,2,11], Pierre Merville[12,13], Nicolas Grenier[14], Dominique Joly[1,2,11], Valérie Cormier-Daire[2,5,15], Caroline Michot[2,5,15], Christine Bole-Feysot[5], Arnaud Picard[2,16], Véronique Soupre[16], Stanislas Lyonnet[2,5,1]
Cécile Laroche-Raynaud[18], Laurent Guibeud[19], Christine Bro
Fabiola Terzi[1,2] & Guillaume Canaud[1,2,11]*





Merci à tous mes collègues

Necker

Y.Aigrain
Y.Heloury
C.Chardot
C.Capito
H.Lottmann
T.Blanc
N.Khen
V.Rousseau
S.Beaudoin
N.Botto
C.Cretolle

institutCurie
Ensemble, prenons le cancer de vitesse.

F.Doz
D.Orbach
G.Schleiermacher
F.Bourdeaut
H.Pacquement
I.Aerts
H.Brisse
C.Cordero
A.Leruste
Y.Bouchoucha

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

D.Valteau-Couannet
L.Brugières
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V.Minard
C.Pasqualini
C.Dufour
N.Gaspard
B.Fresneau
P.Berlanga
L.Guerrini

Aux patients et à leurs familles