PROJET PILOTE NATIONAL « ANDDI-PRENATOME » D'EXOME EN DIAGNOSTIC PRÉNATAL

Dr Frédéric Tran Mau-Them
CHU Diion

CPDPN - Rennes

Rennes, le 14 Octobre 2022

UN ENJEUR MAJEUR EN PERIODE PRENATALE

- Anomalies à l'échographie = 5-10%

  Causes multiples: infectieuses, ischémiques, génétiques…

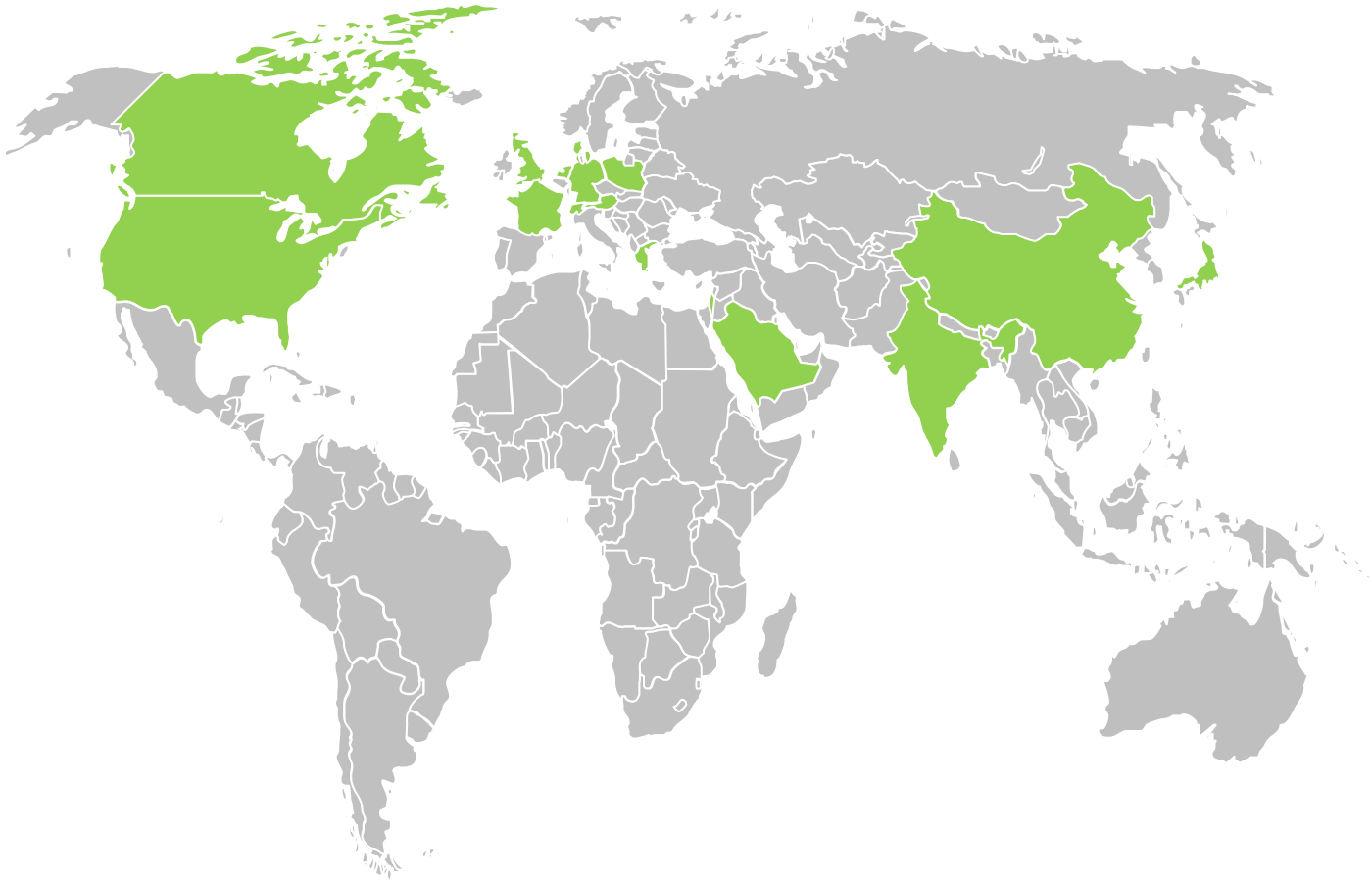
- Diagnostic
  - Non invasif : imageries, DPNI
  - Invasif : PVC, PLA, PSF

    Biochimie, microbiologie, cytogénétique, moléculaire…

- Projets internationaux de DPN maladies rares

  Taux diagnostique très variable
  - Cohorte hétérogène
  - Base moléculaire des phénotypes extrêmes

TAUX DIAGNOSTIC et DELAIS VARIABLES



Taux diagnostique variable = 5–89 %

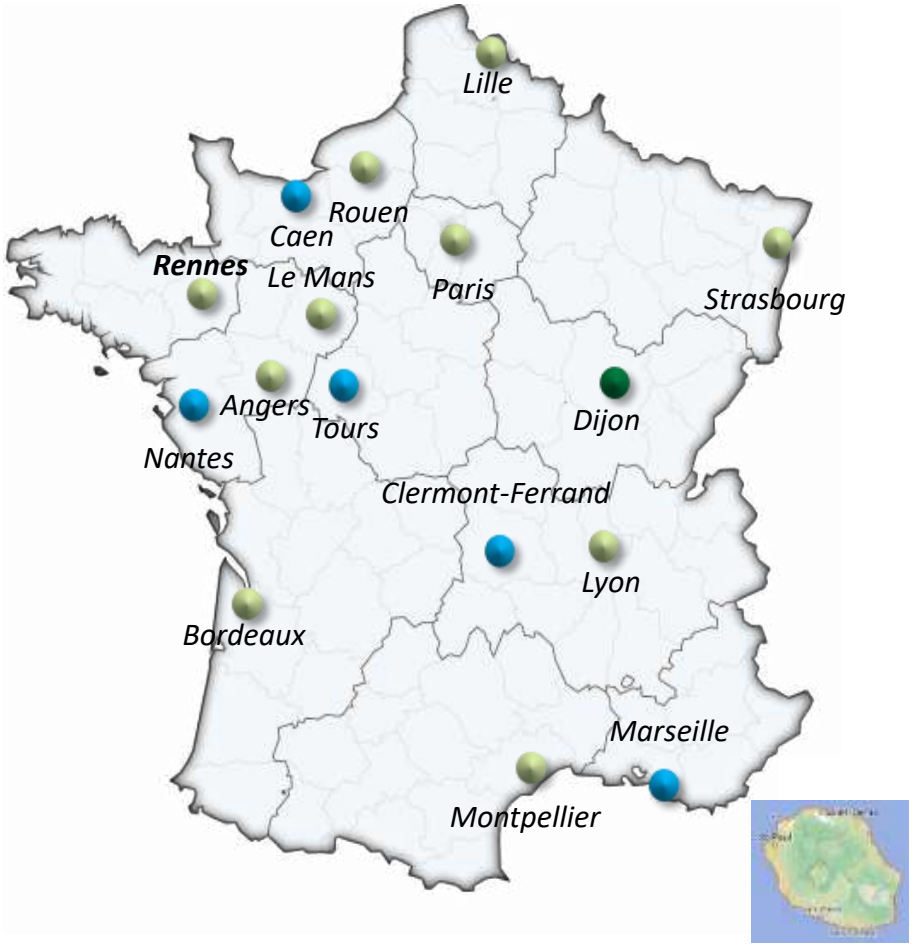
Taux diagnostique médian = 27.6 %

Délais variable = 4–365 jours

Délai médian = 17 jours

PROJET NATIONAL AnDDI-PRENATOME (2019-2021)

19 centres inclueurs
150 couples



Critères d'inclusion

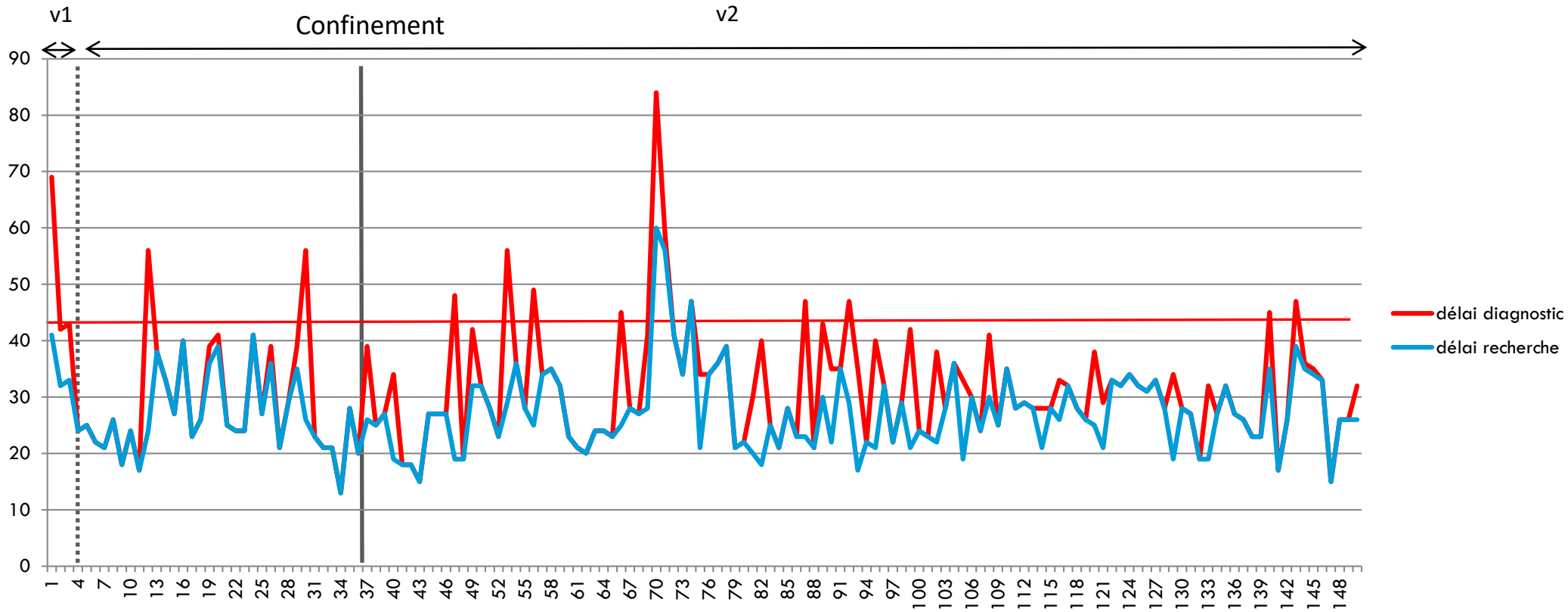
- Grossesses 10-34 SA
- 2 anomalies à l'échographie fœtale
  - 2 malformations majeures
  - 1 malformation majeure + 1 malformation mineure
  - 1 malformation isolée + forte suspicion génétique
- Quantité suffisante de LA / sang fœtal
- Exome trio

Objectifs

- Faisabilité
  - Rendre un résultat **d'exome**
  - **Rapide**
  - En **situation de DPN**
- Délai de rendu
  - 5 à 6 semaines
  - 35 à 42 jours ouvrés
  - **J0 = prélèvement**

UN DELAI MAXIMAL CIBLE ATTEINT, MAIS…

Délai de 5-6 semaines (35-42 jours)

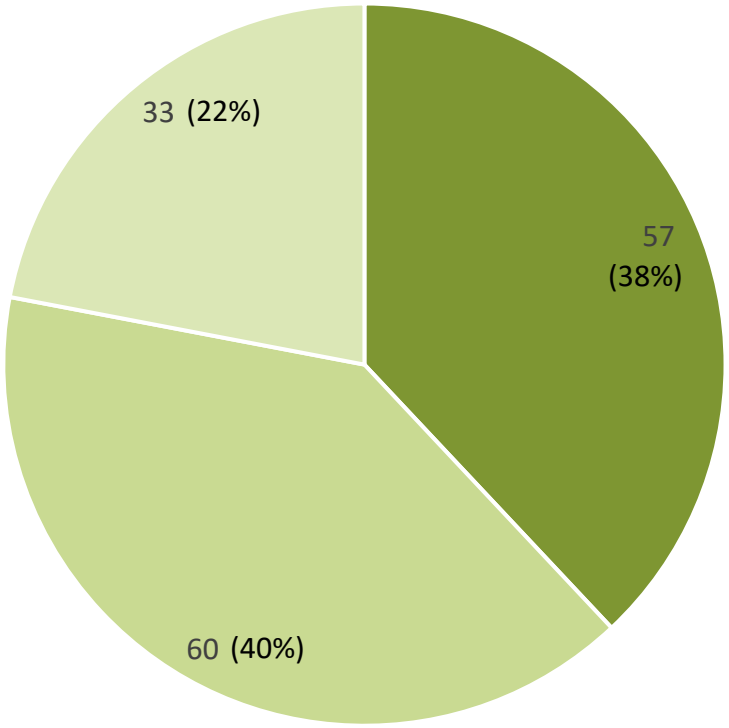


Délai médian CR total

Avant validation = 26 jours

Après validation = 39 jours

CARACTERISTIQUES CLINIQUES



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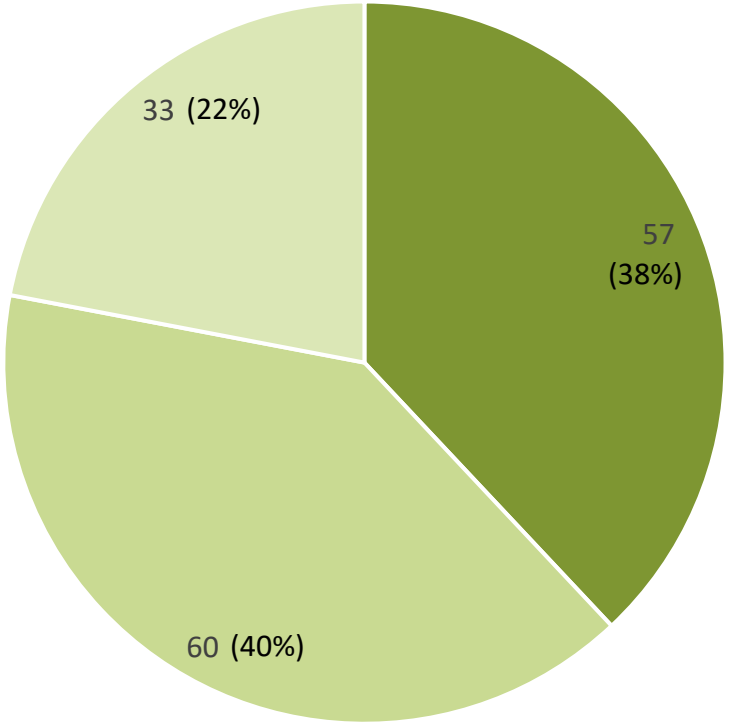
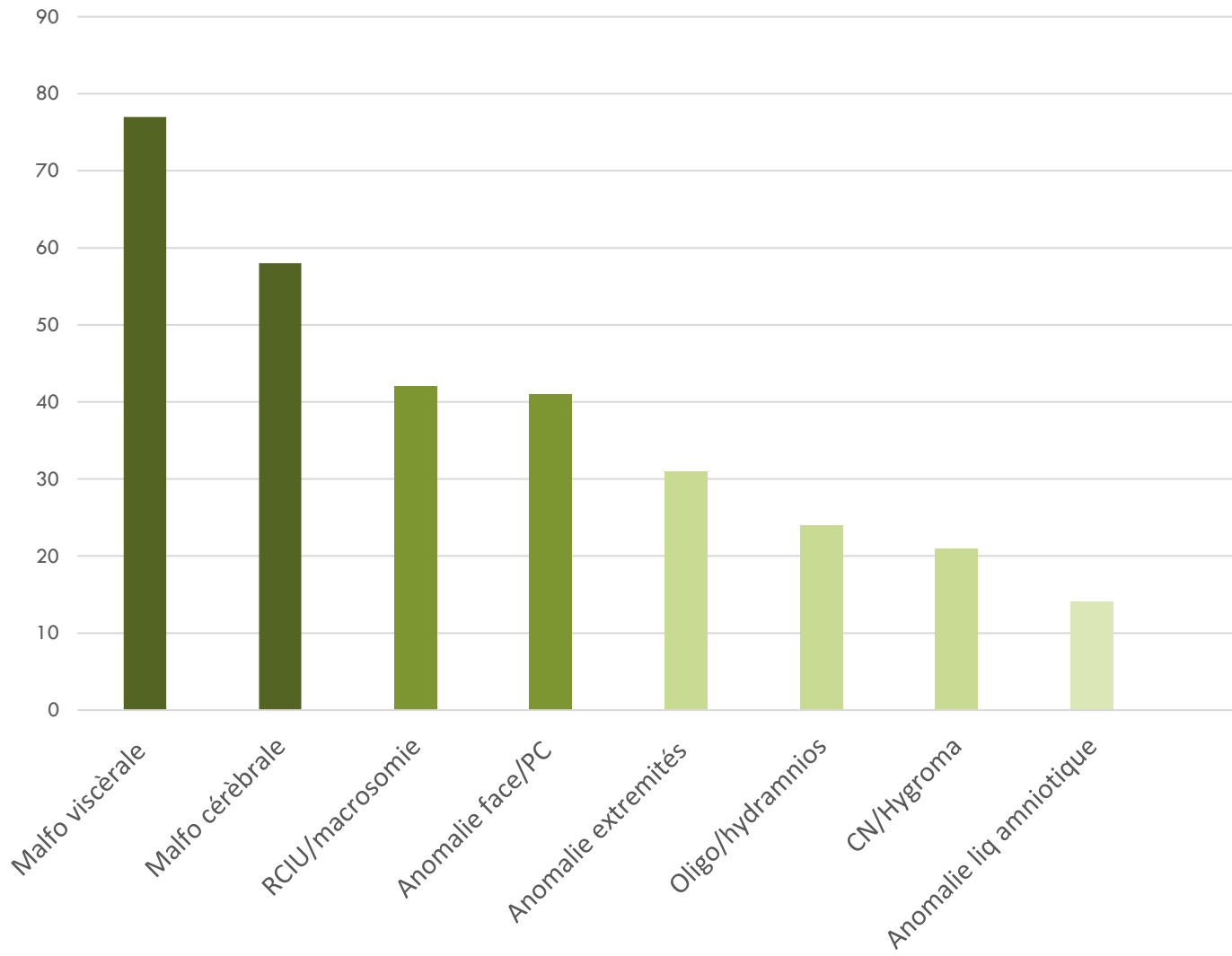
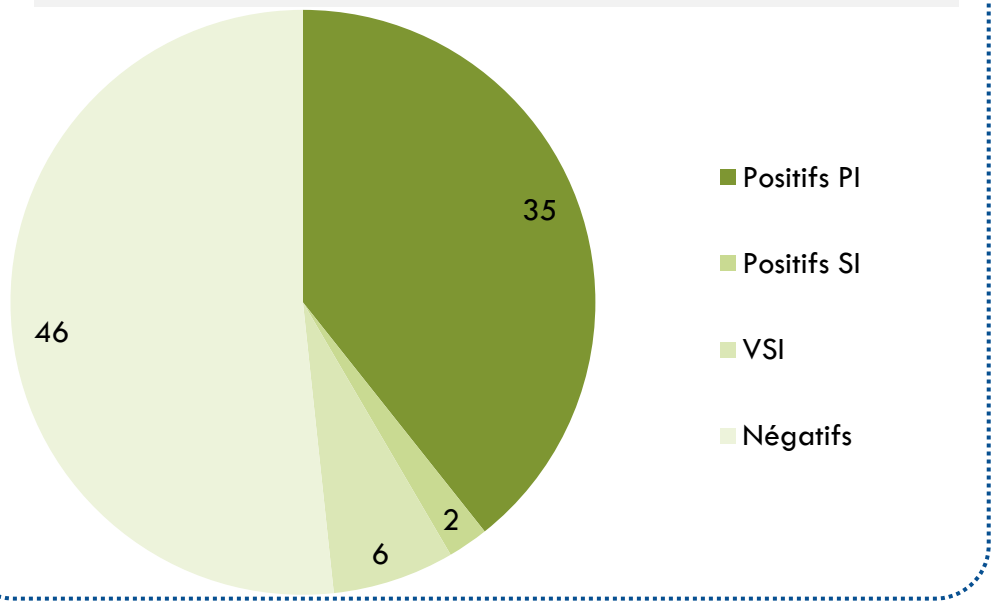


- 2 anomalies majeures
- 1 anomalie majeure et 1 mineure
- 1 anomalie et 1 forte suspicion génétique



UN TAUX DIAGNOSTIQUE SIMILAIRE AU POSTNATAL

EN PARALLELE ACPA (n= 89)



35/89 positifs d'emblée (40.5%)

- 31 SNV
- 9 CNV (100% concordance avec CGH)

2/89 positifs après analyse complémentaire (2,2%)

- 2 SNV (*EFEMP2, NUP188*)

6/89 VSI (6.7%)

- 4 SNV (*CUX1, DLL1, DNAH11, GREB1L*)
- 2 CNV (*BRD2*, del1q21.1)

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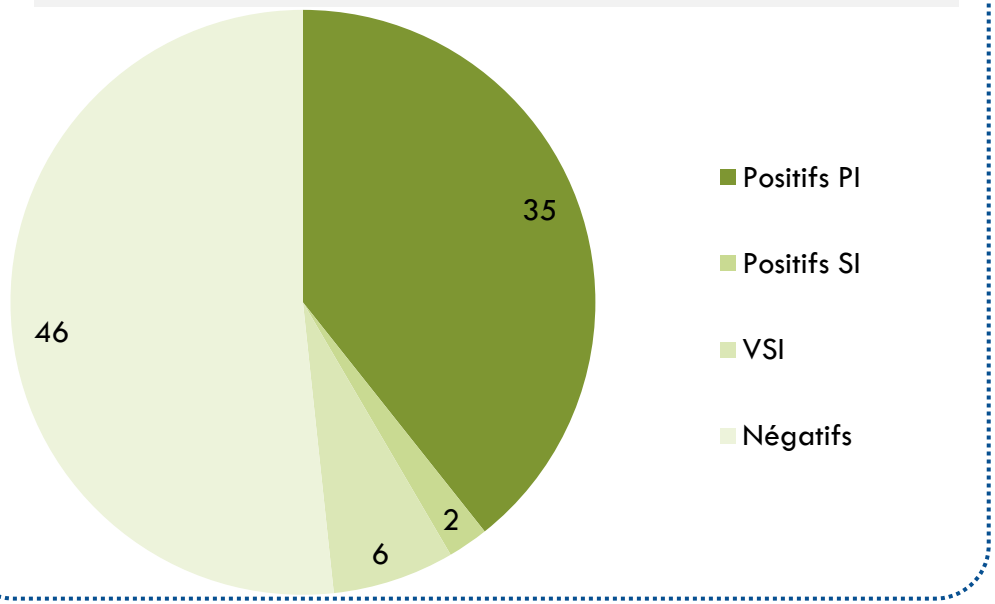

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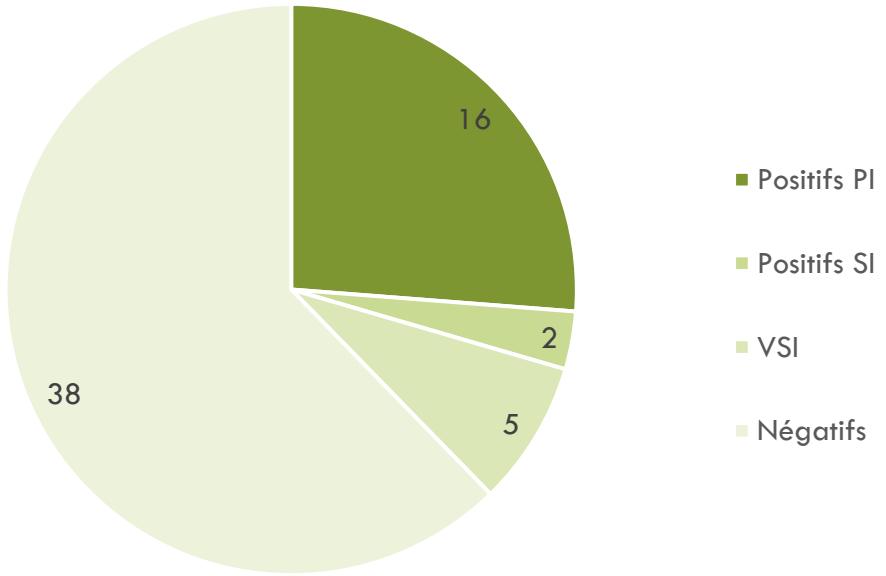
APRES ACPA (n = 61)



16/61 positifs première intention (26.2%)

- 19 SNV

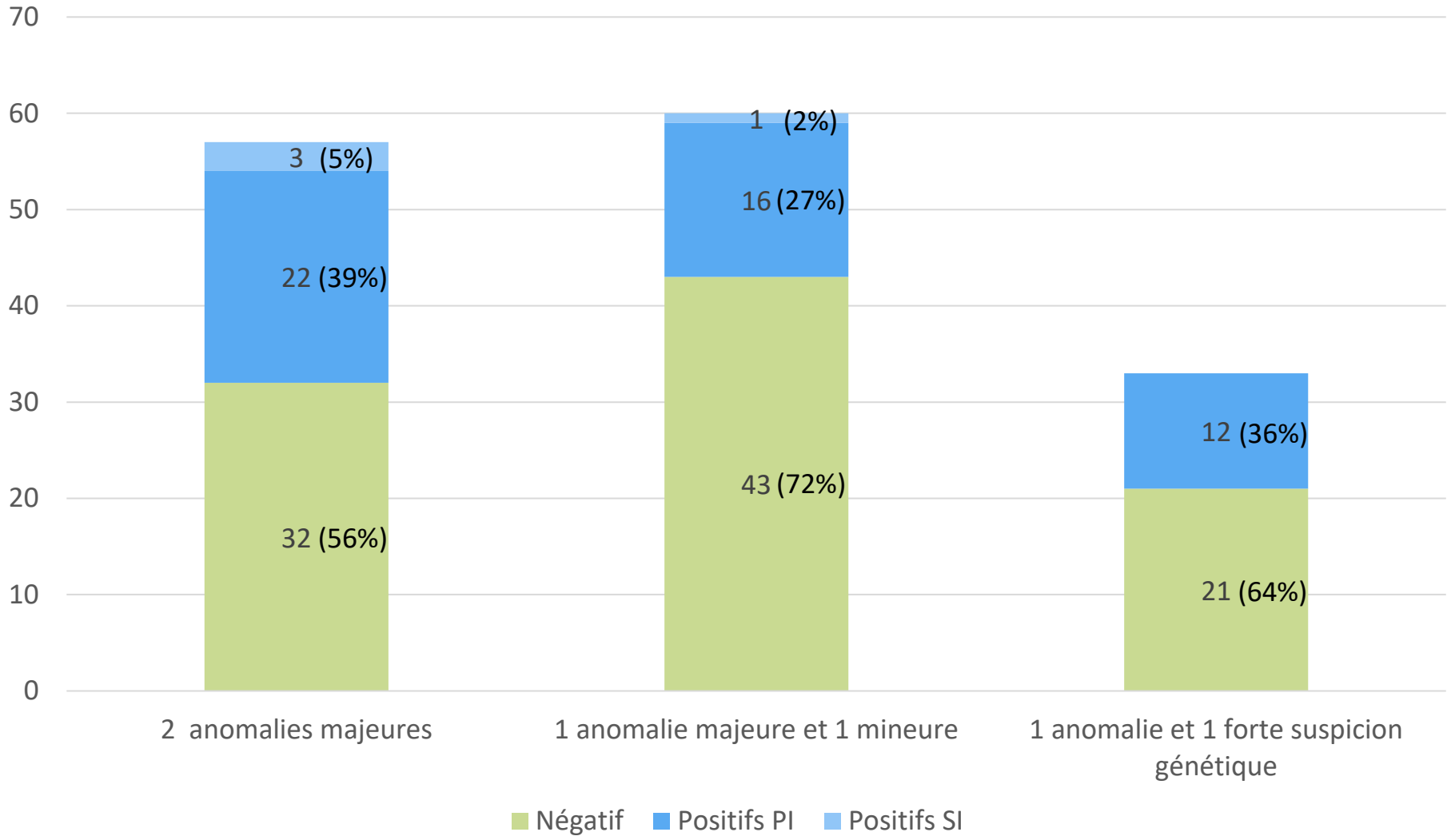
2/61 positifs après analyse complémentaire (3,3%)

- 2 SNV (*FGF8*, *MYCN*)

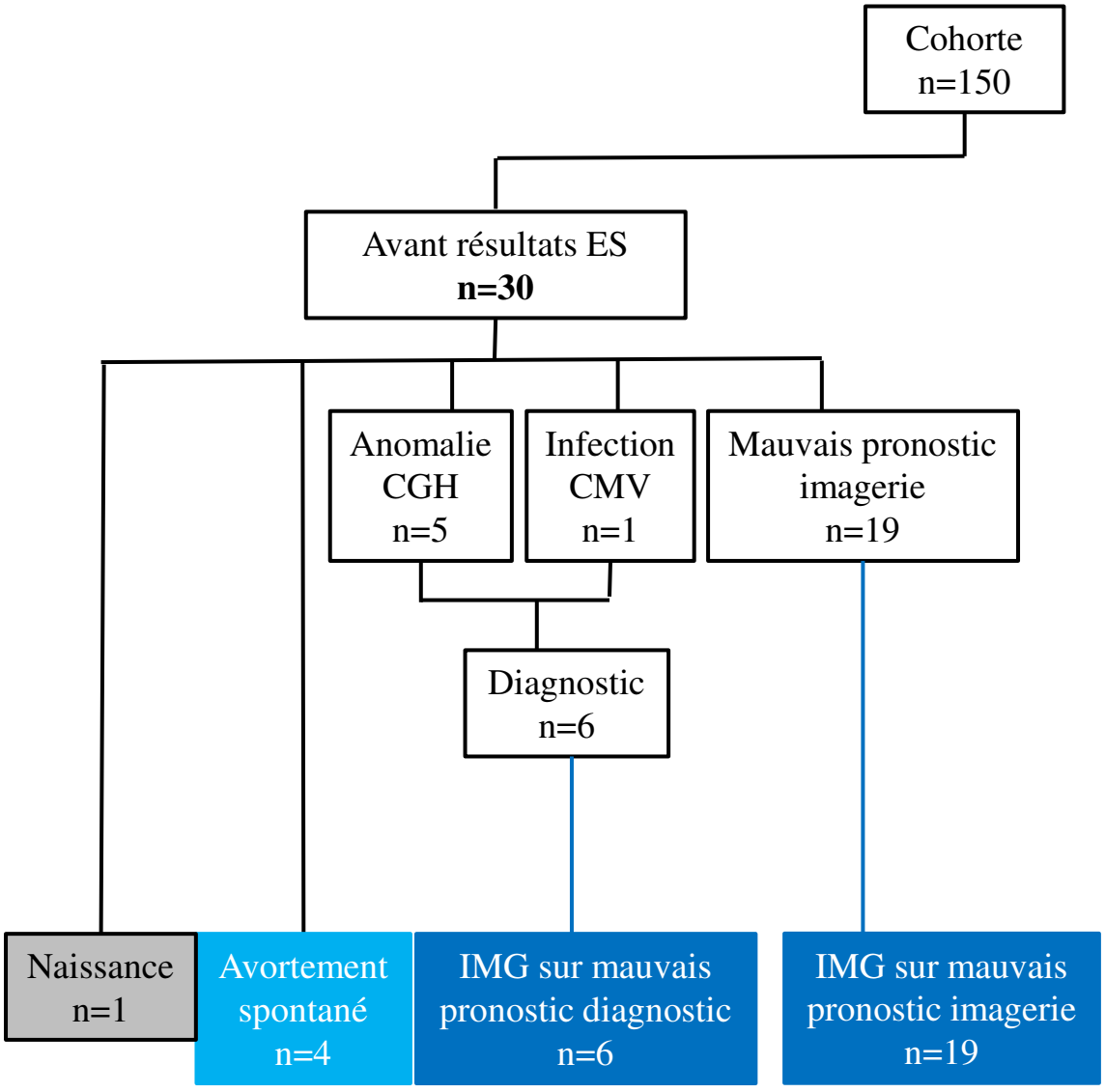
5/61 VSI (8,2%)

- 4 SNV (*KAT7, KMT2E, IDS, LZTR1*)
- 1 CNV (dup1q21)

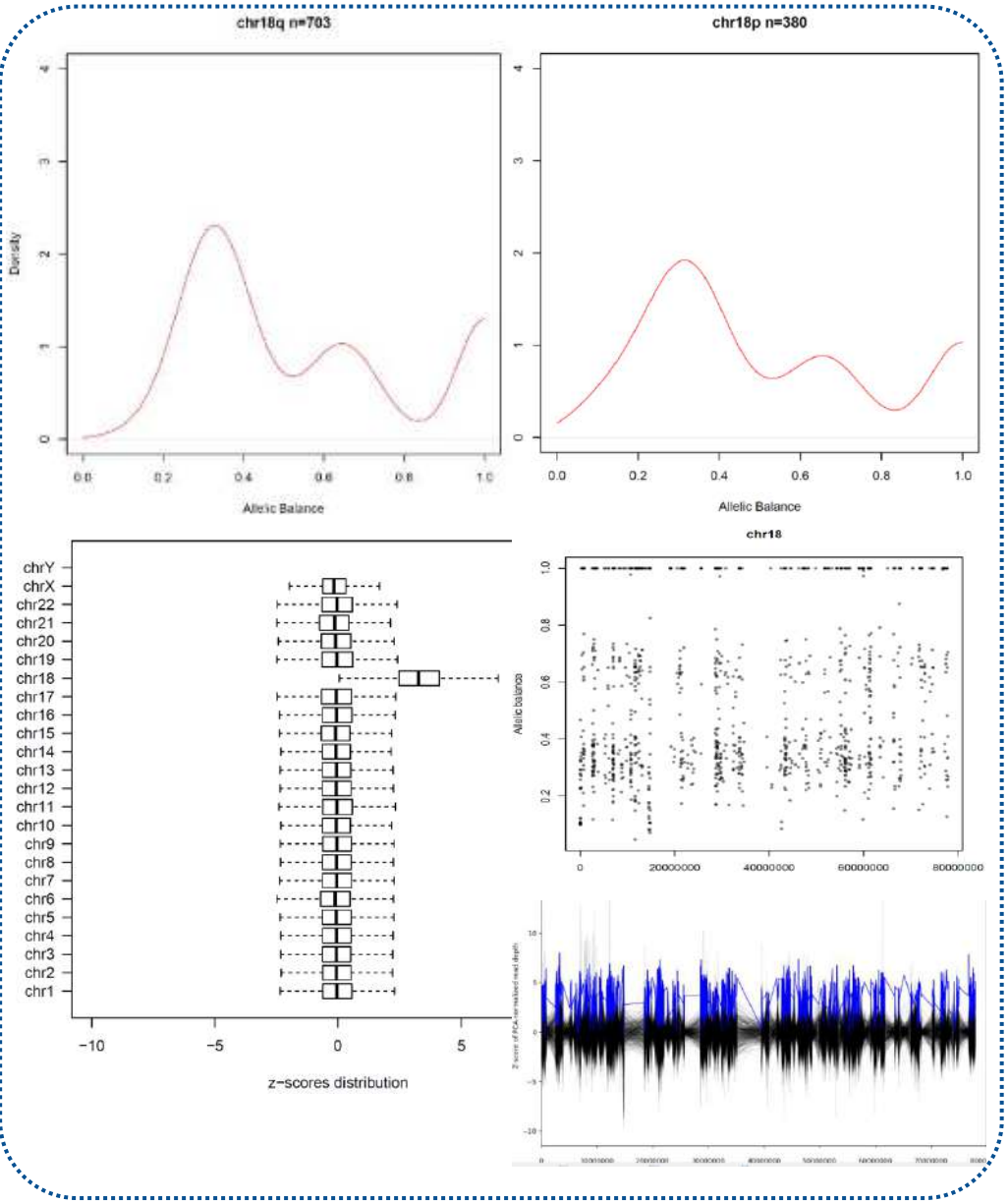
POSITIFS par INDICATION



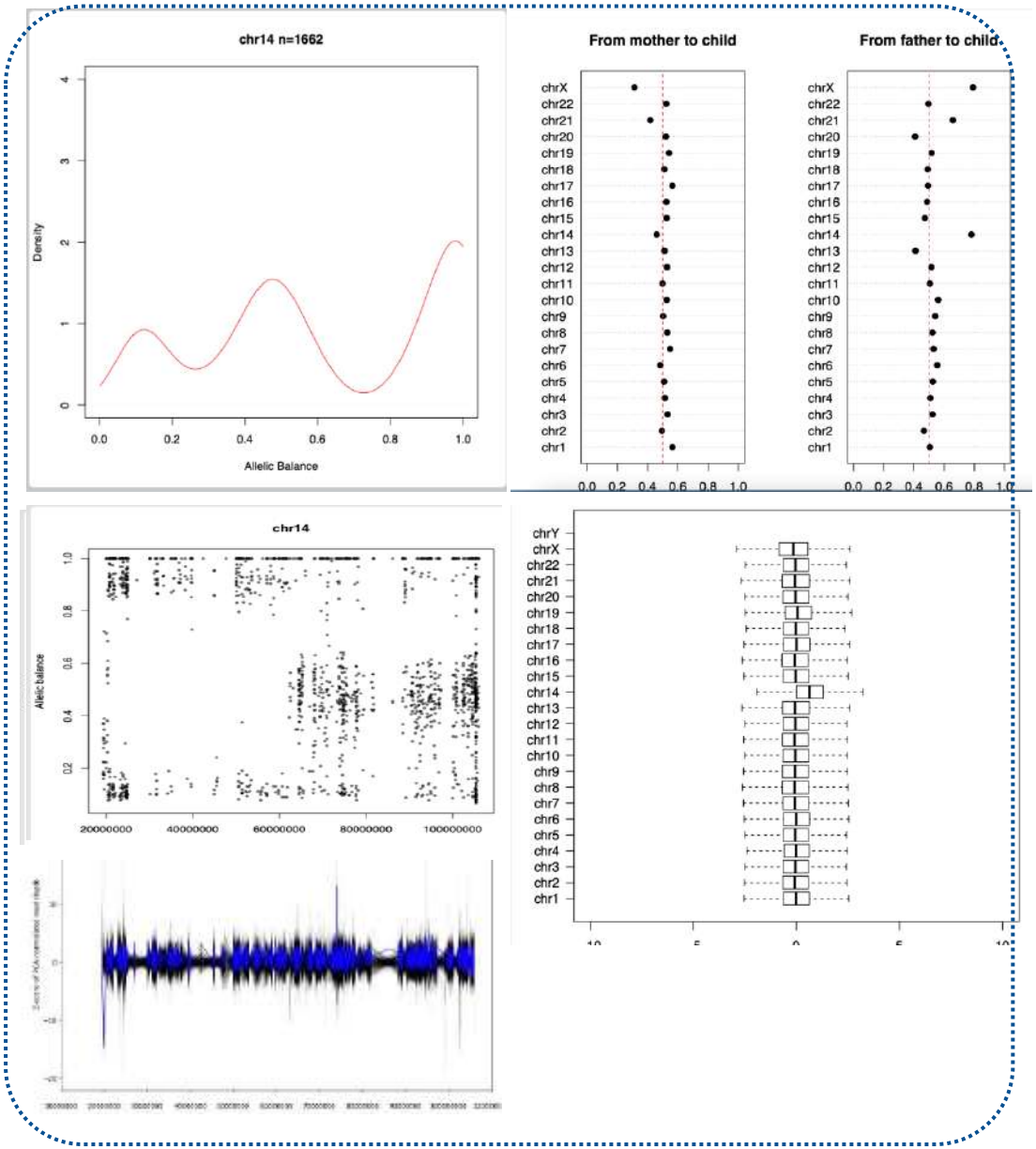
ISSUES de GROSSESSES



IMG **avant résultats : 83%**



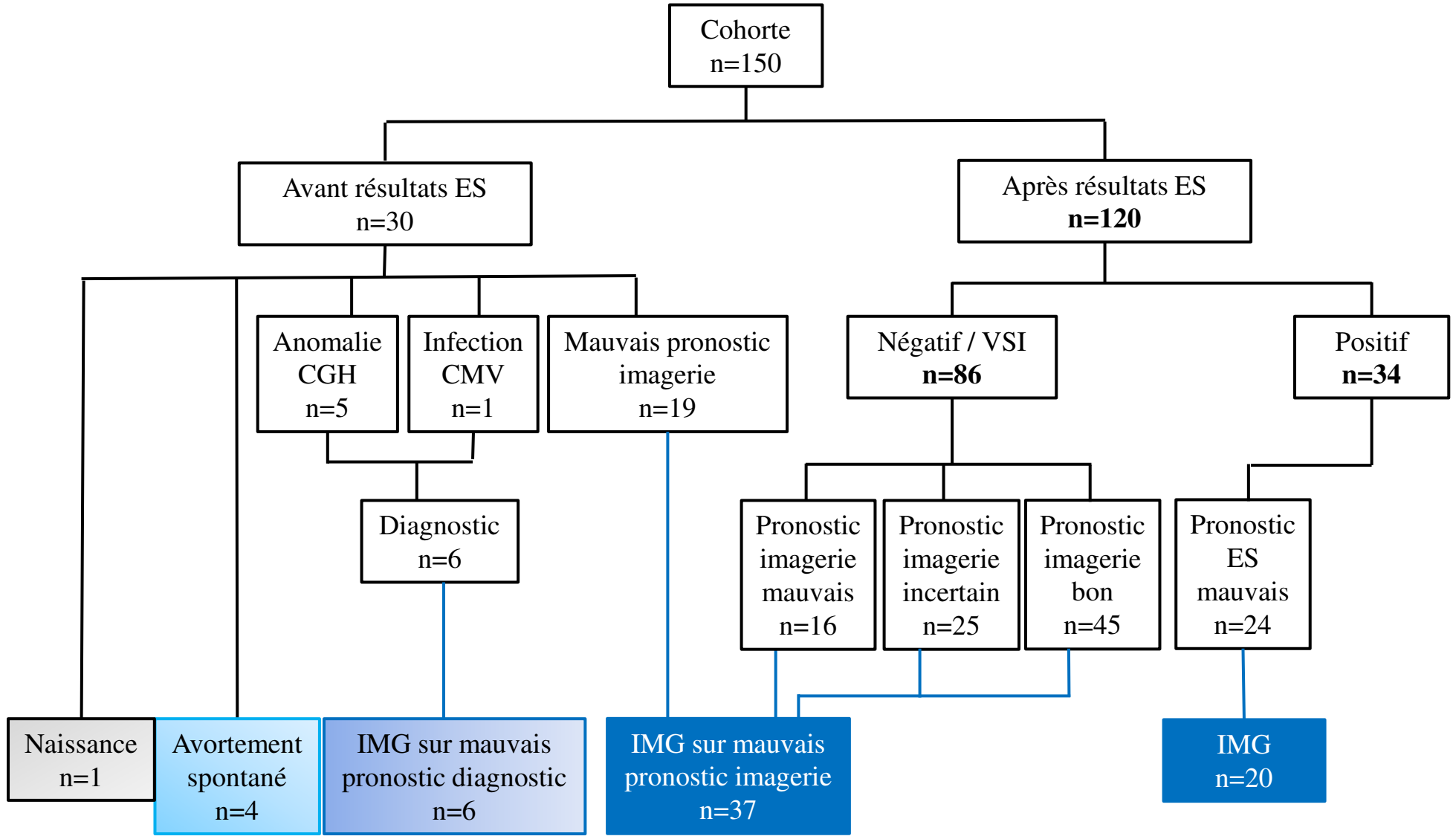
Trisomie du chromosome 18



Trisomie en mosaïque du chromosome 14

100% concordance entre exome et CGH pour la détection des CNV

ISSUES de GROSSESSES



IMG **après résultats - : 21%**

IMG **après résultats + : 59%**

- Echo 26+5 SA
  - Hypoplasie du corps calleux
  - Ventriculomégalie

Brain Dev. 2018 Sep;40(8):634-641. doi: 10.1016/j.braindev.2018.04.012. Epub 2018 May 23.

Neurodevelopmental outcomes in children with prenatally diagnosed corpus callosal abnormalities

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Dr Sébastien Moutton

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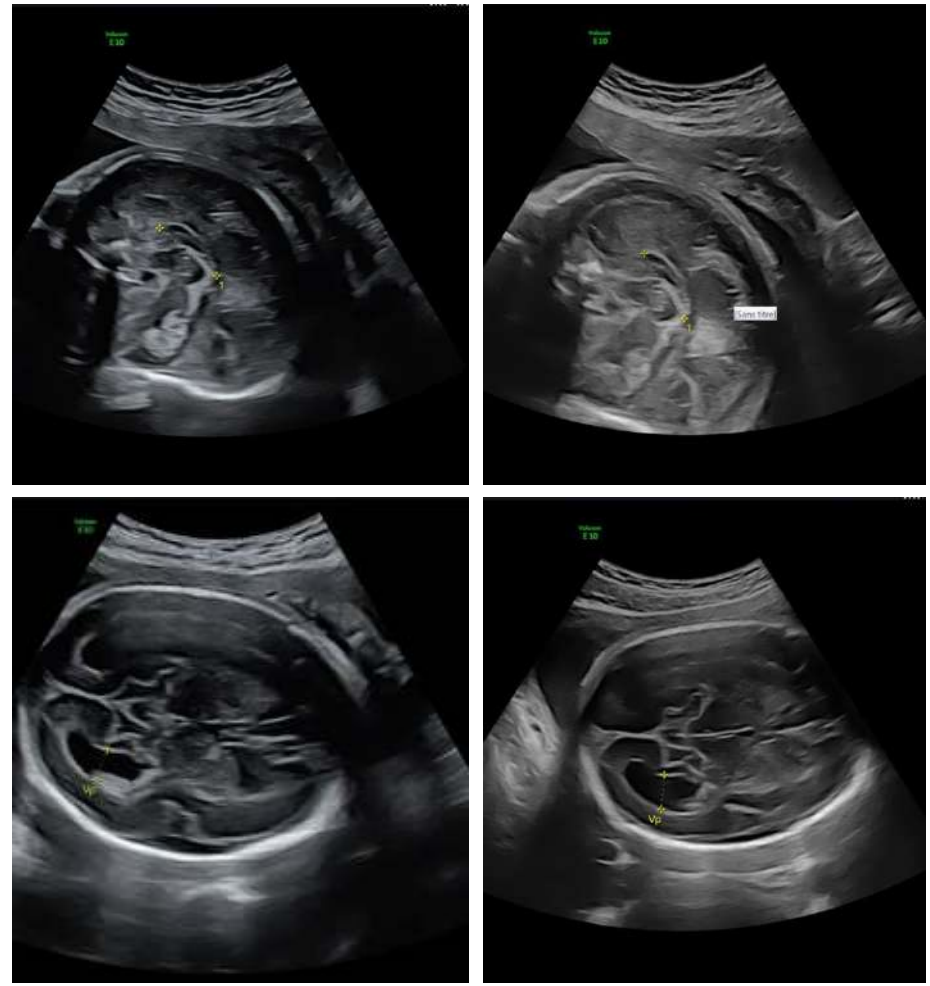

Variant ***L1CAM*** **hémizygote héritée**

LRG_14t1:c.719C>T; p.(Pro240Leu)

IMG après résultat ES

Gene-Phenotype Relationships

Location	Phenotype Clinical Synopses
Xq28	Corpus callosum, partial agenesis of
	CRASH syndrome
	Hydrocephalus due to aqueductal stenosis
	Hydrocephalus with congenital idiopathic intestinal pseudoobstruction
	Hydrocephalus with Hirschsprung disease
	MASA syndrome

- Echo 23 SA
  - Agénésie du corps calleux
  - Microcéphalie

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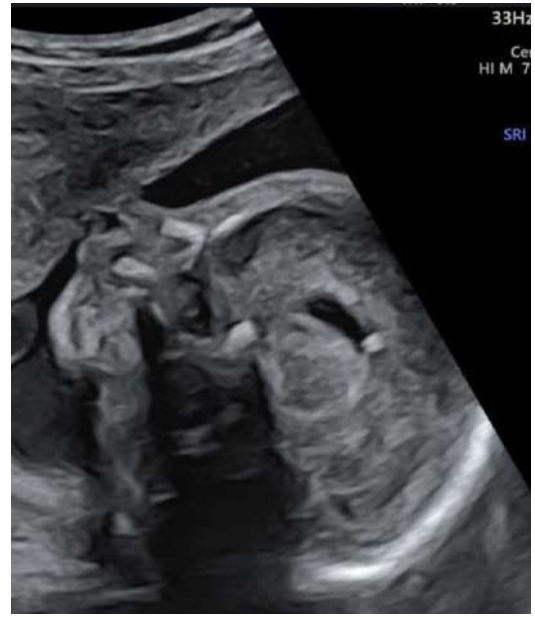

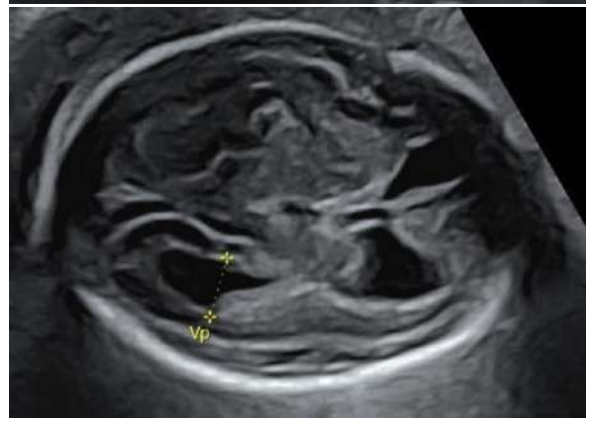

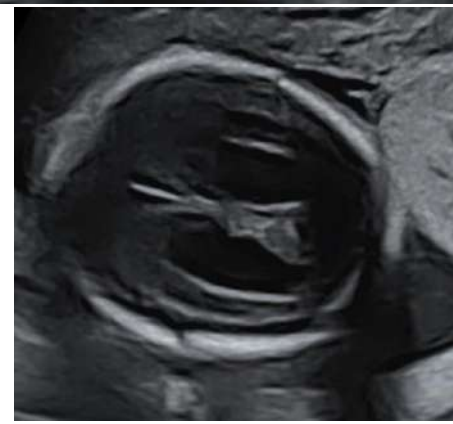

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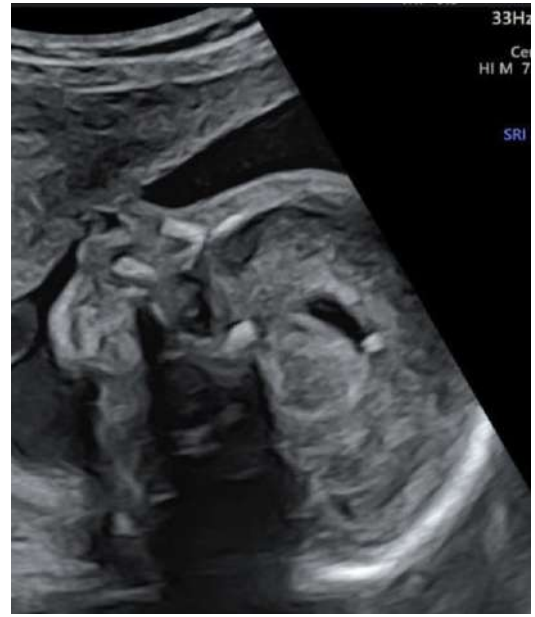
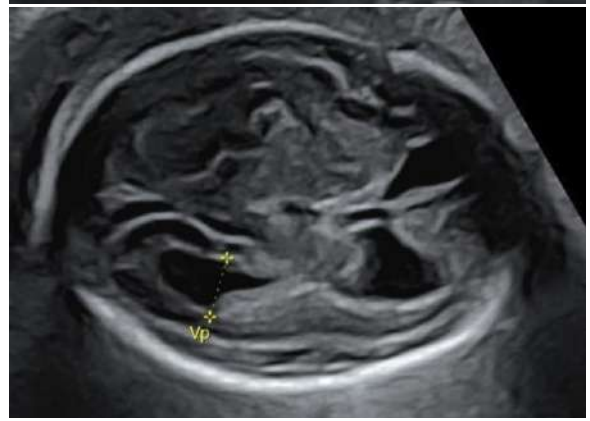
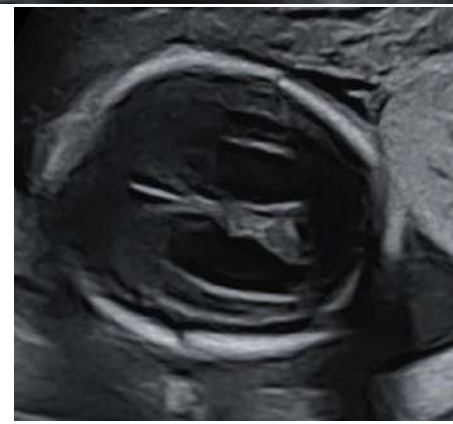






ES trio négatif

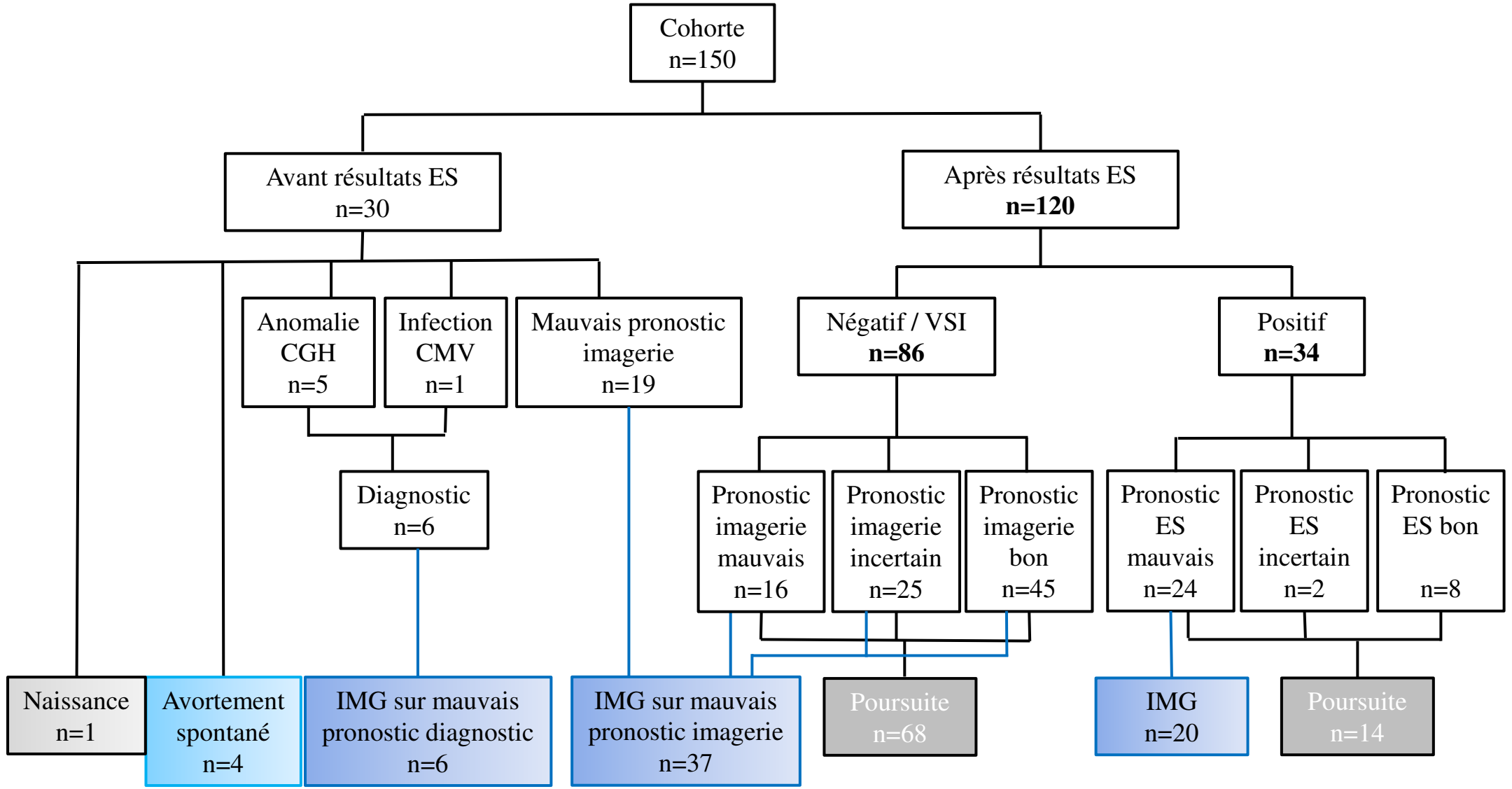
IRM cérébral 29 SA

Kyste septum pellucidum, retard de gyration

IMG après résultat imagerie

Dr Sébastien Moutton

ISSUES de GROSSESSES



Poursuite **après résultats - : 79%**

Poursuite **après résultats + : 41%**

- Taille mère: 155 cm
- Taille père: non communiqué
- Echo 32+5 SA:
  - Retard de croissance intra-utérin (2-10ème per)
  - Hypotélorisme

Dr Julian Delanne

- Taille mère: 155 cm
- Taille père: non communiqué
- Echo 32+5 SA:
  - Retard de croissance intra-utérin (2-10ème per)
  - Hypotélorisme

Variant *IGF1R* hétérozygote hérité

NM_000875.3:c.1906_1907dup; p.(Pro637Cysfs*6)

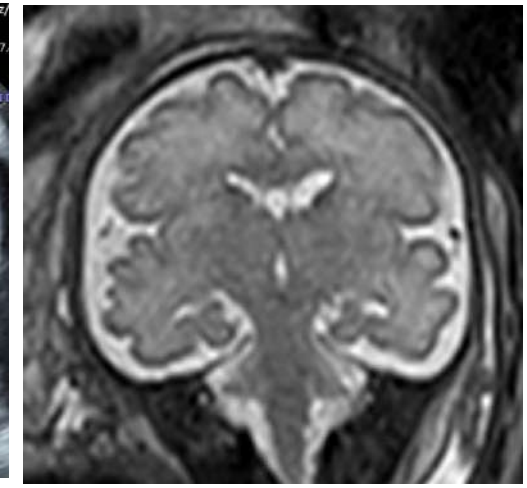
IGF1R Variants in Patients With Growth Impairment: Four Novel Variants and Genotype-Phenotype Correlations

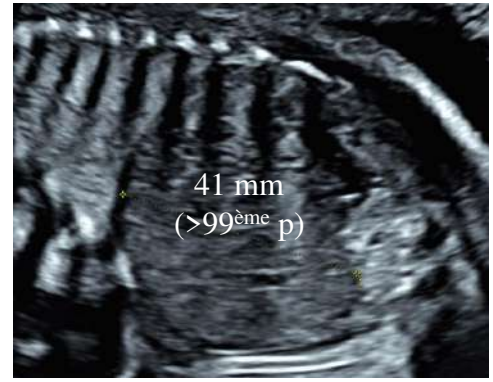
Lin Yang,[1] Dan-dan Xu,[1] Cheng-jun Sun,[1] Jing Wu,[1] Hai-yan Wei,[2] Yu Liu,[3]

	PMID	Inheritance	*IGF1R* Gene Variant (NM_000875)	Zygosity
Case 1	—	AD	p.M1247T	Het
Case 2	—	AD	p.C248W	Het
Case 3	—	AR	p.R895Q/E769Q	Het/het
Storr *et al.* (7), 2015	25411237	AD	p.D38N	Het
Prontera *et al.* (3), 2015	26252249	ID	p.R734I	Hom
Juanes *et al.* (8), 2015	25040157	AD	p.R1256S	Het
Juanes *et al.* (8), 2015	25040157	AD	p.N359Y	Het
Juanes *et al.* (8), 2015	25040157	AD	p.Y865C	Het
Fujimoto *et al.* (9), 2015	25866162	AD	p.Q1250X	Het
Fujimoto *et al.* (9), 2015	25866162	AD	p.W1249X	Het
Kawashima *et al.* (10), 2014	24033502	AD	p.D1105E	Het
Wang *et al.* (11), 2013	23771920	AD	p.A140Gfs*5	Het
Leal *et al.* (12), 2013	22998174	AD	p.R511W	Het
Labarta *et al.* (13), 2013	22738321	AD	p.Y487F	Het
Kawashima *et al.* (14), 2012	22309212	AD	p.R431L	Het
Fang *et al.* (15), 2012	22130793	AR	p.E121K/E234K	Het/het
Mohn *et al.* (16), 2011	21811077	AD	p.Y387X	Het
Choi *et al.* (17), 2011	20962017	AD	p.A110fs*20	Het
Wallborn *et al.* (18), 2010	20357178	AD	p.V599E	Het
Kruis *et al.* (19), 2010	20103656	AD	p.G1125A	Het
Fang *et al.* (20), 2009	19240156	AD	19Dup in exon 18	Het
Raile *et al.* (21), 2006	16569742	AD	p.R59X	Het
Kawashima *et al.* (2), 2005	15928254	AD	p.R709Q	Het
Abuzzahab *et al.* (1), 2003	14657428	AR	p.R108Q/p.K115N	Het/het
Abuzzahab *et al.* (1), 2003	14657428	AD	p.R59X	Het

Poursuite de la grossesse

- Echo 26 SA
  - Macrocéphalie
  - Dilatation ventriculaire modérée
  - Augmentation CN
  - Hépatomégalie





BIP osseux : 81,9 mm (>97e percentile)
BIP cérébral : 70,9 mm (95e percentile)
DFO osseux : 110 mm (>> 97e percentile)
DFO cérébral : 101 mm (>> 97e percentile)
Lg du corps calleux : 45 mm (>> 97e percentile)
DTC : 42,3 mm (>> 97e percentile)
Hauteur vermienne : 20 mm (97e percentile)
diamètre antéropostérieur du pont : 11,7 mm (95e percentile)

Dr Caroline Roorick-Thambo

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  - Dilatation ventriculaire modérée
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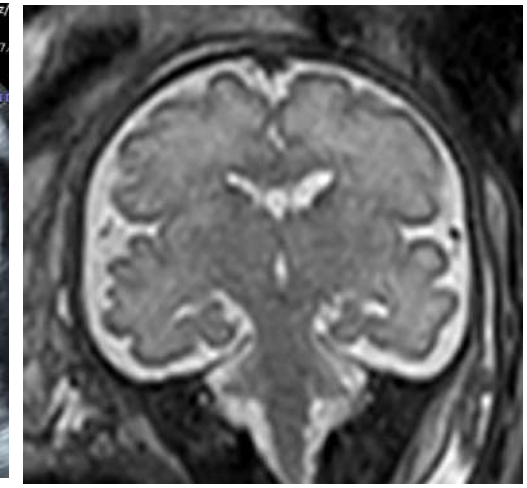
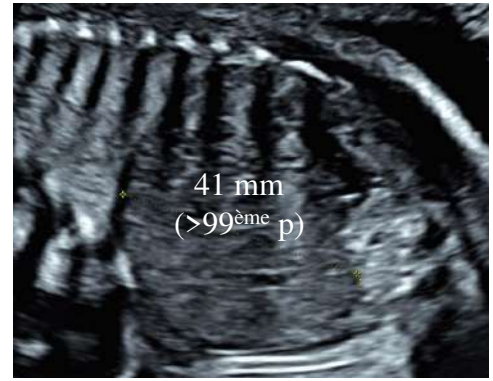


MTOR hétérozygote *de novo*

LRG_734t1:c.5663T>G; p.(Phe1888Cys)



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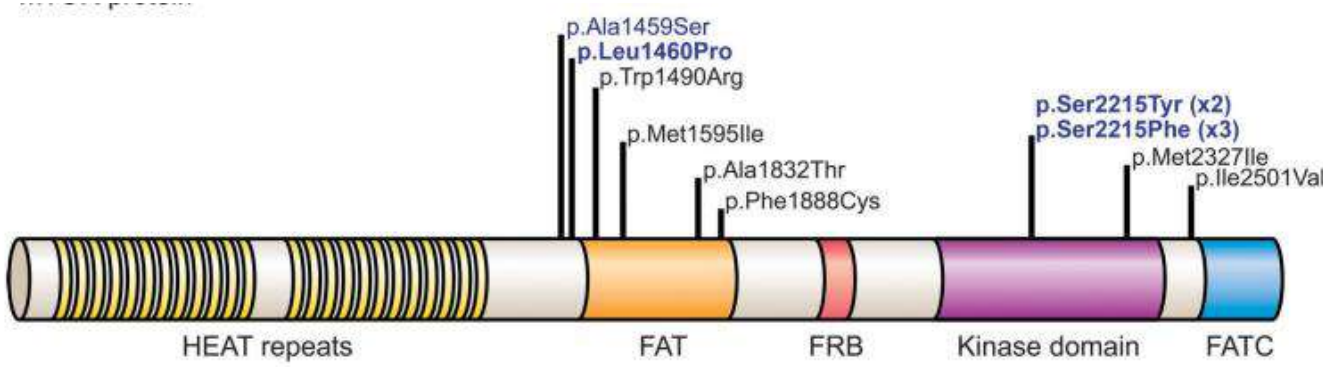
Germline and somatic mutations in the *MTOR* gene in focal cortical dysplasia and epilepsy

OPEN



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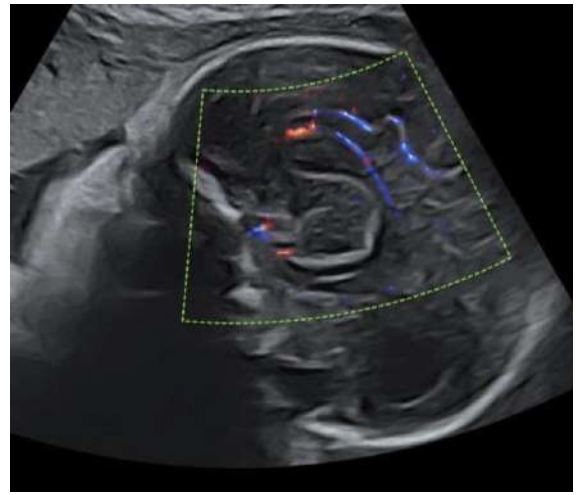
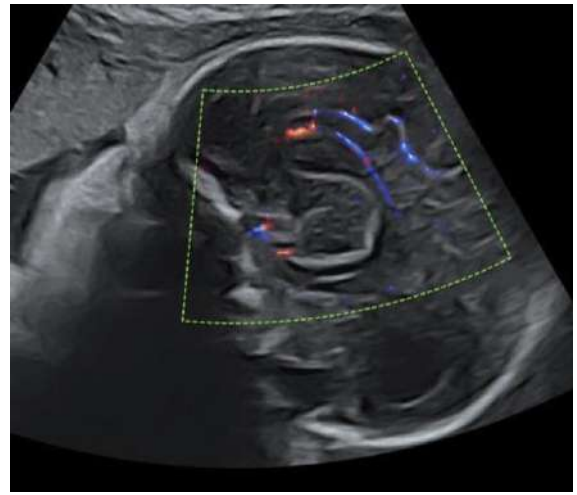


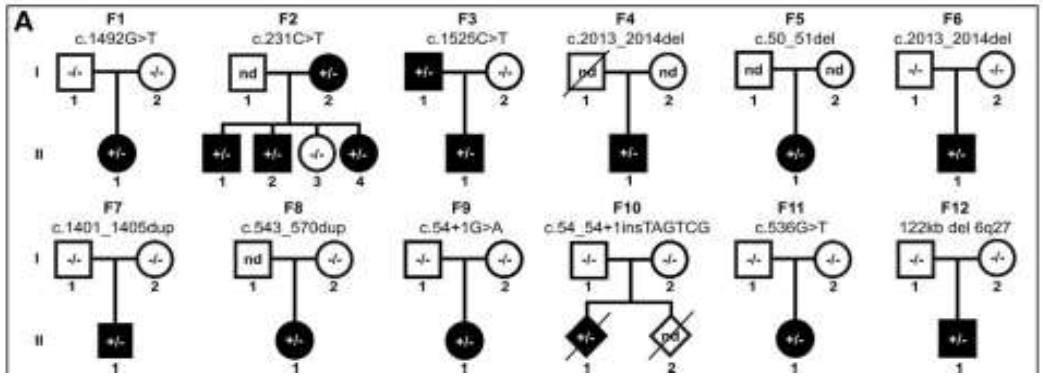
Pr Christel Thauvin

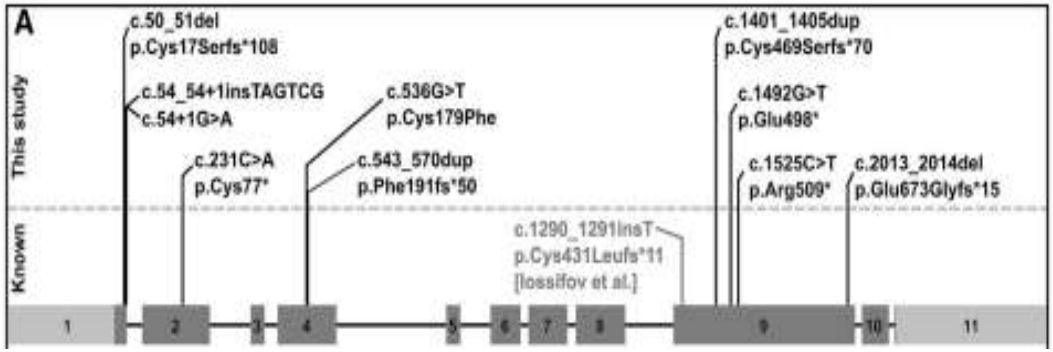
- Echo 31 SA
  - Agénésie partielle CC
  - Hypoplasie cérébelleuse
  - Ventriculomégalie



Variant *DLL1* hétérozygote *de novo*

NM_005618.4:c.152del; p.(Pro51Hisfs*72)





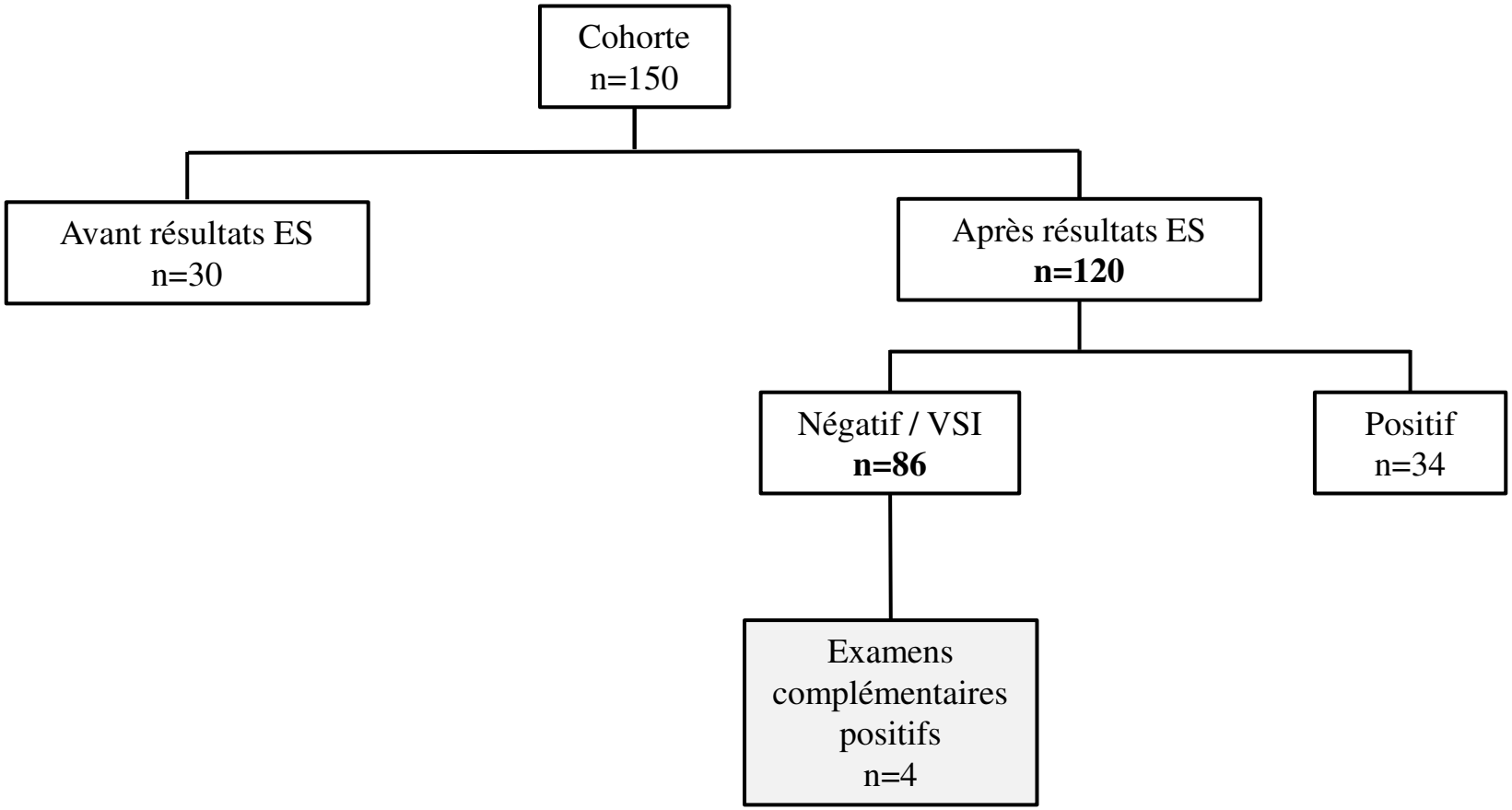
Haploinsufficiency of the Notch Ligand DLL1 Causes Variable Neurodevelopmental Disorders

Björn Fischer-Zirnsak,[1,23] Lara Segebrecht,[1,2,23] Max Schubach,[1,2] Perrine Charles,[3] Emily Alderman,[4]

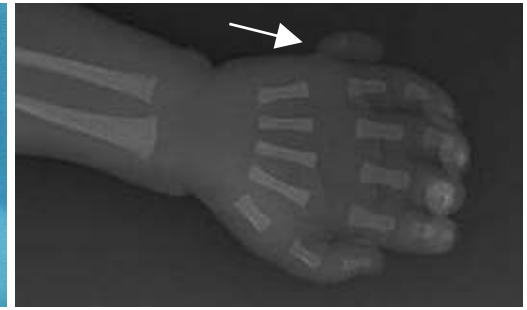
Signes	N (%)
DD/DI	12/14 (85%)
Epilepsie	6/14 (43%)
Hypotonie	6/14 (43%)
TSA	6/14 (43%)
Anomalie IRM	11/15 (73%)

Poursuite de la grossesse

Situations complexes



- Echo 19 SA:
  - Polydactylie post-axiale bilatérale
  - Ventricules cérébraux à la limite supérieure
  - PC: 99ème percentile
  - Hydramnios



Dr Quelin, Dr Proisy, Dr Tardif

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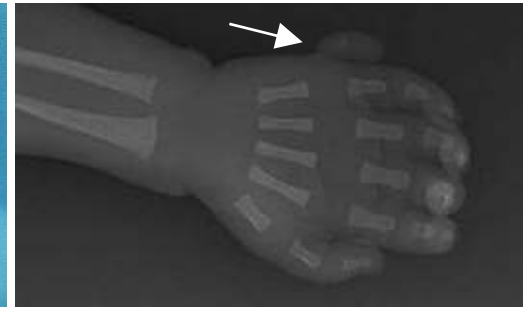

MYCN hétérozygote *de novo*

NM_005378.4:c.179C>T; p.(Pro60Leu)

HEAD & NECK

Head

- Microcephaly (79% of cases)
- Small anterior fontanelle
- Prominent occiput

Face

- Micrognathia
- Triangular face
- Facial asymmetry

Ears

- Posteriorly angulated ears
- Low-set ears
- Hearing loss

Eyes

- Short palpebral fissures
- Narrow palpebral fissures
- Epicanthal folds
- Upslanting palpebral fissures

Nose

- Broad nasal bridge
- Anteverted nostrils
- Flat nasal tip

Mouth

- Prominent lips
- High-arched palate

CARDIOVASCULAR

Vascular

- Patent ductus arteriosus

RESPIRATORY

Larynx

- Vocal cord paralysis

ABDOMEN

Pancreas

- Annular pancreas

Spleen

- Supernumerary spleen
- Congenital asplenia

Gastrointestinal

- Tracheoesophageal fistula
- Esophageal atresia
- Duodenal atresia

SKELETAL

Hands

- Thumb symphalangism
- Absent/hypoplastic middle phalanx of 2nd finger
- Absent/hypoplastic middle phalanx of 5th finger

Feet

- Syndactyly of toes 2-3 (56%) and 4-5 (86%)
- Short toes

NEUROLOGIC

Central Nervous System

- Mental retardation
- Learning disability (90% patients)

PRENATAL MANIFESTATIONS

Movement

- Decreased fetal movement

Amniotic Fluid

- Polyhydramnios

Dr Quelin, Dr Proisy, Dr Tardif

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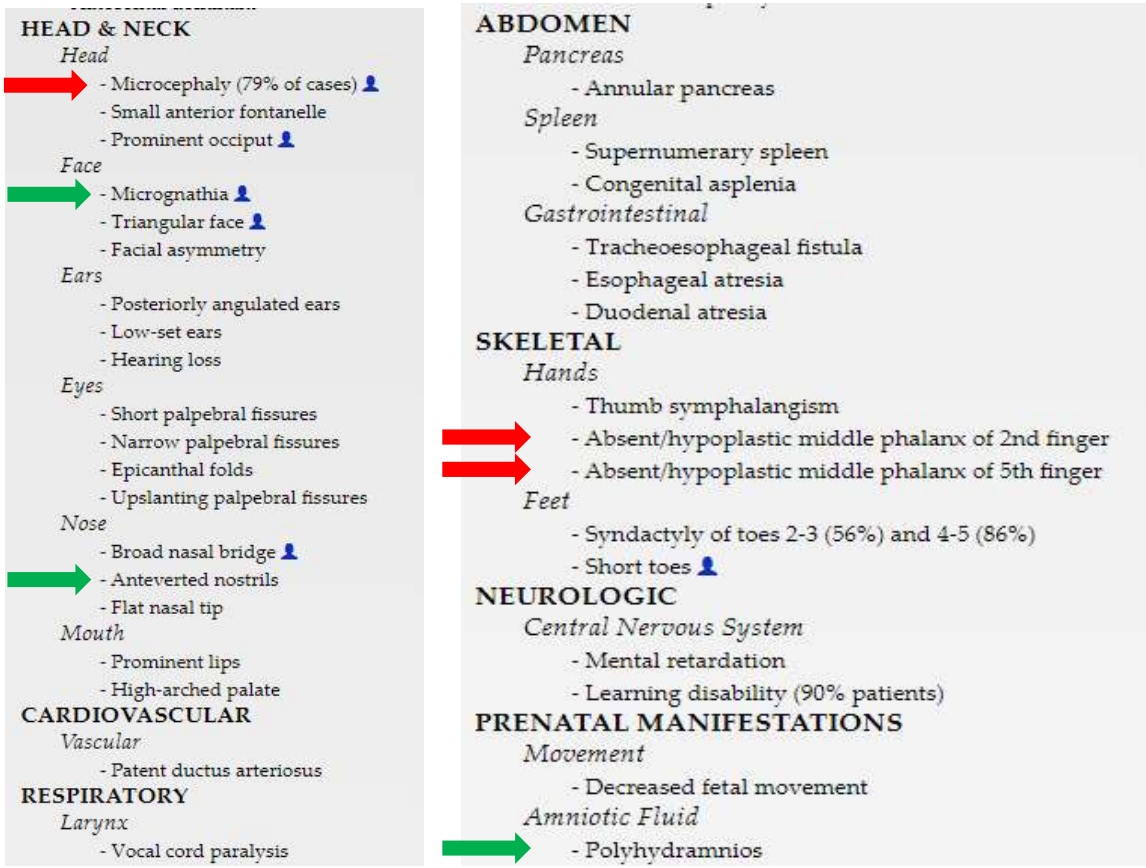

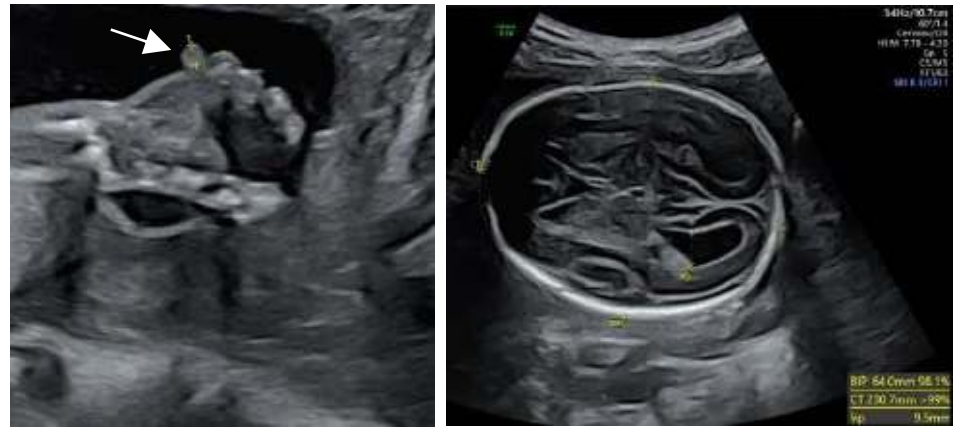

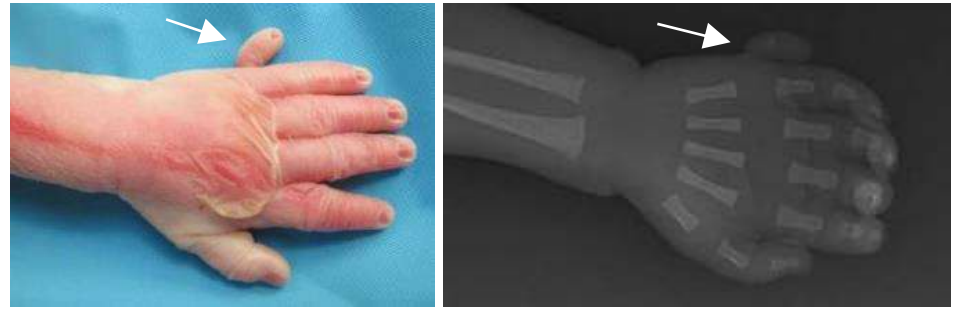

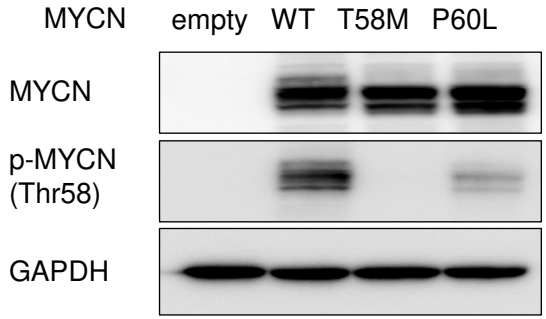

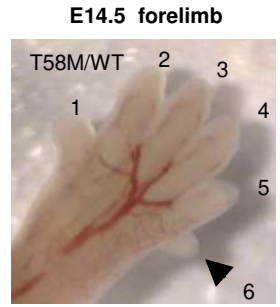

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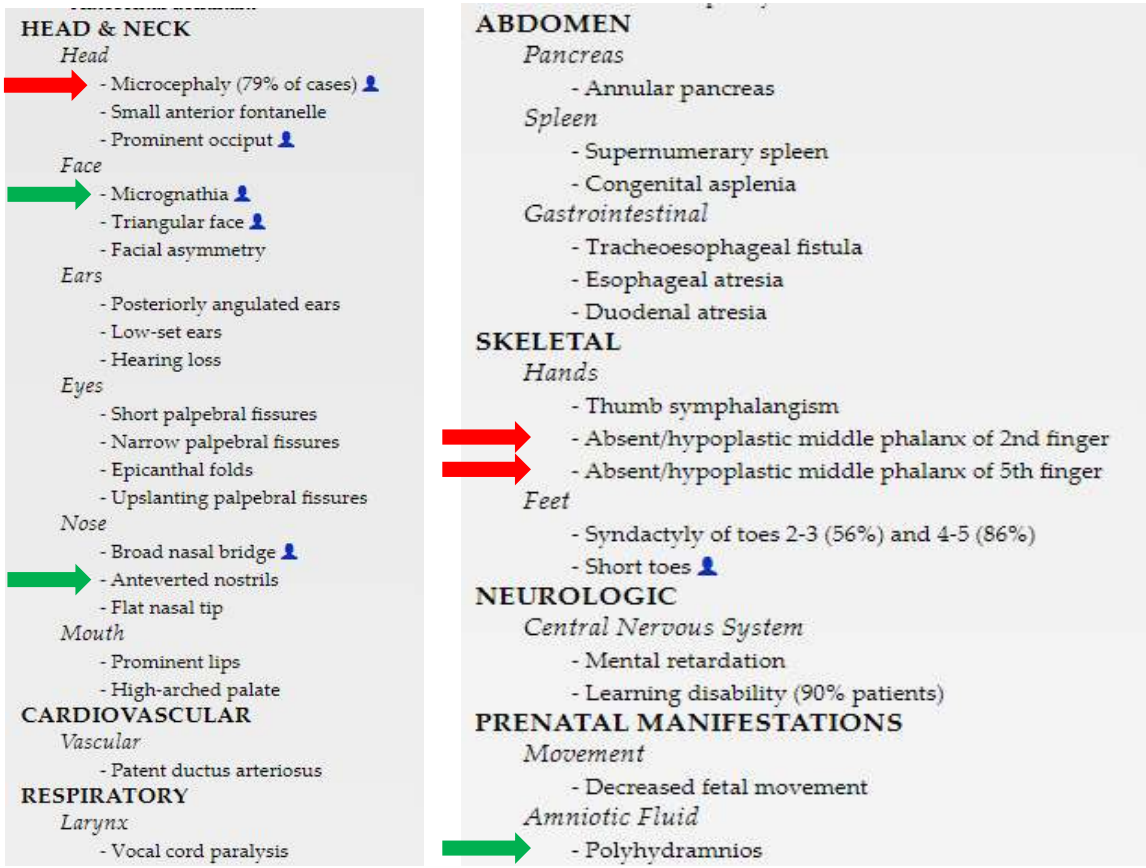

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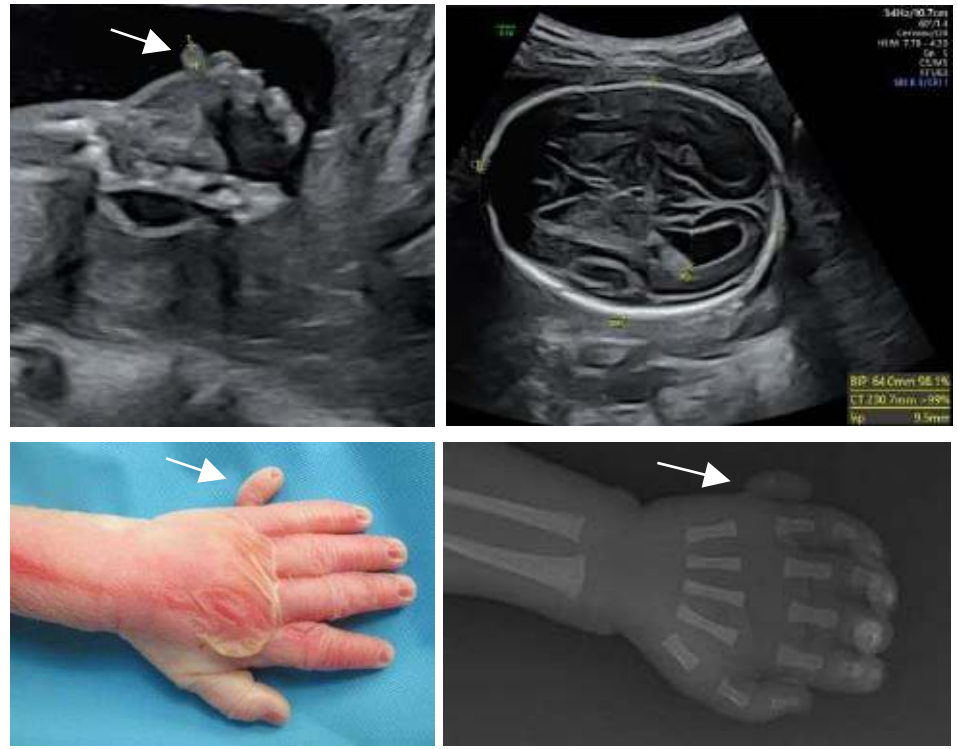

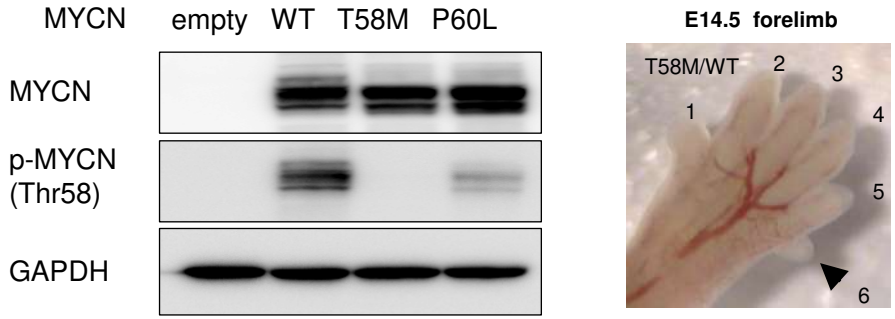

Intérêt des VSI

Recherche translationnelle

Conseil génétique

- Echo 30 SA:
  - Rétrognathisme
  - Œdème préfrontal
  - Hypoplasie des OGE
  - Cardiopathie
  - Aorte dilatée/tortueuse

Dr Rodolph Dard

– Echo 30 SA:

- Rétrognathisme
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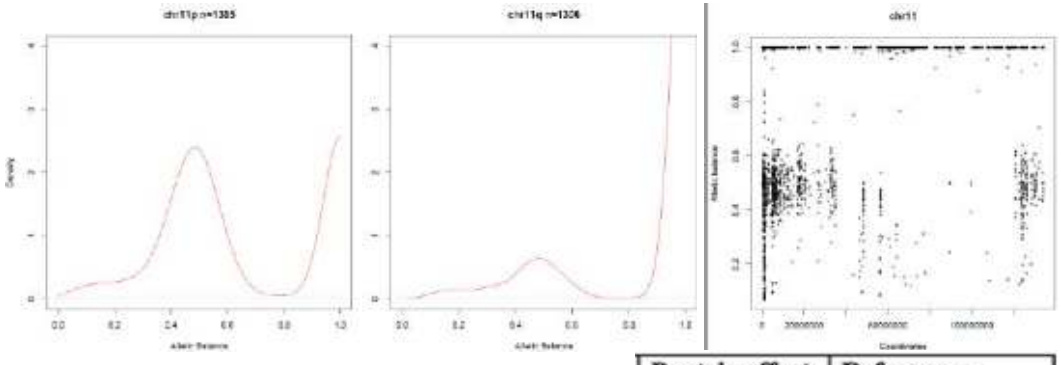
EFEMP2 homozygote hérité des 2 parents

NM_016938.4:c.379T>C; p.(Cys127Arg)



Severe Phenotype of Cutis Laxa Type 1B with Antenatal Signs due to a Novel Homozygous Nonsense Mutation in *EFEMP2*

Pascaline Letard[a] Dorien Schepers[f] Juliette Albuisson[d] Patrick Bruneval[e]

Protein effect	References
p.Asp29Ilefs*31	Erickson, 2012
p.Glu57Lys	Hucthagowder, 2006 Iascone, 2012
p.Glu126Lys	Renard, 2010 Sawyer, 2012 Hebson, 2014
p.Glu126Val	Renard, 2010
p.Glu161Lys	Al-Hassan, 2012
p.Gln193fs*12	Renard, 2010
p.Asp203Ala	Kappanayil, 2012 Rajeshkannan, 2014
p.Cys213*	This report
p.Arg227Cys	Kappanayil, 2012 Rajeshkannan, 2014

GROWTH
Other
- Fetal overgrowth (in some patients)

HEAD & NECK
Head
- Microcephaly (rare)
Face
- Prominent forehead
- Prominent premaxilla
- Micrognathia
Ears
- Dysplastic ears
- Low-set ears
Eyes
- Prominent eyes
- Small palpebral fissures
- Downslanting palpebral fissures
- Hypertelorism, mild
Nose
- Bulbous nasal tip (in some patients)
- Hooked nose (in some patients)
- Depressed nasal bridge (in some patients)
Mouth
- High-arched palate

CARDIOVASCULAR
Heart
- Thickened myocardium (rare)
- Bradycardia (rare)
Vascular
- Aortic aneurysm
- Pulmonary artery aneurysm
- Arterial aneurysms, multiple
- Arterial tortuosity, general
- Venous tortuosity
- Arterial stenoses, multiple
- Vascular fragility
- Vascularization increased in upper dermis

RESPIRATORY
Lung
- Emphysema

CHEST
Ribs Sternum Clavicles & Scapulae
- Pectus excavatum
Diaphragm
- Hypoplastic diaphragm
- Diaphragmatic hernia

GENITOURINARY
External Genitalia (Male)
- Inguinal hernia

SKELETAL
- Joint hypermobility, generalized
- Fractures at birth
Hands
- Arachnodactyly
- Contractures of third to fifth fingers
Feet
- Arachnodactyly

SKIN, NAILS, & HAIR
Skin
- Cutis laxa
- Velvety skin
- Normal scarring
Skin Histology
- Collagen bundles smaller than normal
- Vascularization increased in upper dermis
- Underdeveloped elastic fibers, severe

NEUROLOGIC
Central Nervous System
- Hypotonia
- Brain hemorrhage

PRENATAL MANIFESTATIONS
Amniotic Fluid
- Oligohydramnios (in some patients)

MISCELLANEOUS
- Relatively mild cutis laxa, associated with severe vascular abnormalities
- Massive aortic aneurysm can cause airway compression in affected infants

Dr Rodolph Dard

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NM_016938.4:c.379T>C; p.(Cys127Arg)

RAG1 homozygote hérité des 2 parents

LRG_98t1:c.1767C>G; p.(Tyr589*)

Location	Phenotype Clinical Synopses
11p12	Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity
	Combined cellular and humoral immune defects with granulomas
	Omenn syndrome
	Severe combined immunodeficiency, B cell-negative

Clinical & Experimental Immunology
The Journal of Translational Immunology
British Society for immunology
Clinical and Experimental Immunology ORIGINAL ARTICLE doi: 10.1111/cei.13222

Phenotypical heterogeneity in RAG-deficient patients from a highly consanguineous population

p.	Patient no.	Patient phenotype	Previously reported
R142X	P1	OS	Atypical SCID/leaky SCID [17] OS [17,18]
E425del	P2	OS	[13]
Q812X	P3	OS	[13]
	P29	Atypical SCID/CID	
R975Q	P4	OS	[13] OS [11] CID-G/A [19,20]
R559S	P5	OS	OS [17,21]
Q407H	P21	SCID	[16]
N591Pfs*14	P22,P23	SCID	(Novel)
K621E	P24	SCID	(Novel)
R829S fs*	P24,P25	SCID	[13]
A565P	P26	SCID	(Novel)
R841W	P27	T^-B^+SCID	Hypomorphic SCID with CMV infection [20] Atypical SCID/OS [11] T^-B^+SCID [2]
C335R	P29	Atypical SCID/CID	(Novel)
R973H	P30	Atypical SCID/CID	OS [22]

Dr Rodolph Dard

– Echo 17 SA:
  - Hygroma isolé persistant

Dr Julian Delanne

– Echo 17 SA:

- Hygroma isolé persistant

ASCC1 homozygote hérité des 2 parents

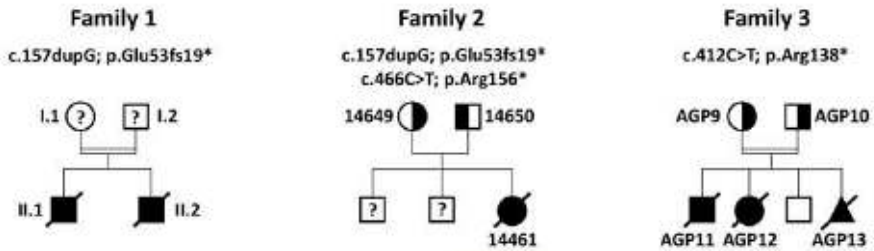
NM_001198800.3:c.157dup; p.(Glu53Glyfs*19)

Novel *ASCC1* mutations causing prenatal-onset muscle weakness with arthrogryposis and congenital bone fractures

Johann Böhm,[1] Edoardo Malfatti,[2,3] Emily Oates,[4,5] Kristi Jones,[4,6] Guy Brochier,[2]

Biallelic ASCC1 variants including a novel intronic variant result in expanded phenotypic spectrum of spinal muscular atrophy with congenital bone fractures 2 (SMABF2)

Kristen K Rosano [1], Daniel J Wegner [1], Marwan Shinawi [2], Dustin Baldridge [2], Robert C Bucelli [3],



HEAD & NECK
- *Face*
  - Myopathic facies
  - Microretrognathia
- *Mouth*
  - High-arched palate
  - Tented mouth
- *Teeth*
  - Abnormal bony maturation of the teeth

CARDIOVASCULAR
- *Heart*
  - Congenital heart defects, mild (in some patients)
  - Patent foramen ovale
- *Vascular*
  - Patent ductus arteriosus

RESPIRATORY
- Respiratory distress due to hypotonia
- *Lung*
  - Pulmonary hypoplasia

CHEST
- *Ribs Sternum Clavicles & Scapulae*
  - Abnormal bony maturation of the sternum
  - Thin gracile ribs
  - Thin gracile clavicles

ABDOMEN
- *Gastrointestinal*
  - Poor feeding due to hypotonia

SKELETAL
- Arthrogryposis, distal and proximal
- Abnormal ossification
- *Spine*
  - Increased height of the vertebral bodies
- *Limbs*
  - Fractures, congenital, of the long bones
- *Hands*
  - Clenched fists
  - Camptodactyly
- *Feet*
  - Club feet

MUSCLE, SOFT TISSUES
- Hypotonia, generalized, severe
- Muscles do not contract upon electrical stimulation
- Muscle fiber immaturity
- Muscle fiber size variation
- Muscle fiber atrophy
- Subsarcolemmal oxidative rims
- Central or eccentric oxidative accumulations in muscle fibers
- Disorganized myofibrils on electron microscopy
- Enlarged Z-bands
- Degenerating sarcomeres

NEUROLOGIC
- *Central Nervous System*
  - Lack of spontaneous movements
  - Global developmental delay
  - Spinal muscular atrophy (family A)
  - Alpha-motoneuron degeneration in the spinal cord (family A)
  - Abnormal cortical gyration (family A)
- *Peripheral Nervous System*
  - Axonal neuropathy (family A)
  - Unmyelinated axonal loss (family A)
  - Areflexia

PRENATAL MANIFESTATIONS
- *Movement*
  - Decreased fetal movements
  - Fetal hypokinesia
- *Amniotic Fluid*
  - Polyhydramnios
  - Fetal hydrops (1 patient)

MISCELLANEOUS
- Onset in utero
- Death in the first days or months of life

IMG après résultat ES

Dr Julian Delanne

– Echo 17 SA:

- Hygroma isolé persistant

ASCC1 homozygote hérité des 2 parents

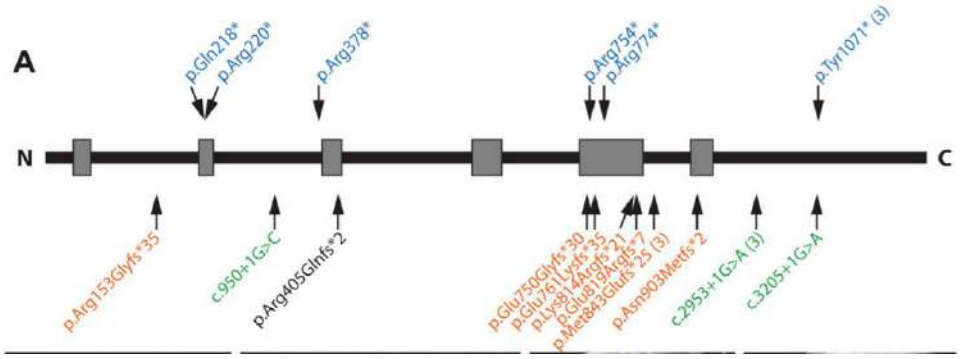
NM_001198800.3:c.157dup; p.(Glu53Glyfs*19)

CSPP1 homozygote hérité des 2 parents

NM_024790.6:c.167_168del; p.(Lys56Serfs*6)

Mutations in *CSPP1* Cause Primary Cilia Abnormalities and Joubert Syndrome with or without Jeune Asphyxiating Thoracic Dystrophy

Karina Tuz,[1,21] Ruxandra Bachmann-Gagescu,[2,3,21] Diana R. O'Day,[4,21] Kiet Hua,[1] Christine R. Isabella,[4]



HEAD & NECK

Ears
- Sensorineural hearing loss (2 patients)

Eyes
- Oculomotor apraxia
- Strabismus
- Ptosis
- Fused eyes (1 family)
- Anophthalmia (1 family)
- Retinopathy (in some patients)

Nose
- Single nostril (1 family)

RESPIRATORY
- Abnormal breathing pattern
- Dyspnea
- Apnea

Lung
- Pulmonary hypoplasia (in some patients)

CHEST

External Features
- Bell-shaped chest (in some patients)

Ribs Sternum Clavicles & Scapulae
- Short, horizontal ribs (in some patients)

ABDOMEN

Liver
- Liver fibrosis (in some patients)

GENITOURINARY

Kidneys
- Hyperechogenic kidneys (in some patients)
- Cystic kidneys (in some patients)

NEUROLOGIC

Central Nervous System
- Delayed psychomotor development
- Mental retardation
- Hypotonia
- Cerebellar ataxia
- Posterior fossa malformations
- Hypoplasia of the inferior cerebellar vermis
- Dysplastic superior cerebellar vermis
- Elongated superior cerebellar peduncles
- Posterior fossa cyst
- Occipital encephalocele (in some patients)
- Molar tooth sign on brain imaging
- Hypoplasia of the brainstem
- Thin corpus callosum

MISCELLANEOUS
- Prenatal onset
- Variable features
- Variable severity
- May result in early death

Dr Julian Delanne

CONCLUSIONS

- **Utilité indéniable pour les couples**
  - Taux diagnostique **avant ACPA** = 40,5% (42,7% avec réanalyse)
  - Taux diagnostique **après ACPA** = 26,2% (29,5% avec réanalyse)
  - Conseil génétique = 34% pour les positifs (36,6% si réanalyse inclus)
    - 34/150 (22,6%) AD *de novo* ou CNV en mosaïque (35/150; 23,3% avec réanalyse)
    - 7/150 (4,6%) AD/XLD hérités (8/150; 5,3% avec réanalyse)
    - 10/150 (6,6%) AR/XLR (12/150; 8% avec réanalyse)
  - Résultats négatifs : 79% poursuite
  - Résultats positifs/VSI: 59% interruptions

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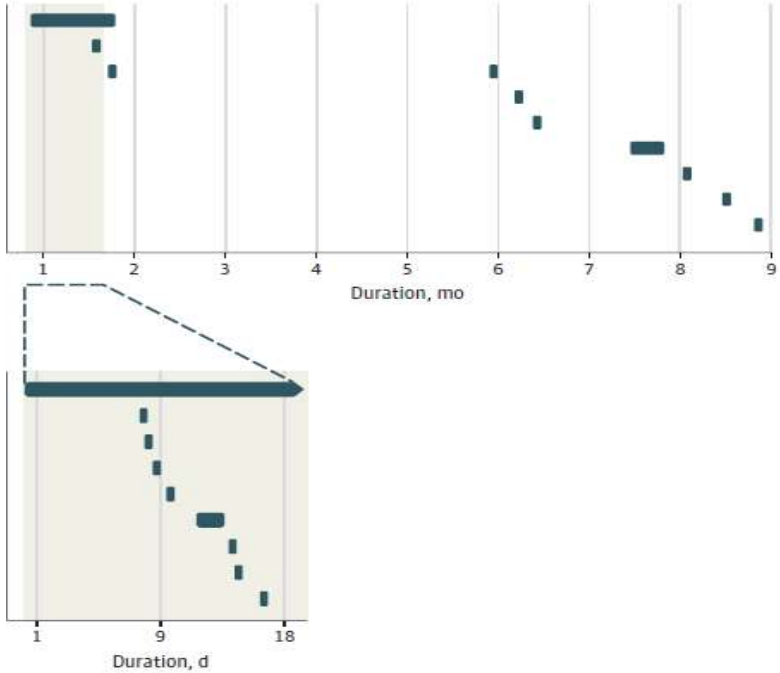
- **Des progrès possibles!**

JAMA | Original Investigation

Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System

Australian Genomics Health Alliance Acute Care Flagship



CONCLUSIONS et PERSPECTIVES

- **Utilité indéniable pour les couples**
  - Taux diagnostique avant ACPA = 40,5% (42,7% avec réanalyse)
  - Taux diagnostique après ACPA = 26,2% (29,5% avec réanalyse)
  - Conseil génétique = 34% pour les positifs (36,6% si réanalyse inclus)
    - 34/150 (22,6%) AD *de novo* ou CNV en mosaïque (35/150; 23,3% avec réanalyse)
    - 7/150 (4,6%) AD/XLD hérités (8/150; 5,3% avec réanalyse)
    - 10/150 (6,6%) AR/XLR (12/150; 8% avec réanalyse)
  - Résultats négatifs : 79% poursuite
  - Résultats positifs/VSI: 59% interruptions

- **Des progrès possibles!**

- **Et maintenant?**
  - Pour quelles indications?
  - Variants signification incertaine ou certaine mais sans signe clinique?
  - Analyse complémentaire et délais?
  - Quels délais / coûts?
  - Comment / par qui?

  - **A discuter à terme dans le cadre du PFMG 2025**

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