SOS1 mutation can mimic Beckwith-Wiedemann syndrome

Sophie COLLARDEAU-FRACHON[1]
Audrey PUTOUX[2]
Jérôme MASSARDIER[3]
Departments of pathology (1) genetics (2) and obstetrics (3)
HOPITAL FEMME-MÈRE -ENFANT

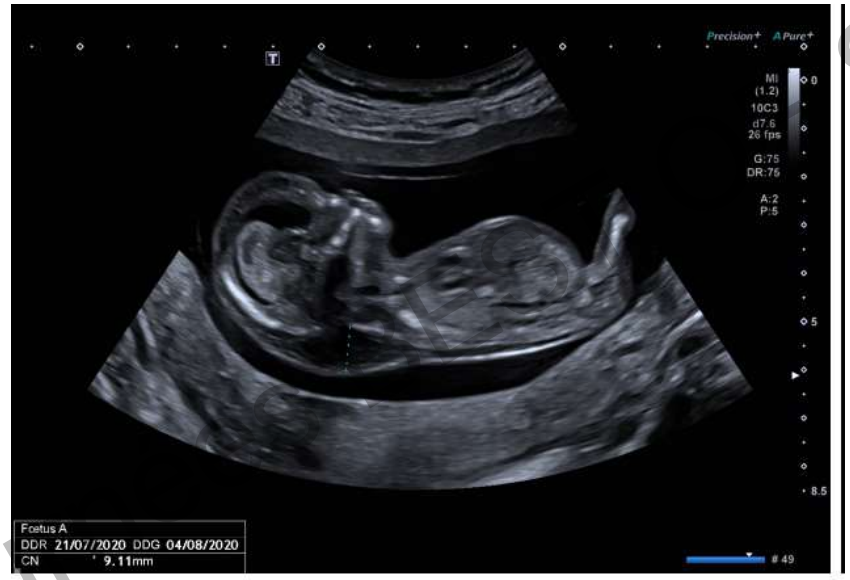
Hospices Civils de Lyon

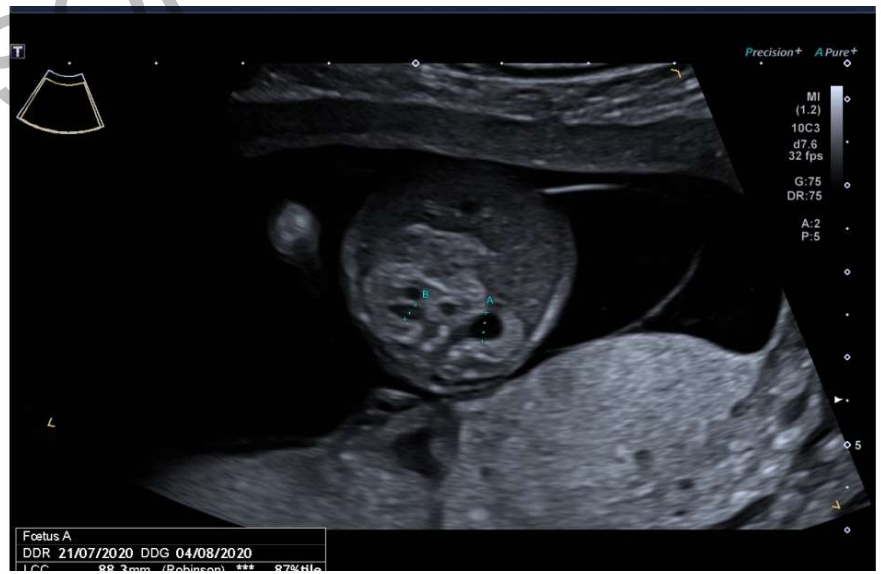
SoFFœt
Société Française de Fœtopathologie

UNIVERSITÉ DE LYON

Intrauterine Fetal Demise

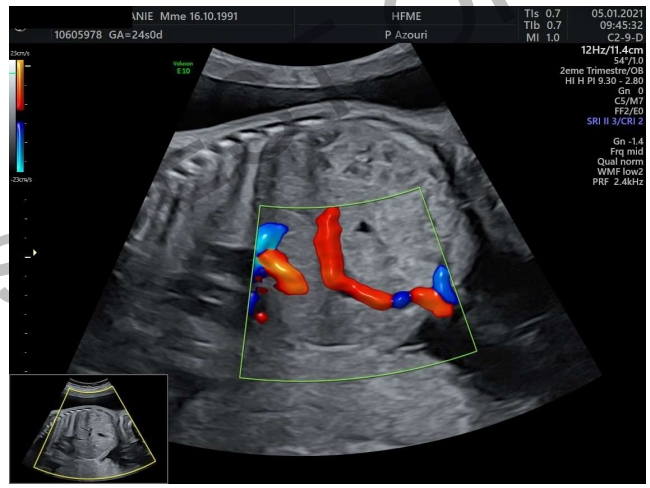
- Mother : 29 years old. G2P1 (1 boy in 2020 in good health)
- Referred in our multidisciplinary prenatal diagnosis center for increased nuchal translucency at 12 GW (10mm)
- Prenatal US : 14GW, 16 GW, 19GW
    - cystic hygroma
    - enlarged kidneys and mild bilateral pyelectasis

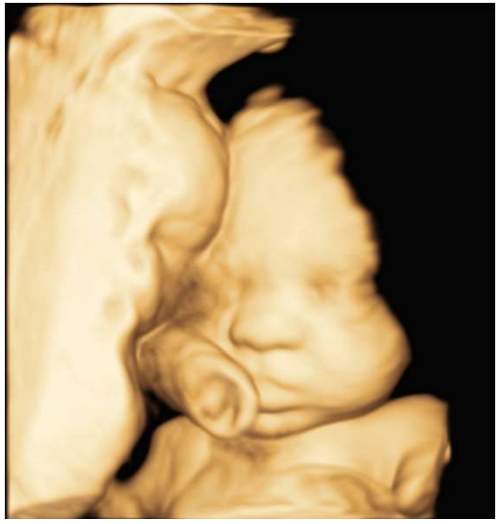




Intrauterine Fetal Demise

- Prenatal US : 24 and 31 GW
    - Macrosomia
    - Macroglossia
    - Hydramnios
    - Ductus venosus agenesis with an extrahepatic shunt draining in the inferior vena cava
- Normal fetal heart ultrasound





Intrauterine Fetal Demise

Investigations

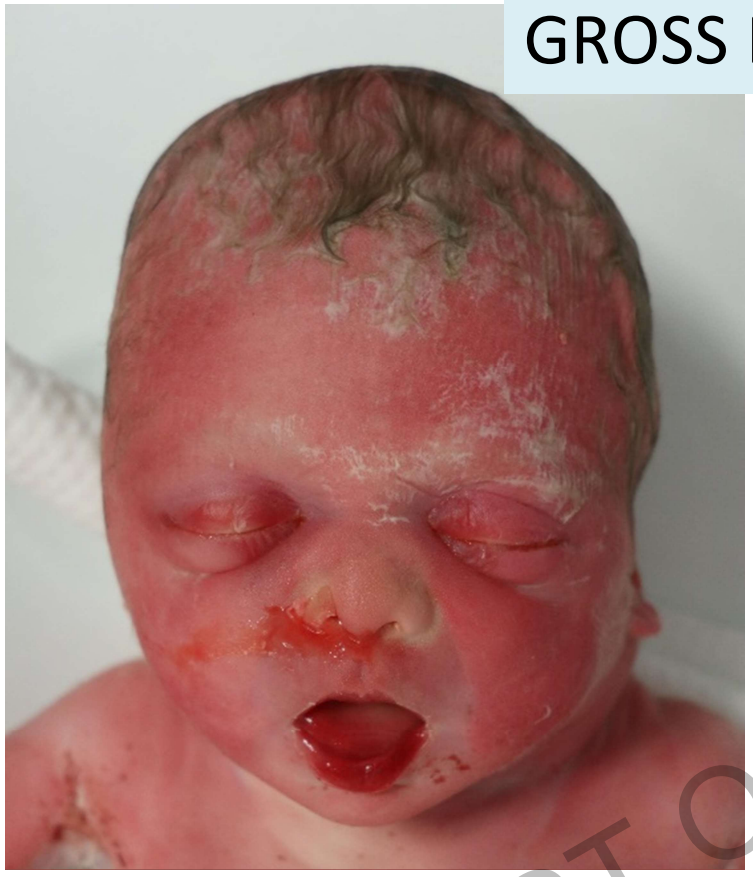
- No gestational diabetes (Oral Glucose Tolerance Test -)
- Amniocentesis 31GW
  - Karyotype: 46, XY
  - Array-CGH without anomaly
- DNA sent to
  - Hopital Trousseau Paris for Beckwith Wiedemann syndrome
  - Prenatal exome (ANDDI-PRENATOME), Dijon

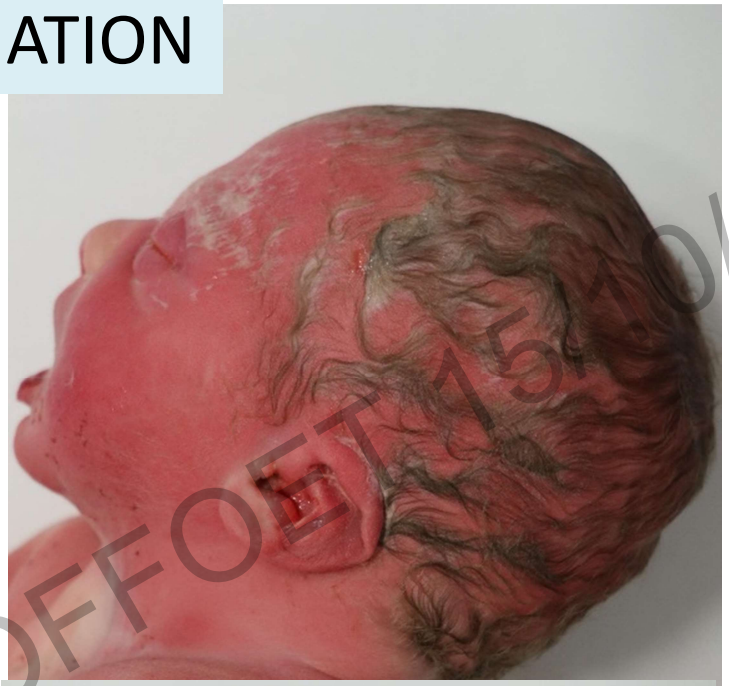
Intrauterine Fetal Demise at 32 + 3 GW

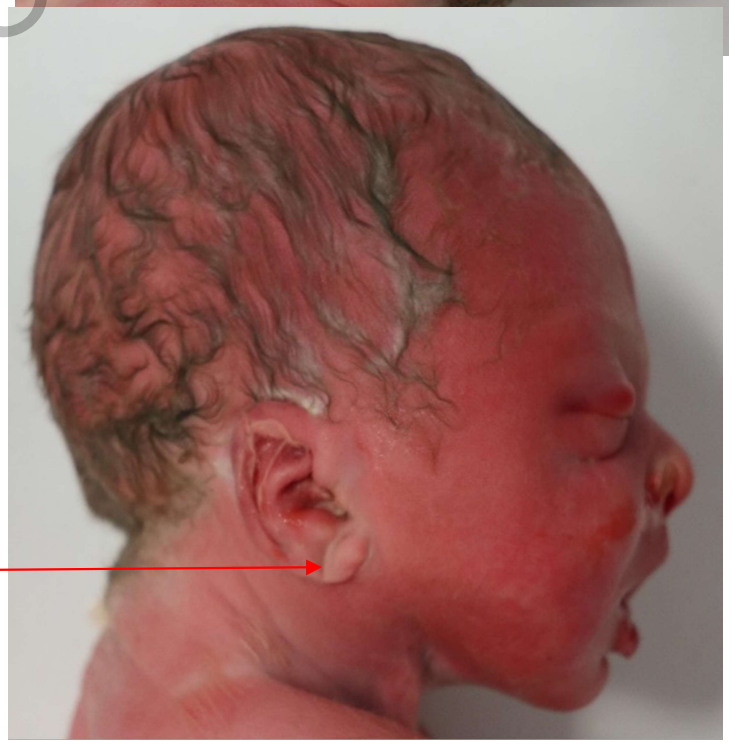
GROSS EXAMINATION

Male fetus
Mild macrosomia (32-33 GW) regarding maceration
No hemihypertrophy
Abdominal distension

GROSS EXAMINATION

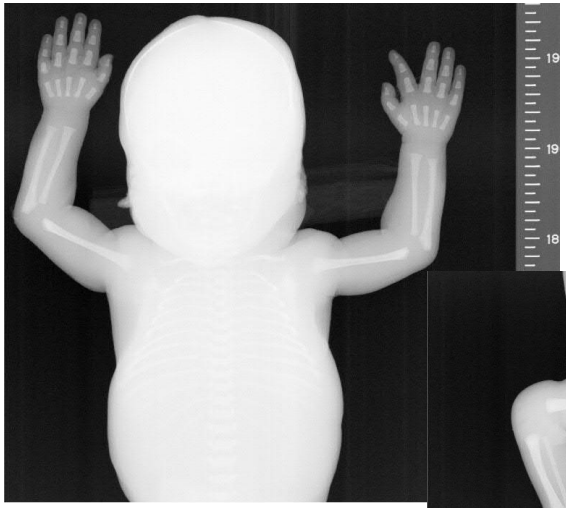
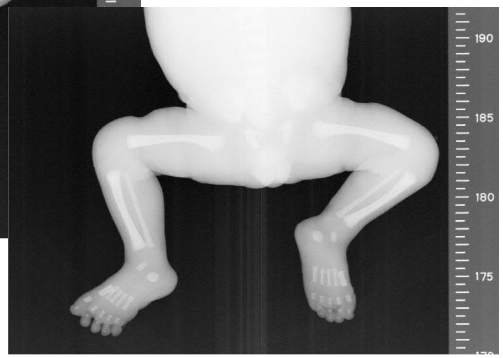
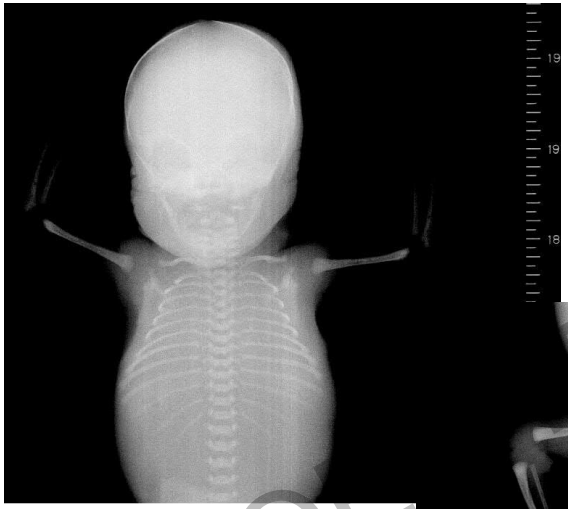
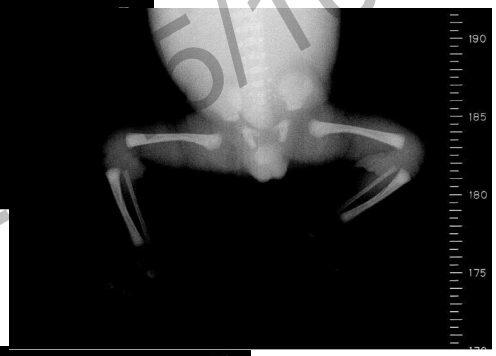




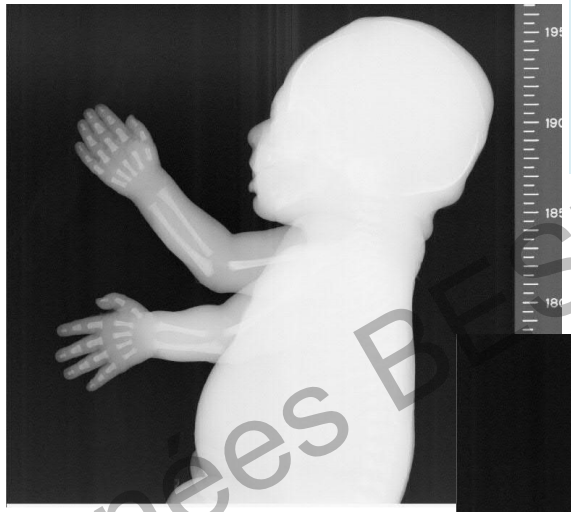
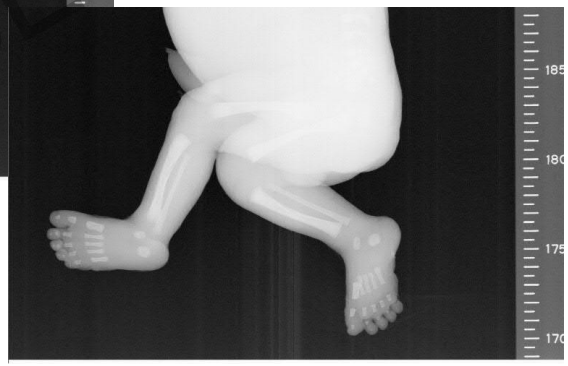
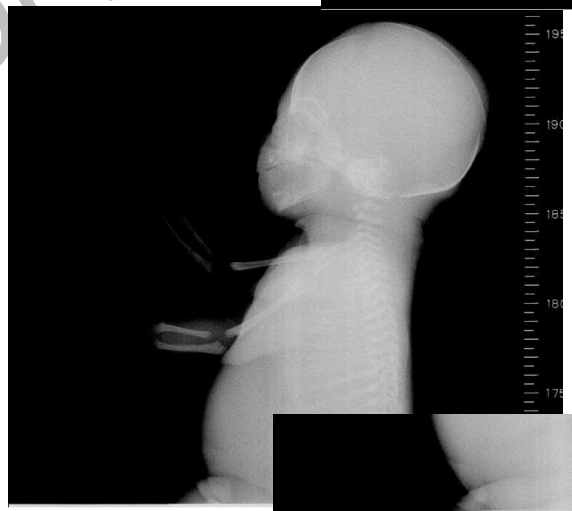
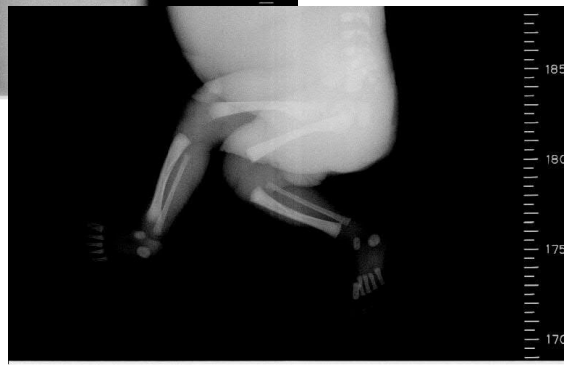


Distance inter canthi internes 21 mm (N=18.8 ± 1.8 mm)

- macroglossia
- eyelid edema
- mild hypertelorism
- anterior linear earlobe crease?
- short and thick neck

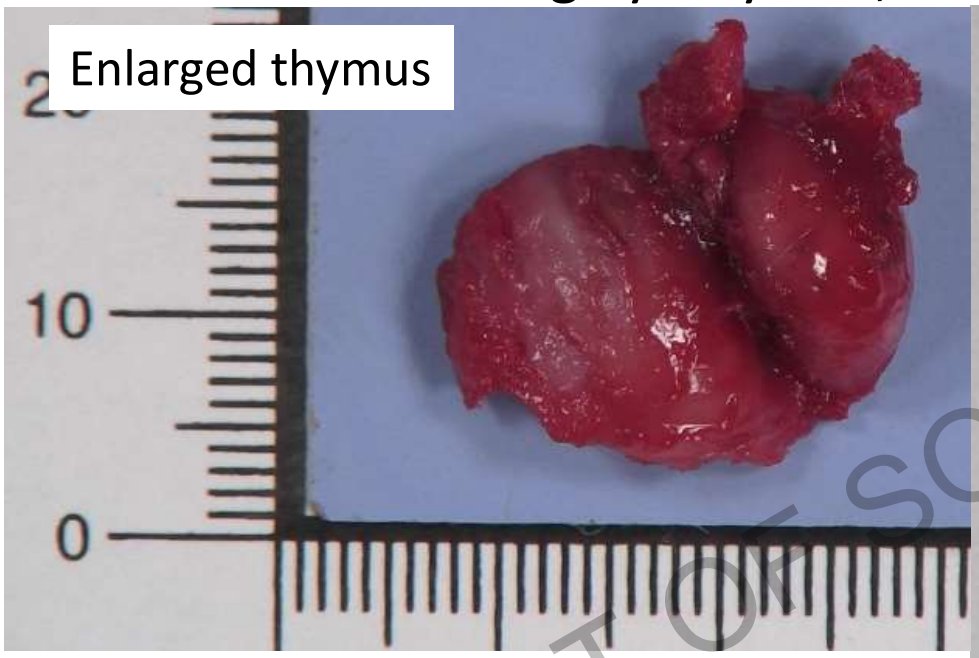





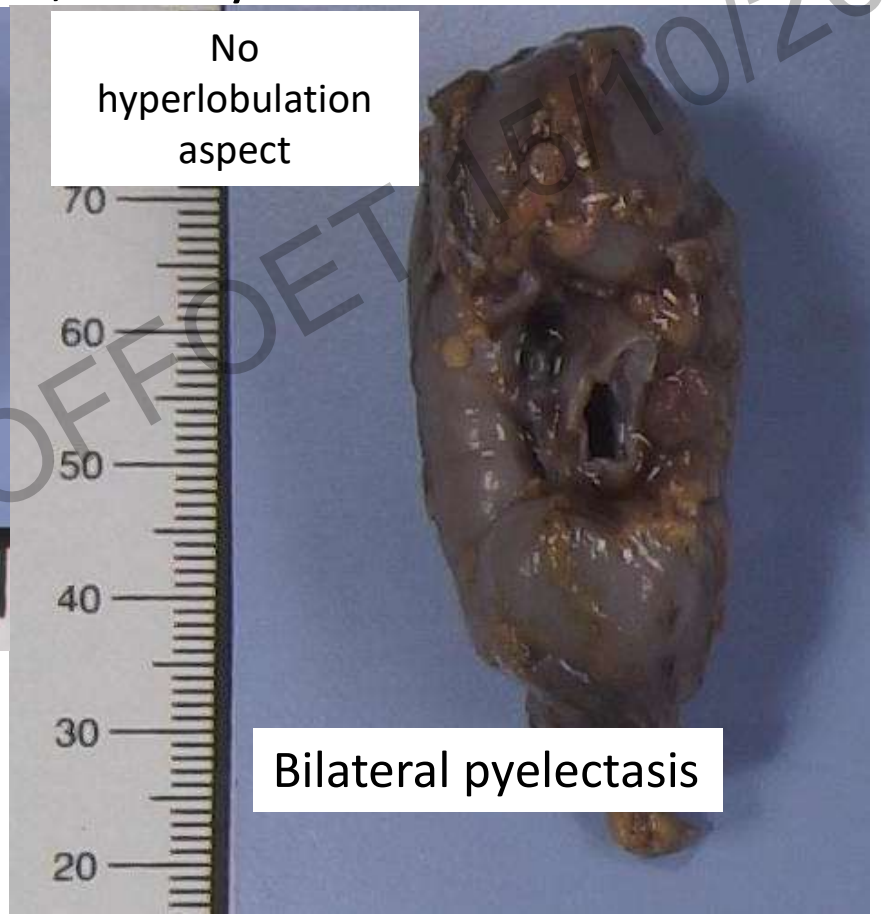
Skeletal X-rays:
no abnormality

Internal examination

visceromegaly: thymus, liver, kidneys and heart





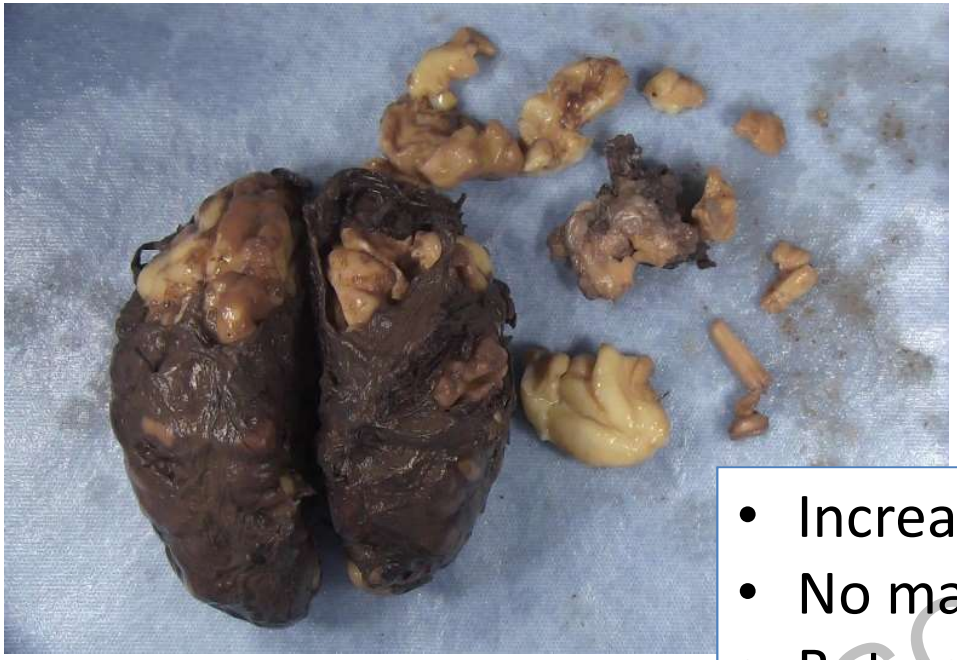
	POIDS		POIDS ATTENDU POUR 32 SA
Foie	97.4 g*		65.0 ± 25.3 g
Rate	4.9 g		3.9 ± 1.8 g
Bloc duodéno-pancréatique	8.3 g*		3.2 ± 1.9 g
Rein D	16.3 g	Total = 35.8 g*	14.9 ± 4.6 g
Rein G	19.5 g		
Surrénale D	1.5 g	Total = 3.5 g	4.1 ± 1.6 g
Surrénale G	2 g		
Poumon D	35.6 g	Total = 67.4 g*	30.0 ± 11.8 g
Poumon G	31.8 g		
Thymus	11.2 g*		4.2 ± 2.5 g
Cœur	15.5 g*		10.6 ± 2.6 g

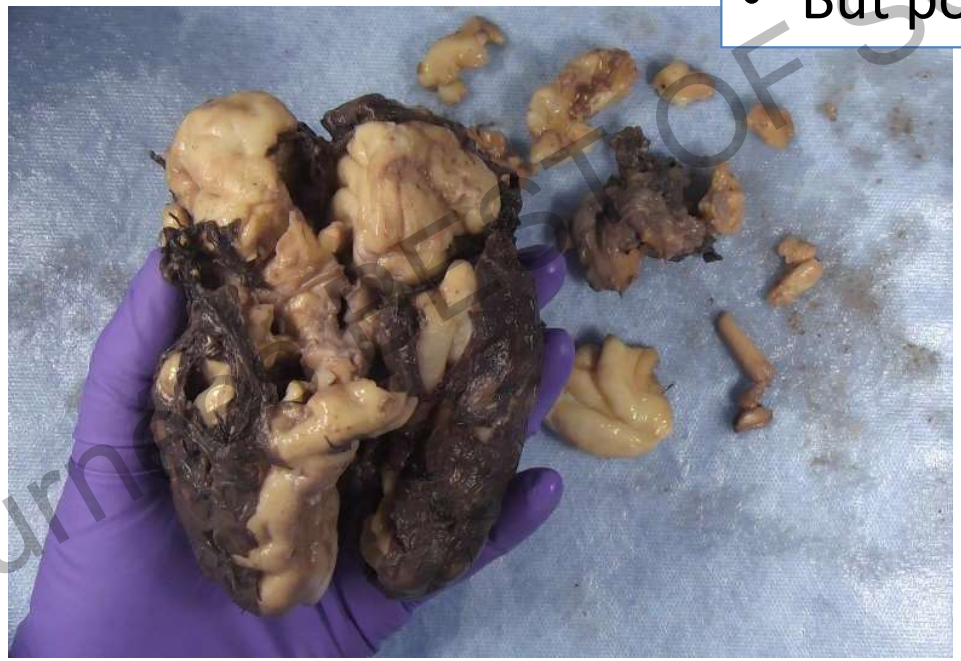
Ref: Maroun (2005)

Ductus venosus agenesis

- no cytomegaly in adrenal cortical and pancreatic islets of Langerhans
- no medullary dysplasia in the kidneys

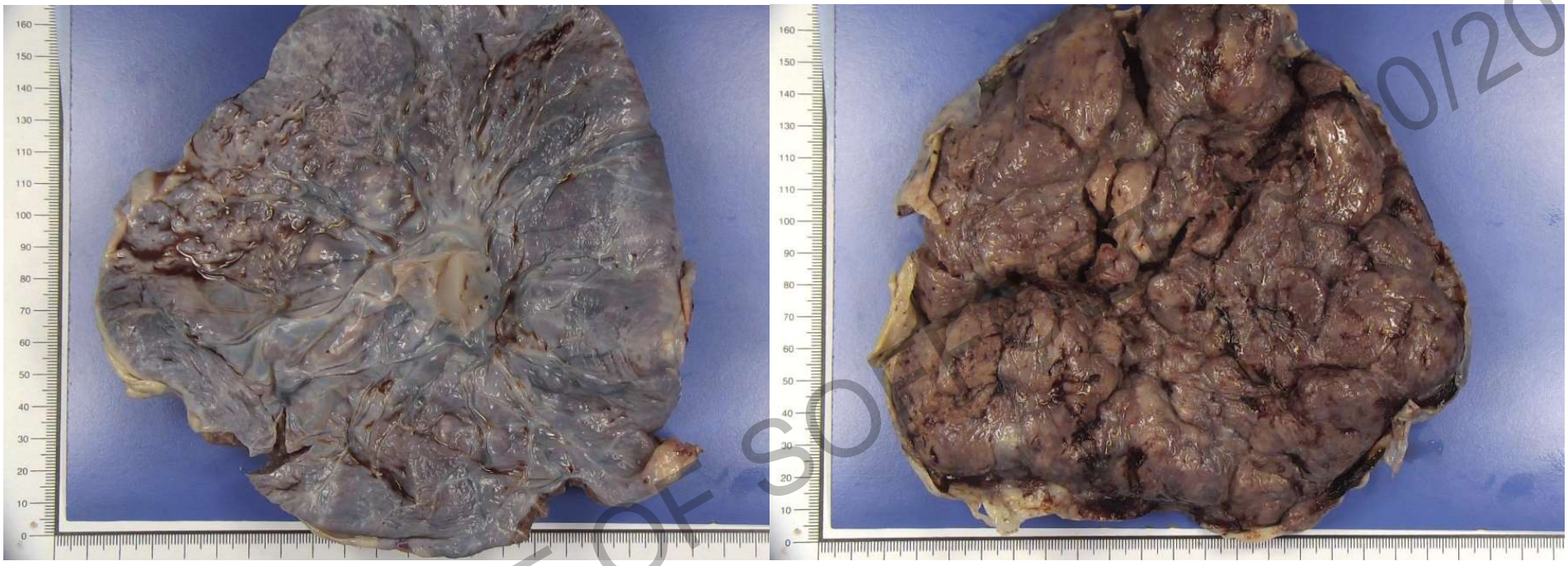
BRAIN EXAMINATION





- Increased weight (90p) and size (95p)
- No malformative abnormality
- But poorly preserved

PLACENTA EXAMINATION



Eutrophic placenta, without macroscopic and microscopic abnormality.
No features suggestive of mesenchymal dysplasia

In conclusion: all these anomalies should indeed lead to look for Beckwith Wiedemann syndrome.

GENETIC RESULTS

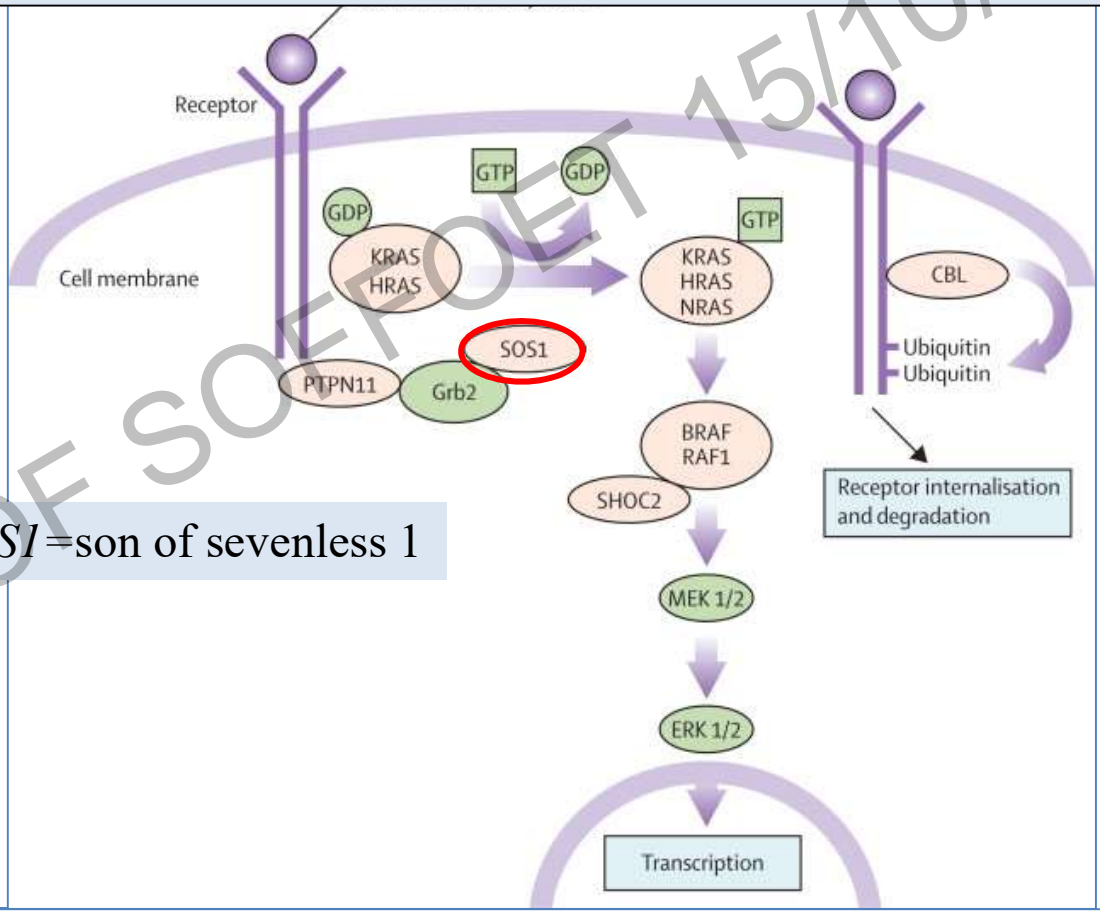
- No methylation abnormality suggestive of Beckwith-Wiedemann syndrome
- Prenatal exome: **heterozygous mutation of SOS1 gene**
  - **pathogenic variant**
  - c.1300G> A; p. (Gly434Arg)
  - chromosome 2p22
  - de novo
  - already reported in the literature in patients **with Noonan syndrome type 4** (OMIM 610733)

- Roberts, A. E., Araki, T., Swanson, K. D., Montgomery, K. T., Schiripo, T. A., Joshi, V. A., Li, L., Yassin, Y., Tamburino, A. M., Neel, B. G., Kucherlapati, R. S. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nature Genet. 39: 70-74, 2007
- Lepri F, De Luca A, Stella L, et al. SOS1 mutations in Noonan syndrome: molecular spectrum, structural insights on pathogenic effects, and genotype-phenotype correlations. Hum Mutat. 2011 Jul;32(7):760-72. doi: 10.1002/humu.21492.

Noonan Syndrome

Mutated genes are involved in the RAS/MAPK cell signaling pathway

- PTPN11 (NS 1)≈ 50%
- SOS1 (NS 4)≈ 15%
- RAF1 (NS 5)≈ 5%
- RIT1 (NS 8)≈ 5%
- KRAS (NS 3)< 5%
- Other<1%
  - BRAF (NS 7)
  - LZTR1(NS 2 et 10)
  - MAP2K1 (NS13)
  - NRAS (NS 6)
  - SOS 2 (NS 9)
  - MRAS (NS11)
  - RRAS2 (NS 12)



SOS1 =son of sevenless 1

The RAS/MAPK pathway is required for cell division, proliferation, differentiation, and migration

Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet*. 2013;381(9863):333-342.

DIAGNOSTIC CRITERIA: NS/BWS

Diagnostic Criteria for Noonan Syndrome

Feature	A = Major	B = Minor
1. Facial	Typical facial dysmorphology (facial features vary with age and are described in Figures 1 through 4)	Suggestive facial dysmorphology
2. Cardiac	Pulmonary valve stenosis, hypertrophic cardiomyopathy, and/or electrocardiographic results typical of Noonan syndrome	Other defect
3. Height	< 3rd percentile	< 10th percentile
4. Chest wall	Pectus carinatum/excavatum	Broad thorax
5. Family history	First-degree relative with definite Noonan syndrome	First-degree relative with suggestive Noonan syndrome
6. Other features	All of the following: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia	One of the following: intellectual disability, cryptorchidism, or lymphatic vessel dysplasia

van der Burgt, I. Noonan syndrome. *Orphanet J Rare Dis* **2,** 4 (2007).

Clinical features of Beckwith–Wiedemann Spectrum

Cardinal features (2 points per feature)	Suggestive features (1 point per feature)
Macroglossia	Birth weight >2 SDS above the mean
Exomphalos	Facial naevus simplex
Lateralised overgrowth	Polyhydramnios and/or Placentomegaly
Multifocal and/or bilateral Wilms tumour or nephroblastomatosis	Ear creases and/or pits
Hyperinsulinism (lasting beyond one week and requiring escalated treatment)	Transient hypoglycaemia (lasting less than a week)
Pathology findings:adrenal cortex cytomegaly, placental mesenchymal dysplasia orpancreatic adenomatosis	Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adrenocortical carcinoma or phaeochromocytoma)
-	Nephromegaly and/or Hepatomegaly
-	Umbilical hernia and/or diastasis recti

SDS, standard deviation score. For a clinical diagnosis of classical BWS, a patient requires a score of ≥4 (this clinical diagnosis does not require the molecular confirmation of an 11p15 anomaly). Patients with a score of ≥2 (including those with classical BWS with a score of ≥4) merit genetic testing for investigation and diagnosis of BWS. Patients with a score of <2 do not meet the criteria for genetic testing. Patients with a score of ≥2 with negative genetic testing should be considered for an alternative diagnosis and/or referral to a BWS expert for further evaluation.

Brioude F, Kalish JM, Mussa A, et al. Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol*. 2018;14(4):229-249.

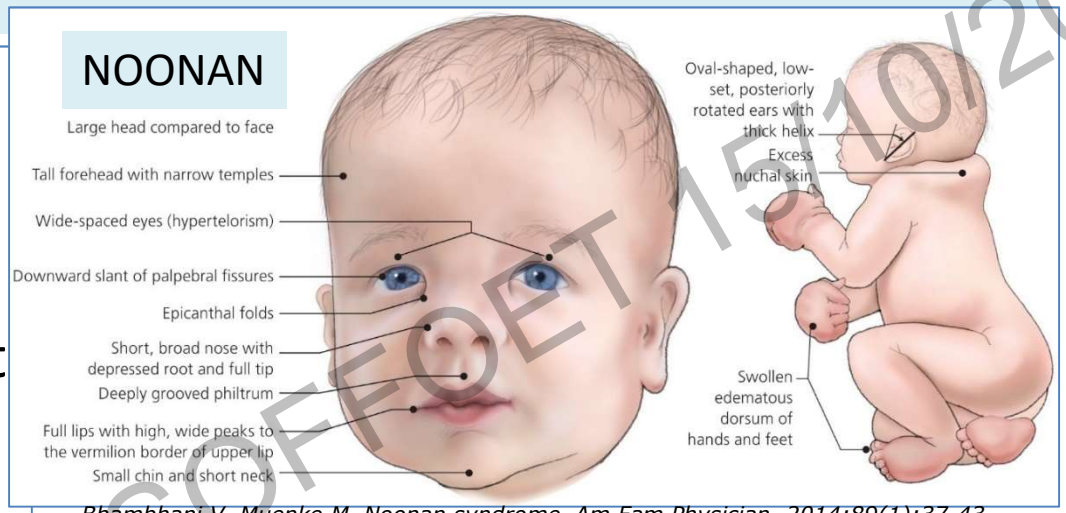
NOONAN SYNDROME: FACIAL DYSMORPHISM

Variation with age:

- most striking in young and middle childhood
- most subtle in the adult

Key features irrespective of age :

- low-set, posteriorly rotated ears with thickened helices
- hypertelorism
- downslanted eyes with epicanthal folds
- ptosis of the upper eyelids



Bhambhani V, Muenke M. Noonan syndrome. Am Fam Physician. 2014;89(1):37-43

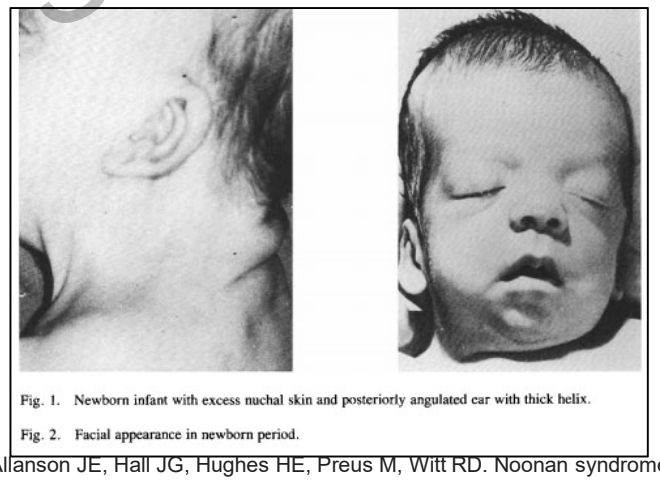
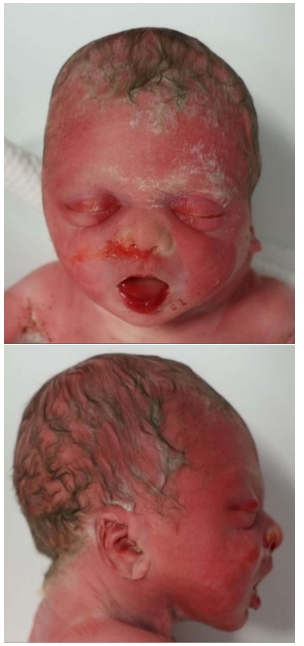


Fig. 1. Newborn infant with excess nuchal skin and posteriorly angulated ear with thick helix.

Fig. 2. Facial appearance in newborn period.

Allanson JE, Hall JG, Hughes HE, Preus M, Witt RD. Noonan syndrome: the changing phenotype. Am J Med Genet. 1985 Jul;21(3):507-14.



Macroglossia with glossoptosis has been reported *(mutation not specified)*

Khirani S, Leboulanger N, Ramirez A, Fauroux B. Life-threatening obstructive sleep apnea caused by adenoid hypertrophy in an infant with noonan syndrome. *Case Rep Pediatr*. 2012;2012:514514.

NOONAN SYNDROME
PRE-PERINATAL FEATURES

- **Increased nuchal translucency and cystic hygroma** (lymphatic dysplasia)+++
- **Polyhydramnios**
- **Relative macrocephaly**
- Cardiac anomalies
- **Genitourinary anomalies**
  - **Dilatation of the renal pelvis is most common**. Duplex collecting systems, minor rotational anomalies, distal ureteric stenosis, renal hypoplasia, unilateral renal agenesis, unilateral renal ectopia, and bilateral cysts with scarring are reported less commonly
- **Hepato**splen**omegaly** is frequent; the cause is likely related to subclinical myelodysplasia
- Mild limb shortening
- **Fetal macrosomia**

For many Noonan syndrome, there are no clinical manifestations at birth!

Myers A, Bernstein JA, Brennan ML, et al. Perinatal features of the RASopathies: Noonan syndrome, cardiofaciocutaneous syndrome and Costello syndrome. Am J Med Genet A. 2014 Nov;164A(11):2814-21.
Croonen EA, Nillesen WM, Stuurman KE, et al. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. *Eur J Hum Genet*. 2013;21(9):936-942.

Ductus venosus agenesis

- More frequent in Noonan

Volpe P, Marasini M, Caruso G, et al. Prenatal diagnosis of ductus venosus agenesis and its association with cytogenetic/congenital anomalies. Prenat Diagn. 2002 Nov;22(11):995-1000.

Demirci O, Yavuz T, Arisoy R, et al. Agenesis of the ductus venosus--a case with Noonan syndrome. Genet Couns. 2015;26(3):373-6.

- Than in Beckwith Wiedemann Syndrome

Strizek B, Zamprakou A, Gottschalk I, et al. Prenatal Diagnosis of Agenesis of Ductus Venosus: A Retrospective Study of Anatomic Variants, Associated Anomalies and Impact on Postnatal Outcome. Ultraschall Med. 2019 Jun;40(3):333-339.

Increased nuchal translucency

- Rare in BWS
  - Drut RM, Drut R. Nonimmune fetal hydrops and placentomegaly: diagnosis of familial WiedemannBeckwith syndrome with trisomy 11p15 using FISH. Am J Med Genet 1996;62:145–9.
  - Fert-Ferrer S, Guichet A, Tantau J, et al. Subtle familial unbalanced translocation t(8;11)(p23.2;p15.5) in two fetuses with Beckwith-Wiedemann features. Prenat Diagn 2000;20:511–5

NOONAN SYNDROME TYPE 4

The phenotype associated with SOS1 defects is distinctive, although within NS spectrum

16 cases with SOS1 missense mutations

Clinical Feature	No./Total (%) of Subjects		
	SOS1 Mutation	All[a]	Without *PTPN11* Mutation[b]
Polyhydramnios	8/15 (53)	43/130 (33)	NA
Fetal Macrosomia	9/15 (60)	NA	NA
Short Stature (<3rd centile)	2/15 (13)	84/115 (73)***	45/64 (70)***
Macrocephaly	9/16 (56)	19/151 (12)***	NA
Downslanting Palpebral Fissures	15/16 (94)	NA	NA
Ptosis	16/16 (100)	NA	NA
Low-Set Ears with Thickened Helix	16/16 (100)	NA	NA
Thick Lips/Macrostomia	14/16 (88)	NA	NA
Short/Webbed Neck	15/16 (94)	NA	NA
Abnormal Pectus	16/16 (100)	144/151 (95)	46/61 (75)*
Cardiac Involvement	13/16 (81)	132/151 (87)	42/66 (64)
Pulmonary Valve Stenosis	10/16 (62)	93/151 (62)	30/65 (46)
Septal Defect	4/16 (25)	29/151 (19)	11/63 (18)
HCM	2/16 (12)	30/151 (20)	17/65 (26)
Facial Keratosis Pilaris	8/16 (50)	21/151 (14)***	NA
Curly Hair	14/16 (88)	44/151 (29)***	NA
Cryptorchidism	6/9 (67)	64/83 (77)	25/35 (71)
Mental Retardation	1/16 (6)	32/105 (30)*	21/59 (36)*
Bleeding Diathesis	5/16 (31)	37/151 (25)	NA

[a]From Ref. [27]. [b]From Ref. 5. Significance: *, < .05; **, < .01; ***, < .001. Definitions: HCM, hypertrophic cardiomyopathy; NA, not available.

Tartaglia M, Pennacchio LA, Zhao C, et al. Gain-of-function SOS1 mutations cause a distinctive form of Noonan syndrome. Nat Genet. 2007 Jan;39(1):75-9. doi: 10.1038/ng1939.

Table 2

Correlations between genotype and phenotype in Noonan syndrome

	Cardiovascular	Growth	Developmental	Skin and hair	Other
PTPN11 (roughly 50%)	More pulmonary stenosis; less hypertrophic cardiomyopathy, and atrial septal defect (ostium secundum type)	More short stature; lower IGF1 concentrations	Patients with N308D and N308S have little or no intellectual disability	..	More bleeding diathesis and juvenile myelomonocytic leukaemia
SOS1 (roughly 10%)	Less atrial septal defect	Less short stature	Less intellectual disability, language delays	Similar to cardiofaciocutaneous syndrome	..
RAF1 (roughly 10%)	More hypertrophic cardiomyopathy	..	..	More naevi, lentigines, café au lait spots	..
KRAS (<2%)	..	..	More severe cognitive delay	Similar to cardiofaciocutaneous syndrome	..
NRAS (<1%)	..	..	..	..	..

Percentages in parentheses are the proportion of patients with Noonan syndrome who have the mutation.

Allen MJ, Sharma S. Noonan Syndrome. 2021 Jul 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan

Risk of solid tumors rather than leukemia

mandibular multiple giant cell lesions , abdominal rhabdomyosarcoma, cerebral glioma, skin granular cell tumors, Lepri et al .

NOONAN SYNDROME TYPE 4

WILEY HUMAN MUTATION
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Hum Mutat. 2011 Jul; 32(7): 760–772.
Published online 2011 Mar 8. doi: 10.1002/humu.21492
PMCID: PMC3118925
NIHMSID: NIHMS276847
PMID: 21387466

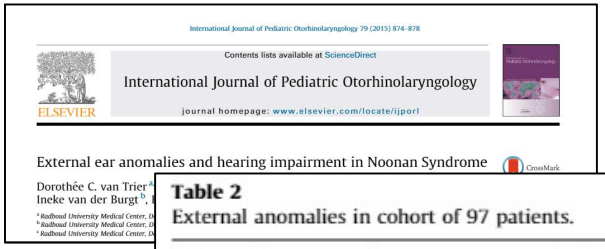
***SOS1* Mutations in Noonan Syndrome: Molecular Spectrum, Structural Insights on Pathogenic Effects, and Genotype–Phenotype Correlations**

Francesca Lepri,[1,17] Alessandro De Luca,[1] Lorenzo Stella,[2] Cesare Rossi,[3] Giuseppina Baldassarre,[4] Francesca Pantaleoni,[5] Viviana Cordeddu,[5] Bradley J Williams,[6] Maria L Dentici,[1,17] Viviana Caputo,[5] Serenella Venanzi,[5] Michela Bonaguro,[3] Ines Kavamura,[7] Maria F Faienza,[8] Alba Pilotta,[9] Franco Stanzial,[10] Francesca Faravelli,[11] Orazio Gabrielli,[12] Bruno Marino,[13] Giovanni Neri,[14] Margherita Cirillo Silengo,[4] Giovanni B Ferrero,[4] Isabella Torrente,[1] Angelo Selicorni,[15] Laura Mazzanti,[16] Maria C Digilio,[17] Giuseppe Zampino,[18] Bruno Dallapiccola,[17] Bruce D Gelb,[19] and Marco Tartaglia[5,*]

***"more than one-third of subjects with mutated SOS1 allele exhibited fetal macrosomia**, which however, did not appear to correlate with the extent of their postnatal growth, being length/stature in these subjects below the third centile in a comparable proportion of cases"*

Facial dysmorphism and other features of subjects with Noonan syndrome heterozygous for mutations in the *SOS1* gene. *SOS1* mutation-positive subjects generally exhibit typical facial features, including macrocephaly, hypertelorism, ptosis, downslanting palpebral fissures, sparse eyebrows with keratosis pylaris, a short and broad nose with upturned tip, low-set and posteriorly angulated ears, and high forehead commonly associated with bitemporal narrowing and prominent supraorbital ridges. Curly hair is present in most of the patients. Other common features include pectus anomalies (NS10, NS19, NS37), short and/or webbed neck (NS6, NS10, NS19, NS22, NS38), and cubitus valgus (NS37). Keloid scars (NS16), recurrent hemorrhages (NS18), and deep plantar creases (NS38) also occur in these subjects. In some infants, the face is suggestive of cardiofaciocutaneous syndrome due to the coarseness of features (NS39)

NOONAN SYNDROME TYPE 4



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External ear anomalies and hearing impairment in Noonan Syndrome

Dorothée C. van Trier[a]
Ineke van der Burgt[b],

[a] Radboud University Medical Center, D
[b] Radboud University Medical Center, D
[c] Radboud University Medical Center, D

Table 2
External anomalies in cohort of 97 patients.

External ear anomalies	Number of patients	*PTPN11* ($n=48$)	*SOS1* ($n=10$)	*RAF1* ($n=5$)	*SHOC2* ($n=5$)	*KRAS* ($n=1$)	*MAP2K2* ($n=1$)	*A2ML1* ($n=1$)
Low set ears	69 (71%)	34	8	4	4	0	1	0
Posteriorly rotated ears	28 (28%)	11	6	2	3	0	0	0
Thickened helices	18 (18%)	7	1	1	3	0	0	0
Protruding ears	14 (14%)	8	1	1	0	0	0	0
Dysplastic ears	4 (4%)	3	0	0	0	0	0	0
Total external ear anomalies	75 (77%)	39 81%	8 80%	4 80%	4 80%	0 0%	1 100%	0 0%

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PRENATAL **DIAGNOSIS**

ORIGINAL ARTICLE

Retrospective study of prenatal ultrasound findings in newborns with a Noonan spectrum disorder

Fahad Hakami[1,2,3], Mitchell W. Dillon[2], Matthew Lebo[1,2] and Heather Mason-Suares[1,2]*

Gene	mRNA transcript	Newborn	Clinical suspicion	Ultrasound findings	cDNA change	Amino acid change	Class.	Ref.
SOS1	NM_005633	32	NS	Polyhydramnios	c.508A > G	p.Lys170Glu	P	30
		33	NS	Polyhydramnios and short femurs	c.1294T > C	p.Trp432Arg	P	31
		34	NS	Cystic hygroma	c.1642A > C	p.Ser548Arg	P	31
		35	NS	Cystic hygroma and increased NT	c.1655G > A	p.Arg552Lys	P	31
		36	NS	Hydrops and pyelectasis	c.1655G > A	p.Arg552Lys	P	31
		37	NS	Increased NT	c.2536G > A	p.Glu846Lys	P	31

NOONAN SYNDROME TYPE 4

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ORIGINAL ARTICLE

10 family members

WILEY AMERICAN JOURNAL OF medical genetics PART A

Variable phenotypic expression in a large Noonan syndrome family segregating a novel SOS1 mutation

Dorothée C. van Trier[1] | Tuula Rinne[2] | Kees Noordam[1] | Jos M. Draaisma[1] | Ineke van der Burgt[2]

No cardiac abnormalities, short stature, or lymphatic dysplasia were found in these individuals.

3 family members

European Journal of Human Genetics (2015) 23, 1531–1537

www.nature.com/ejhg

ARTICLE

Differential allelic expression of *SOS1* and hyperexpression of the activating *SOS1* c.755C variant in a Noonan syndrome family

Silvia Moncini[1], Maria Teresa Bonati[2], Ilaria Morella[3], Luca Ferrari[1], Riccardo Brambilla[3] and Paola Riva*[,1]

CONCLUSION

- Noonan syndrome can be « atypical », especially type 4
- Be careful when facing macrosomia, macroglossia, visceromegaly and also placenta mesenchymal dysplasia

Presentation of Dr A Konstandidinou, European Society of Pathology 2021: a Noonan case (TOP ar 19 GW) with RAF1 mutation and features of PMD

→Do not systematically suggest macrosomia/overgrowth disorders, such as BWS

- Hydramnios, increased nuchal translucency and DV agenesis are uncommon in BWS

THANK YOU