CERPO
Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Seminario Genética: Rasopatías. Sospecha prenatal

Dra Alejandra Plaza Rasjido
Dra Catherine Diaz Sanhueza

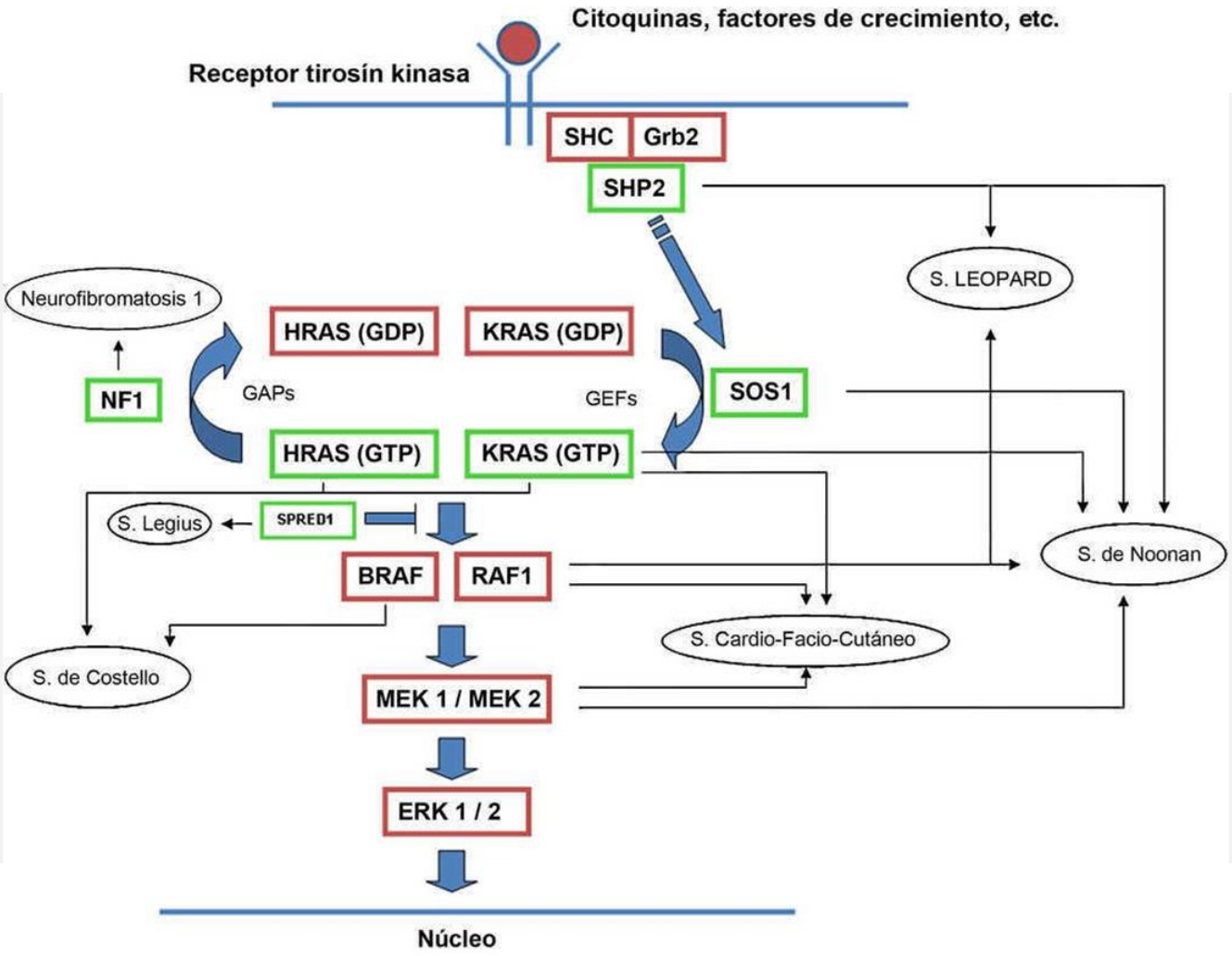
Programa Especialización Ginecología y Obstetricia
Facultad de Medicina, Universidad de los Andes
Agosto 2023

Introducción:

- Grupo de trastornos genéticos causados por mutaciones o variantes en alguno de los componentes de la vía RAS/MAPK
- **Rasgos:** Dismorfia craneo facial, estatura baja, alteraciones cardíacas, cutáneas, musculo esqueléticas y del desarrollo neurocognitivo.
- Hallazgos ecográficos no son específicos

Aoki Y, Niihori T, Inoue S, Matsubara Y. Recent advances in RASopathies. J Hum Genet 2016; 61:33.

Via RAS/MAPK



Actas Dermosifiliogr. 2011;102:402-16

Rasopatías:

CERPO

A. Sindrome de Noonan (SN)
B. Neurofibromatosis tipo 1 (NF1)
C. Sindrome de Noonan con multiples léntigos (Sd Leopard)
D. Sindrome cardio facio cutáneo (CFC)
E. Sindrome de Costello (SC)
F. Sindrome de Legius (SL)
G. Sindrome malformacion AV por malf. capilar (CM-AVM)
H. Diagnóstico prenatal
I. Caso clínico CERPO

Síndrome de Noonan (SN)

- Prevalencia: 1/1000 a 1/2500.
- Trastorno **autosómico dominante**
- Mutación en genes:

- **PTPN11**: 50% de los casos
- **LZTR1:** 10% *(recesivo)*
- **KRAS:** 1,5%
- **RAF1:** 5%
- **SOS1:** 10%

-Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/
-Zenker M, Edouard T, Blair JC, Cappa M. Noonan syndrome: improving recognition and diagnosis. Arch Dis Child. 2022 Dec;107(12):1073-1078.

Gene [1, 2]	Proportion of NS Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detected by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
BRAF	<2% [6]	100%	Unknown [7]
KRAS	<5% [8]	100%	Unknown [7]
LZTR1	~8% [9]	100%	Unknown [7]
MAP2K1	<2% [10]	100%	Unknown [7]
MRAS	<1% [11]	100%	Unknown [7]
NRAS	<1% [12]	100%	Unknown [7]
PTPN11	50% [13]	Nearly 100%	Rare duplication, [14] diagnosis of NS questioned [15]
RAF1	5% [16]	Nearly 100%	1 reported case w/a duplication, [17] diagnosis of NS questioned [15]; 1 reported case of a deletion [18]
RASA2	Unknown [19]	100%	Unknown [7]
RIT1	5% [16]	100%	Unknown [7]
RRAS2	<1% [20]	100%	Unknown [7]
SOS1	10%-13% [21]	100%	Unknown [7]
SOS2	~4% [22]	100%	Unknown [7]
Others [23]	NA		

Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/

Clínica según gen alterado

Table 1 List of syndromes associated with mutations in genes in the RAS-MAPK pathway.

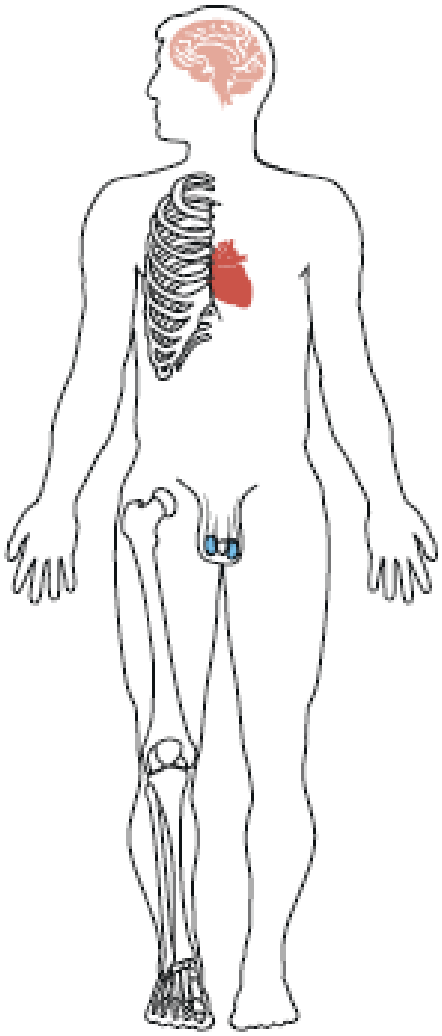
Syndrome	Features	Gene	%	ClinGen	Locus
Noonan OMIM #163950 1:1000/2500	Craniofacial abnormalities Congenital heart disease (70%–80%): Pulmonary valve stenosis 50%–60% Hypertrophic cardiomyopathy 20%–25%	*PTPN*11*	50	Definitive	12q24.1
	Septal defects 10%–20%	*SO*S1*	11	Definitive	2p22.1
	Short stature (70%, usually mild)	*RAF*1*	5	Definitive	3p25.1
	Oncological and haematologic disorders	*BRA*F*	< 2	Moderate	7q34
	Easy bleeding.	*MAP*2K1*	< 2	Limited	15q22.31
	Transient myeloproliferative disorder in	*KRA*S*	1,5	Definitive	12p12.1
	newborns	*NRA*S*	0,2	Definitive	1p15.2
	Juvenile myelomonocytic leukaemia	*RIT*1*	5	Definitive	1q22
	Intellectual disability (10%–30%)	*SHO*C2*	2	Disputed	10q25
	Usually mild	*PPP*1CB*		No evidence	2p23
	CNS abnormalities	*SO*S2*		Moderate	14q21.3
	Seizures (5%–15%), Chiari malformation I	*RR*AS*		Limited	19q13.33
	(infrequent)	*RAS*A2*		Limited	3q23
	Musculoskeletal anomalies	*SP*RY1*		No evidence	4q28.1
	Chest deformities, joint hypermobility,	*LZT*R1*		Strong	22q11.21
	scoliosis, hypotonia,			(limited for	
	Vision and hearing problems			AR)	
	Refraction errors, strabismus, hearing loss	*MA*P3K8*		No evidence	10p11.23
	(infrequent)	*MY*ST4*		No evidence	10q22.2
	Genitourinary disorders	*A2*ML1*		Disputed	12p13.21
	Cryptorchidism.	*RA*SA1*		Disputed	5q14.3

Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/

Características clínicas:

Features highly suggestive of NS (2 or more)

1. Dysmorphic facial features
2. Heart defect
3. Short stature
4. Chest deformity
5. First-degree relative who has NS or any of the above features
6. Developmental delay/learning issues
7. Cryptorchidism
8. Lymphatic dysplasia
9. Delayed puberty



Other potential features

Thick curly or sparse thin hair

Vision/eye problems

Dental/oral issues

Feeding issues

Failure to thrive

Kidney problems

Lymphoedema

Bleeding/clotting problems

Skin conditions

Behavioural issues

Speech disorders

Hearing problems

Zenker M, Edouard T, Blair JC, Cappa M. Noonan syndrome: improving recognition and diagnosis. Arch Dis Child. 2022 Dec;107(12):1073-1078.

Hallazgos prenatales:

- **Alt Sistema linfático:**
  -Aumento de la translucencia nucal
  -Higroma quístico
  -Hidrops fetal
  -Ascitis
- **Renales**: Hidronefrosis
- **Cardíacas:**
  -MCH
  -Estenosis pulmonar

Otras: PHA, microcefalia, macrosomia fetal, extremidades cortas

Croonen EA, Nillesen. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. Eur J Hum Genet. 2013 Sep;21(9):936-42.

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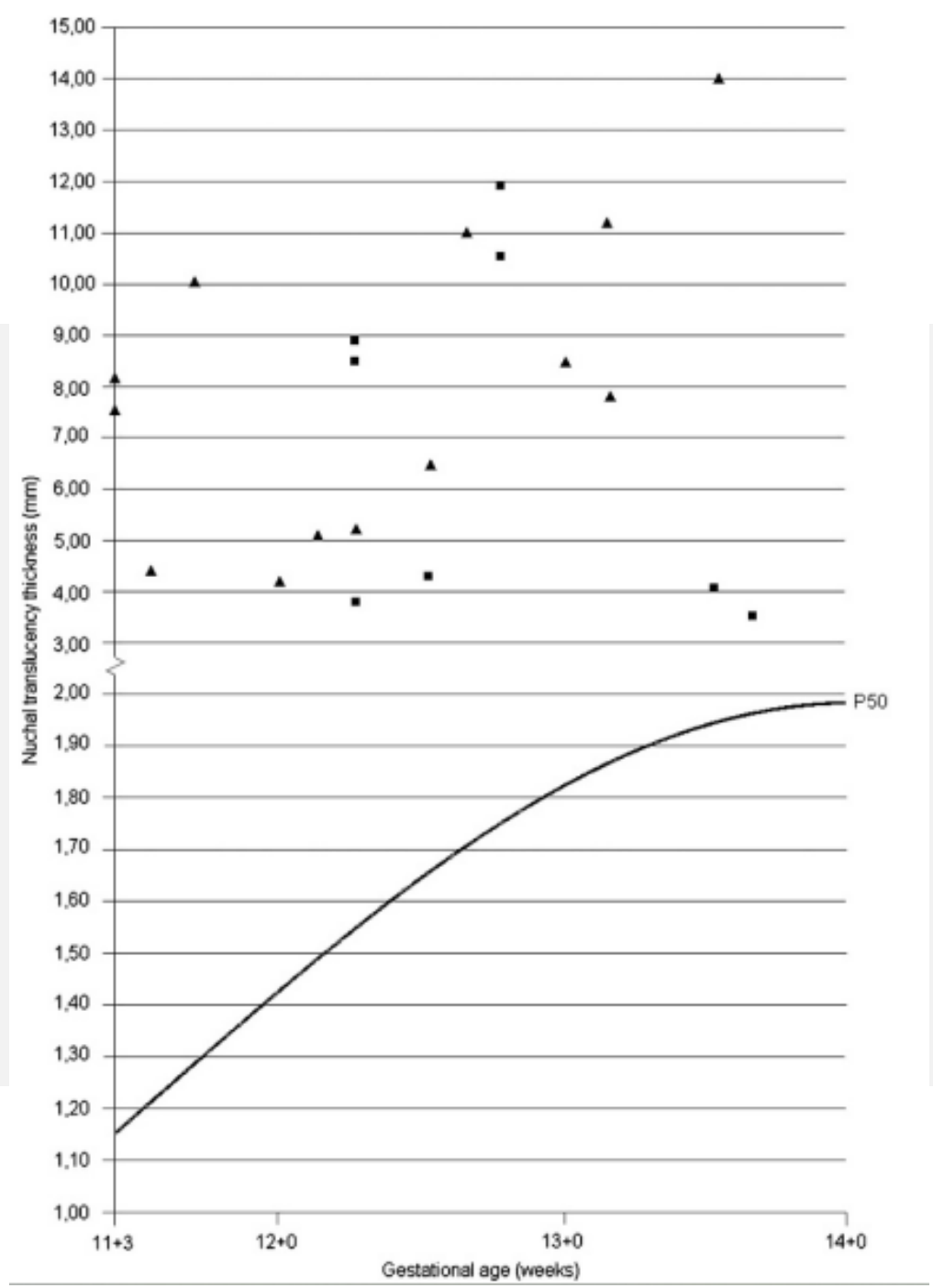
Table 1 Prenatal findings of 75 fetuses with a normal karyotype

Findings	*Total group (n = 75)*	*Mutation-positive group (n = 13) (%)*	*Mutation-negative group (n = 62) (%)*	*P*-value
Increased NT (%)	50/75 (66.7)	13/13 (100)	37/62 (59.7)	0.003[a]
Mean NT (mm) at 11–14 weeks	7.3 (3.6–14)	8.0 (4.2–14)	6.5 (3.6–11.9)	0.854[b]
Cystic hygroma	17/75 (22.7)	4/13 (30.8)	13/62 (21.0)	0.475[a]
Distended JLS	12/75 (16.0)	7/13 (53.8)	5/62 (8.1)	0.000[a]
Ascites	1/75 (1.3)	1/13 (7.7)	0/62 (0.0)	0.173[a]
Hydrothorax	9/75 (12.0)	7/13 (53.8)	2/62 (3.2)	0.000[a]
Cardiac anomalies	15/75 (20.0)	5/13 (38.5)	10/62 (16.1)	0.120[a]
Renal anomalies	7/75 (9.3)	6/13 (46.2)	1/62 (1.6)	0.000[a]
Hydrops fetalis	15/75 (20.0)	4/13 (30.8)	11/62 (17.7)	0.279[a]
Polyhydramnion	3/75 (4.0)	3/13 (23.1)	0/62 (0.0)	0.004[a]

Abbreviations: JLS, jugular lymphatic sacs; NT, nuchal translucency.
[a]Fisher's Exact test.
[b]Student's *t*-test.

Croonen EA, Nillesen. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. Eur J Hum Genet. 2013 Sep;21(9):936-42.

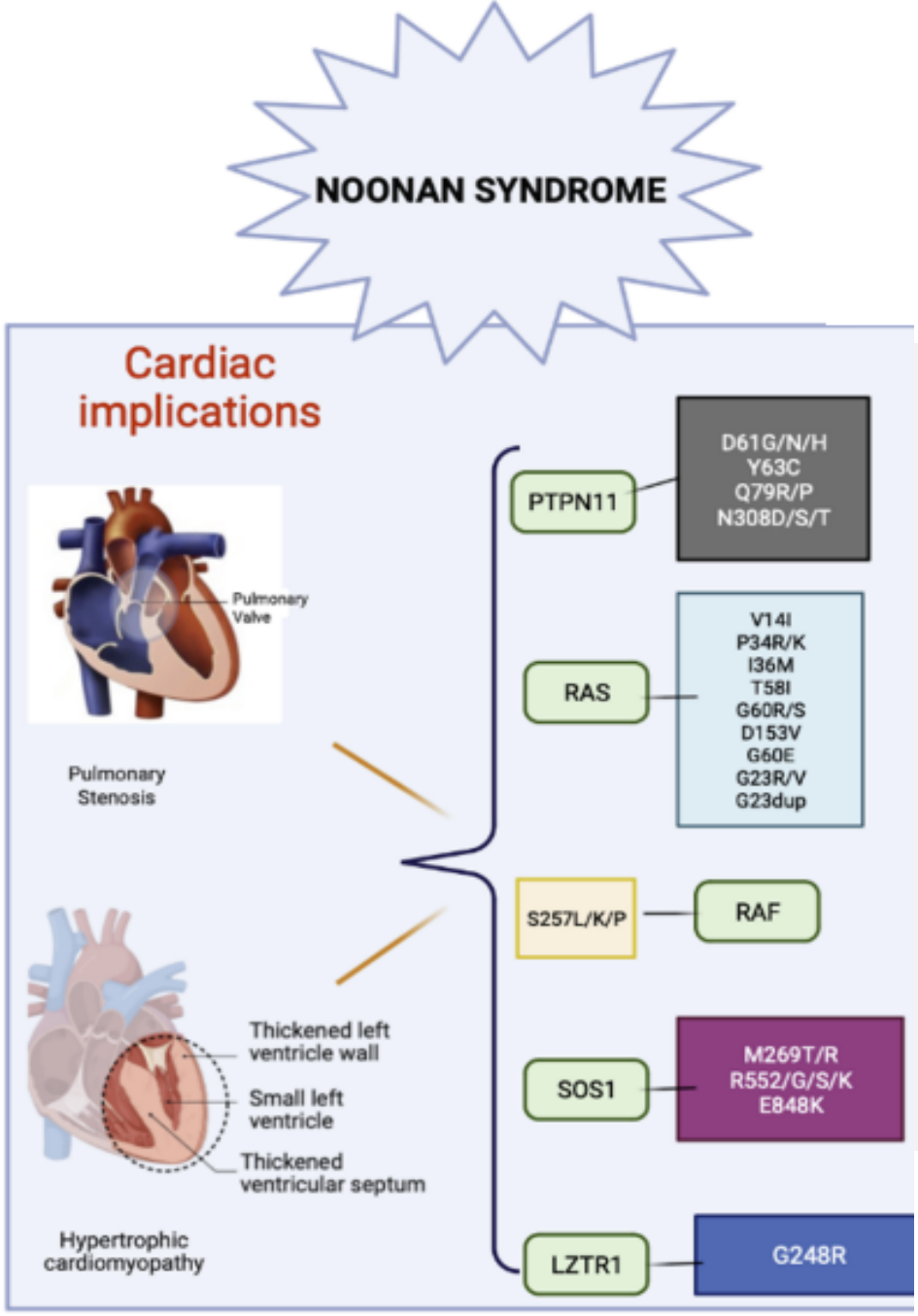


CERPO

Translucencia Nucal

SN (+): TN promedio 8 mm

Croonen EA, Nillesen. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. Eur J Hum Genet. 2013 Sep;21(9):936-42



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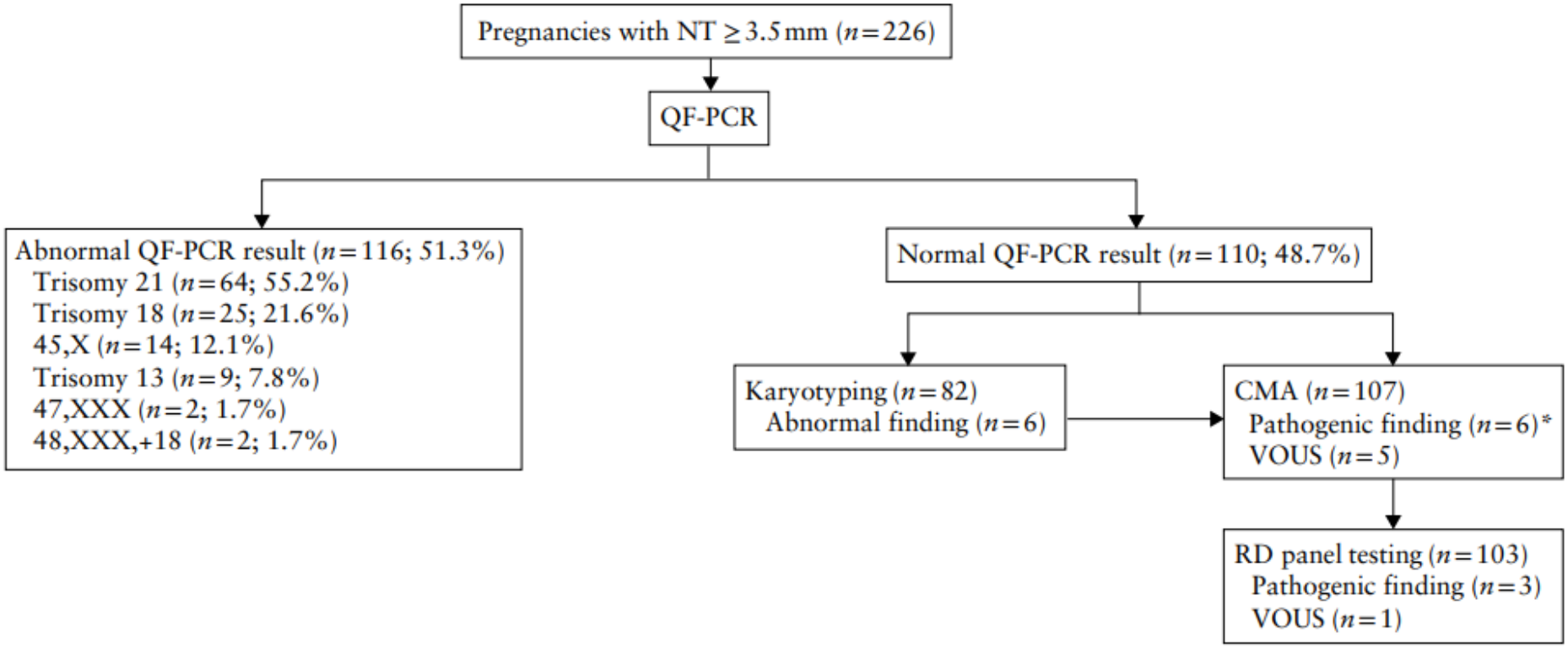
- **Estenosis V pulmonar** 50-60%
- **Cardiopatía hipertrófica** 20%
- Defectos septo atrial 6-10%
- Defecto septo ventricular
- Canal AV
- Coartación aórtica
- Estenosis aortica

Hilal N, Chen Z, Chen MH, Choudhury S. RASopathies and cardiac manifestations. Front Cardiovasc Med. 2023 Jul 17;10:1176828.

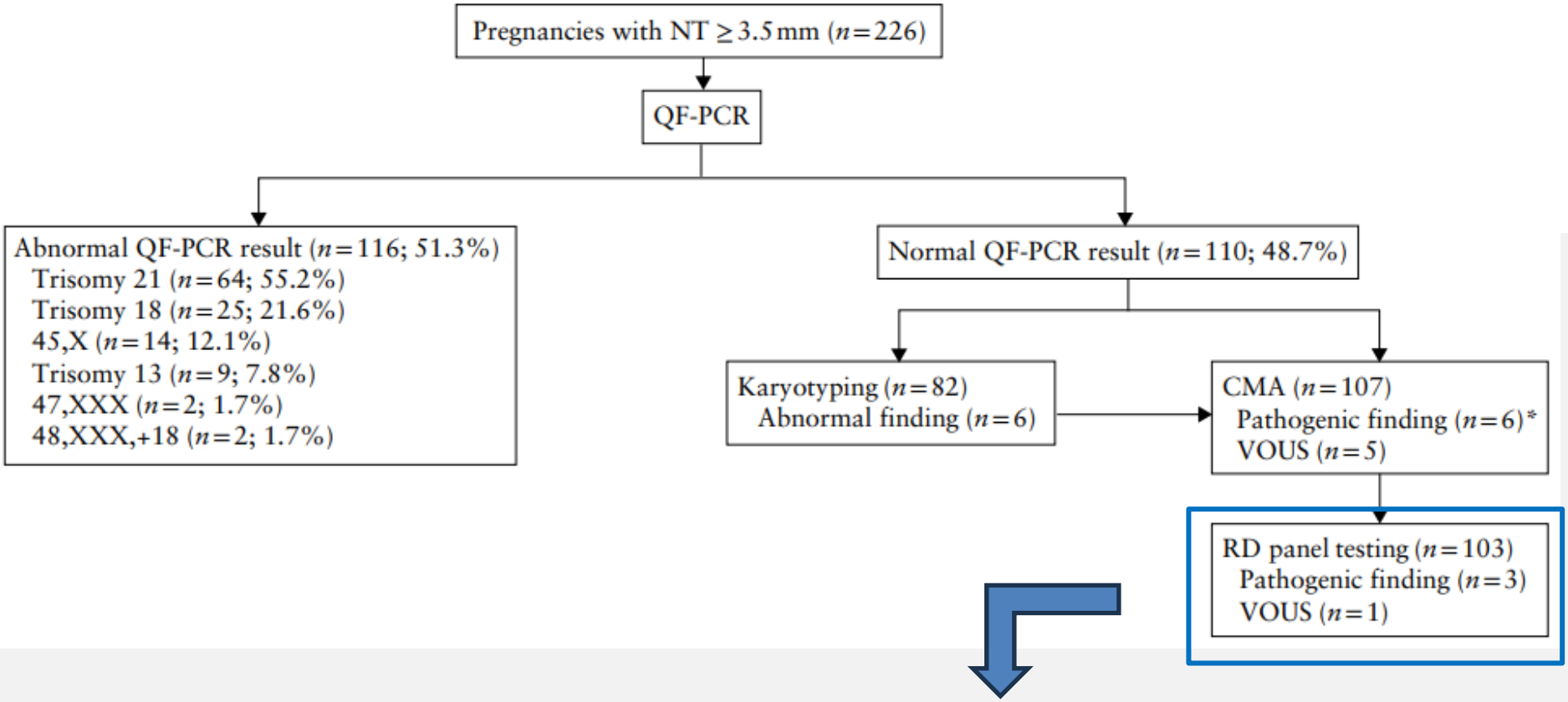
Ultrasound Obstet Gynecol 2020; 55: 383–390
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20352

Microarray and RASopathy-disorder testing in fetuses with increased nuchal translucency

P. SINAJON[1,2], D. CHITAYAT[1,2], M. ROIFMAN[1,2], S. WASIM[3], S. CARMONA[4], G. RYAN[5], A. NOOR[6], E. KOLOMIETZ[6] and K. CHONG[1]



Sinajon P, Chitayat D, Roifman M, Wasim S, Carmona S, Ryan G, Noor A, Kolomietz E, Chong K. Microarray and RASopathy-disorder testing in fetuses with increased nuchal translucency. Ultrasound Obstet Gynecol. 2020 Mar;55(3):383-390.



- 3 casos positivos
- Mediana de TN 10 mm
- EG a la TN: 12+3 semanas
- **TN óptima para screening de RD 7,95 mm (S100% y E 86%)**

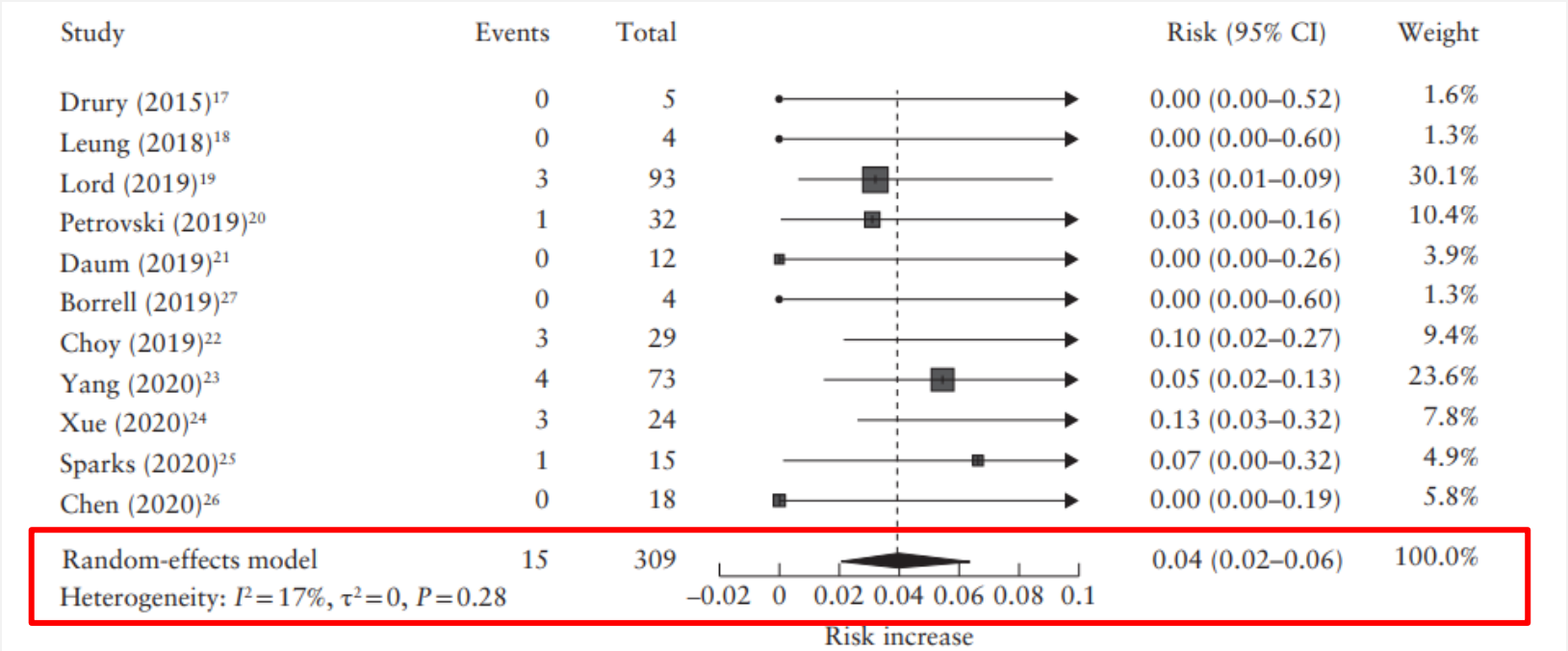
Sinajon P, Chitayat D, Roifman M, Wasim S, Carmona S, Ryan G, Noor A, Kolomietz E, Chong K. Microarray and RASopathy-disorder testing in fetuses with increased nuchal translucency. Ultrasound Obstet Gynecol. 2020 Mar;55(3):383-390.

Ultrasound Obstet Gynecol 2022; **59**: 26–32
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.23746

Diagnostic yield of next-generation sequencing in fetuses with isolated increased nuchal translucency: systematic review and meta-analysis

M. PAUTA[1], R. J. MARTINEZ-PORTILLA[1] and A. BORRELL[1,2]

[1]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain;* [2]*Barcelona Centre for Maternal-Fetal and Neonatal Medicine (BCNatal), Hospital Clínic Barcelona, Universitat de Barcelona, Barcelona, Spain*



e 3 Forest plot of diagnostic yield of exome or genome sequencing for pathogenic and likely pathogenic variants in 309 fetuses with ed increased nuchal translucency and a normal chromosomal microarray analysis result. Only first author is given for each study.

Pauta M, Martinez-Portilla RJ, Borrell A. Diagnostic yield of next-generation sequencing in fetuses with isolated increased nuchal translucency: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2022 Jan;59(1):26-32.

CERPO

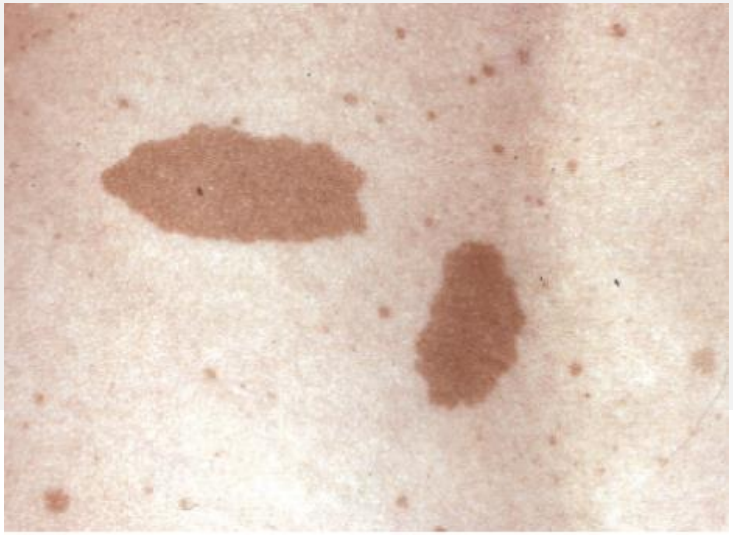
Table 2 Characteristics of 15 fetuses with isolated increased nuchal translucency (NT) in which a causative pathogenic (Pat) or likely pathogenic (L Pat) variant was identified on prenatal exome or genome sequencing

Case	*Ref*	*NT (mm)*	*Gene*	*Variant*	*Type*	*Clin class*	*Inheritance*	*Zygosity*	*Related syndrome or disorder*
1	19	4.5	*PTPN11*	NM_002834.5:c.922A>G	Missense	Pat	Inherited (AD)	Hetero	Noonan syndrome
2	19	4.7	*MID1*	NM_033290.4:c.1102C>T	Nonsense	Pat	*De novo* (X-linked)	Hemi	Opitz GBBB syndrome, type 1
3	19	8.0	*TAB2*	NM_015093.5:c.1407_1408delTC	Frameshift	Pat	*De novo* (AD)	Hetero	Polyvalvular heart disease syndrome
4	20	3.5	*RERE*	NM_001042681.2:c.248dupA	Frameshift	Pat	*De novo* (AD)	Hetero	*RERE*-related disorder
5	22	4.8	*ANKRD11*	NM_001256182:c.2404dupC	Frameshift	L Pat	*De novo* (AD)	Hetero	KBG syndrome
6	22	5	*GATA4*	NM_002052:c.C1325T	Missense	L Pat	Inherited (mat) (AD)	Hetero	Atrial septal defect 2
7	22	3.5	*NSD1*	NM_022455:c.3797-2A>G	Splicing	Pat	N/S (AD)	Hetero	Sotos syndrome
8	23	4.0	*SETD2*	NM_014159:c.4376C>T	Missense	Pat	*De novo* (AD)	Hetero	Luscan–Lumish syndrome
9	23	4.0	*TMEM231*	ENST00000568377:c.525+1G>A; c.661C>T	Splicing/missense	L Pat/Pat	Inherited (AR)	Compound hetero	Meckel syndrome
10	23	5.1	*PTPN11*	NM_002834.4:c.124A>G	Missense	Pat	*De novo* (AD)	Hetero	Noonan syndrome
11	23	6.3	*RAF1*	NM_002880:c.770C>T	Missense	Pat	*De novo* (AD)	Hetero	Noonan syndrome
12	24	3.5	*PIGN*	NM_176787.5:c.963G>A; c.1859+1G>A	Synonymous/splicing	L Pat/L Pat	Inherited (AR)	Compound hetero	Multiple congenital anomalies, hypotonia–seizures syndrome 1
13	24	7.9	*SOS1*	NM_005633.4:c.1297G>A	Missense	Pat	*De novo* (AD)	Hetero	Noonan syndrome 4
14	24	8.8	*ECE1*	NM_001113349.2:c.1930G>A	Missense	L Pat	*De novo* (AD)	Hetero	Hirschsprung disease, cardiac defects, autonomic dysfunction
15	25	4.5	*CHD7*	NM_017780.3:c.3422_3423delTG	Frameshift	Pat	*De novo* (AD)	Hetero	CHARGE syndrome

Pauta M, Martinez-Portilla RJ, Borrell A. Diagnostic yield of next-generation sequencing in fetuses with isolated increased nuchal translucency: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2022 Jan;59(1):26-32.

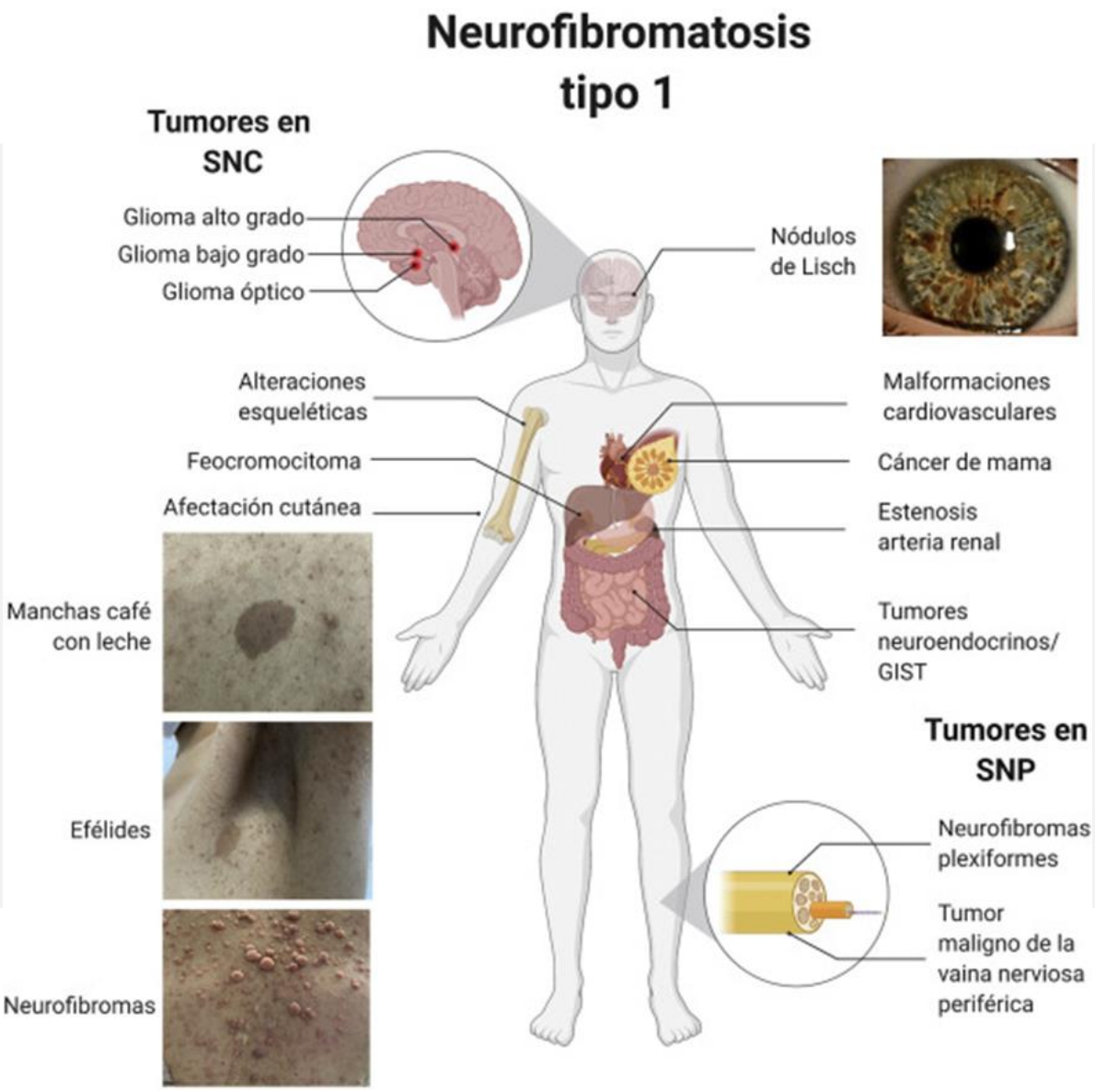
Neurofibromatosis tipo 1 (NF1)

- Trastorno ***autosómico dominante***
- Incidencia 1/2600-1/3000 RN
- Mutación: Gen NF1 en el cromosoma 17q11.2
- Clínica variable
- Alto riesgo de desarrollar tumores malignos

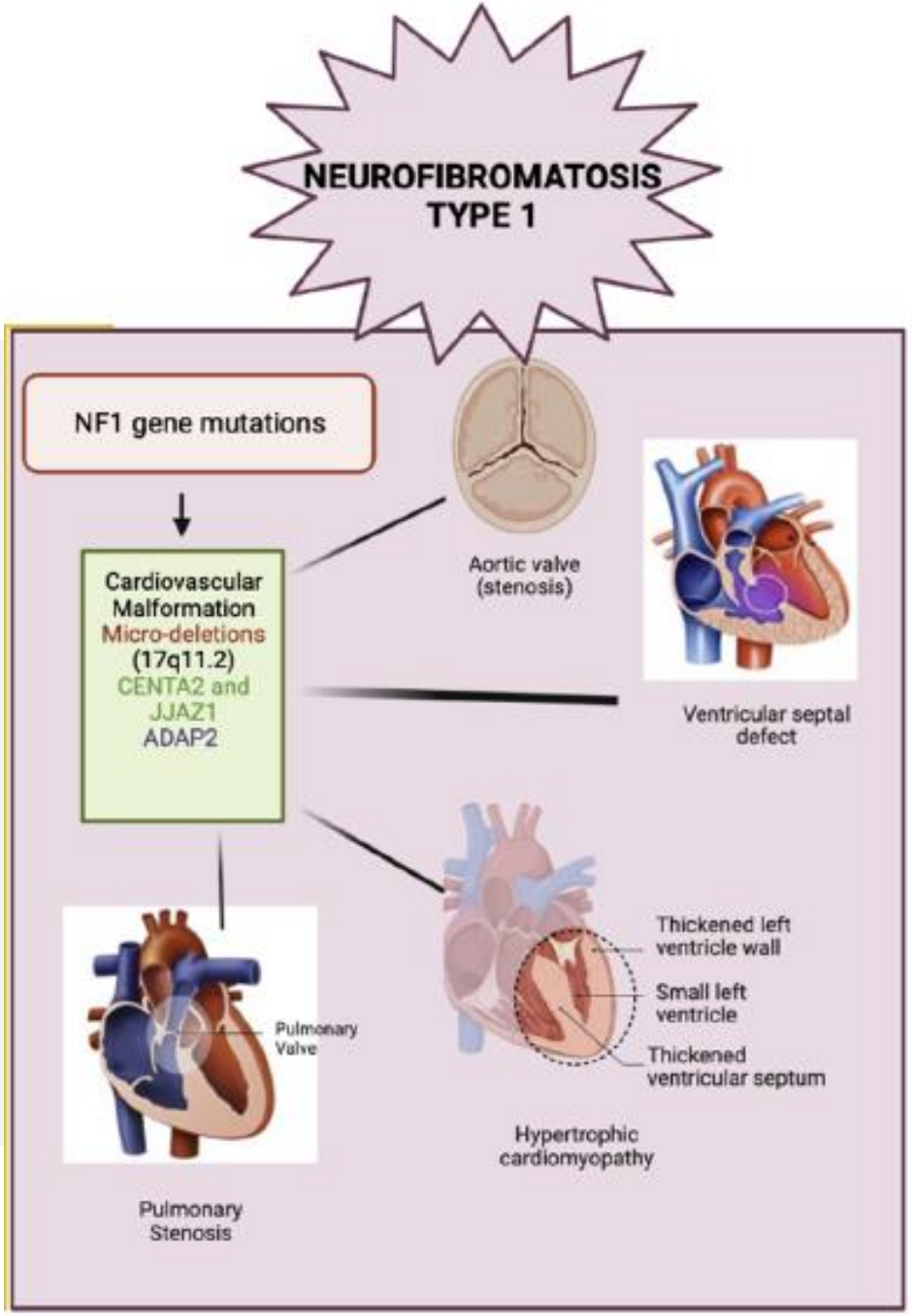


Friedman JM. Neurofibromatosis 1. 1998 Oct 2 [Updated 2022 Apr 21]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1109/

Clínica:



Hebron KE, Hernandez ER, Yohe ME. The RASopathies: from pathogenetics to therapeutics. Dis Model Mech. 2022 Feb 1;15(2):dmm049107.



CERPO

- **Estenosis pulmonar**
- Defecto septo interauricular
- MCPH 2%

Hilal N, Chen Z, Chen MH, Choudhury S. RASopathies and cardiac manifestations. Front Cardiovasc Med. 2023 Jul 17;10:1176828.

Diagnóstico:

- Difícil diagnóstico prenatal
- Postnatal:

Table 1. Revised diagnostic criteria for neurofibromatosis type 1 (NF1).

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals[a] (Supplementary Fig. 6)
- Freckling in the axillary or inguinal region[a] (Supplementary Fig. 7)
- Two or more neurofibromas of any type *or* one plexiform neurofibroma (Supplementary Fig. 8a, b)
- Optic pathway glioma (Supplementary Fig. 9)
- Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging (Supplementary Fig. 10a, b)
- A distinctive osseous lesion such as sphenoid dysplasia,[b] anterolateral bowing of the tibia, or pseudarthrosis of a long bone (Supplementary Fig. 11)
- A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

Legius E, Messiaen L, Wolkenstein P,nternational Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC); Huson SM, Evans DG, Plotkin SR. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021 Aug;23(8):1506-1513.

Manifestaciones por edad

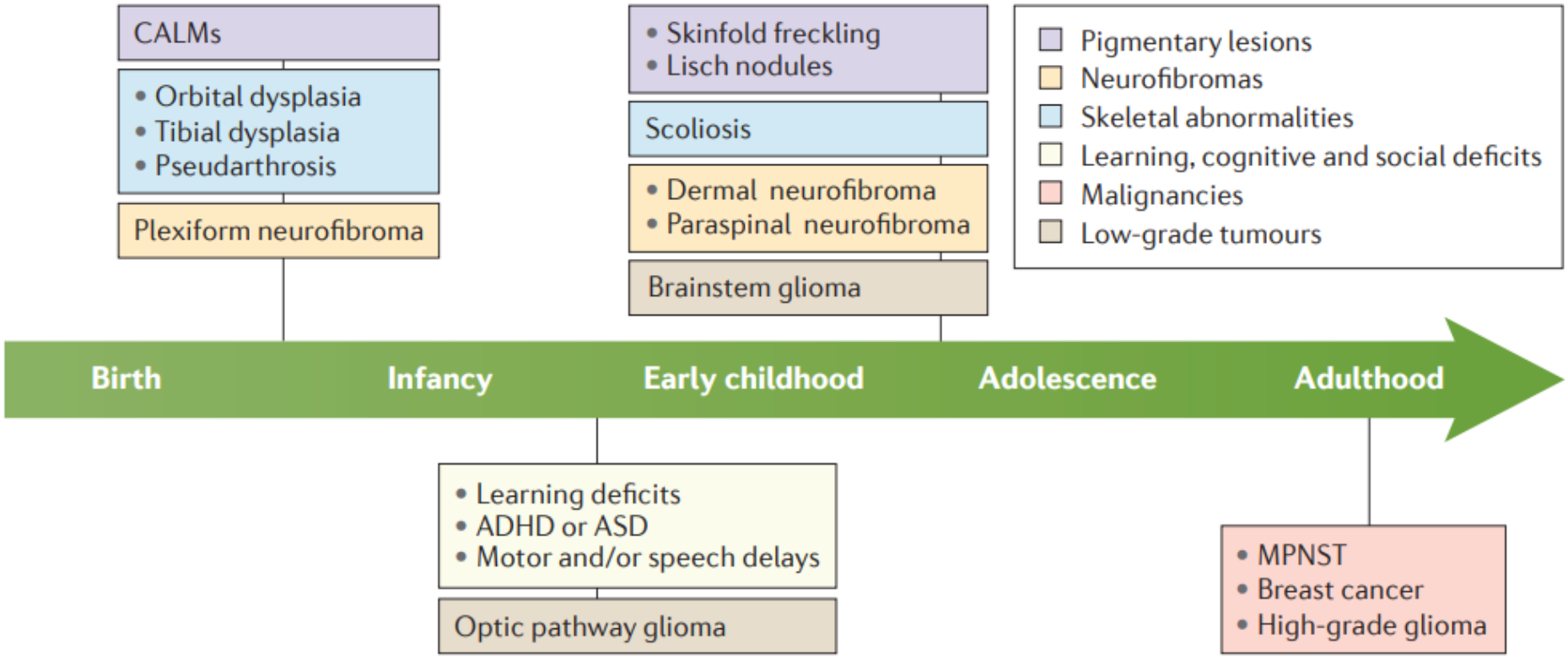


Figure 2 | **Development of clinical features of neurofibromatosis type 1.**

Gutmann, D., Ferner, R., Listernick, R. et al. Neurofibromatosis type 1. Nat Rev Dis Primers 3, 17004 (2017).

PRENATAL DIAGNOSIS
Prenat Diagn 2006; **26**: 1110–1114.
Published online 18 September 2006 in Wiley InterScience

CERPO

Prenatal diagnosis of neurofibromatosis type 1: sonographic and MRI findings

Rachael L. McEwing*, Roume Joelle, Marc Mohlo, Jean-Pierre Bernard, Yvette Hillion and Yves Ville
Departments of Obstetrics and Gynecology, Genetics, Radiology and Pathology, CHI Poissy, Poissy, Cedex, France

- **Ecografía:** Hidrocefalia, macrocefalia, cardiomegalia, hipertrofia miocárdica, dilatación senos coronarios, derrame pleural.
- **RNM 32 E.G:** Masa faríngea, macroglosia, hematomegalia, derrame pericárdico, derrame pleural, ascitis, ventriculomegalia.

McEwing, R.L., Joelle, R., Mohlo, M., Bernard, J.-P., Hillion, Y. and Ville, Y. (2006), Prenatal diagnosis of neurofibromatosis type 1: sonographic and MRI findings. Prenat. Diagn., 26: 1110-1114.

Clin Chem Lab Med 2018; 56(5): 728–738 DE GRUYTER

Non-invasive prenatal diagnosis of paternally inherited disorders from maternal plasma: detection of *NF1* and *CFTR* mutations using droplet digital PCR

Aurélia Gruber[a], Mathilde Pacault[a], Laila Allach El Khattabi, Nicolas Vaucouleur, Lucie Orhant,

CERPO

Family	Paternal genotype	Maternal genotype	Gestational age, weeks	Fetal fraction	NIPD interpretation	Fetal genotype from invasive sampling
1	*NF1* c.499_502del (p.Cys167Glnfs*10)/WT	*NF1* WT/WT	12 + 1	4%	Paternal mutation → Affected by NF1	*NF1* c.499_502del (p.Cys167Glnfs*10)/WT
2	*NF1* c.1316T>G (p.Leu439Arg)/WT	*NF1* WT/WT	10	7%	Paternal mutation → Affected by NF1	*NF1* c.1316T>G (p.Leu439Arg)/WT
3	*NF1* c.1381C>T (p.Arg461*) /WT	*NF1* WT/WT	15	2%	No paternal mutation → Unaffected by NF1	*NF1* WT/WT
4	*NF1* c.1885G>A (p.Gly629Arg)/WT	*NF1* WT/WT	11	4%	Paternal mutation → Affected by NF1	*NF1* c.1885G>A (p.Gly629Arg)/WT

- Comparación cfADN con estudio invasivo (LA, BVC) en 4 casos
- Se logra el diagnóstico en el total de los casos

Gruber A. Non-invasive prenatal diagnosis of paternally inherited disorders from maternal plasma: detection of NF1 and CFTR mutations using droplet digital PCR. Clin Chem Lab Med. 2018 Apr 25;56(5):728-738.

VOL. 103 NO. 3 / MARCH 2015
ORIGINAL ARTICLE: GENETICS
Fertility and Sterility®

Outcomes of preimplantation genetic diagnosis in neurofibromatosis type 1

Vanessa L. Merker, B.S.,[a] Timothy P. Murphy,[a] J. Bryan Hughes, B.A.,[d] Alona Muzikansky, M.A.,[b] Mark R. Hughes, M.D., Ph.D.,[d] Irene Souter, M.D.,[c] and Scott R. Plotkin, M.D., Ph.D.[a]

[a] Department of Neurology and Cancer Center, [b] Biostatistics Center, and [c] Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, Massachusetts; and [d] Genesis Genetics, Plymouth, Michigan

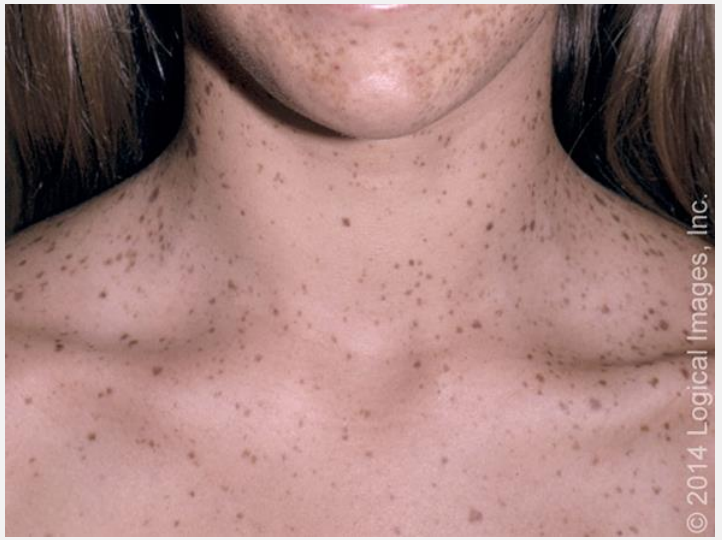
CERPO

- Parejas con mutación de gen NF1 sometidas a FIV y PGD para reducir la transmisión de NF1 a su descendencia
- Se logró estudiar el 80% de los embriones
- 46% de los embriones no tenian la mutación NF1

Merker VL, Murphy TP, Hughes JB, Muzikansky A, Hughes MR, Souter I, Plotkin SR. Outcomes of preimplantation genetic diagnosis in neurofibromatosis type 1. Fertil Steril. 2015 Mar;103(3):761-8.e1.

Sindrome de Noonan con multiples lentigos (Sd Leopard)

- Patología ***autosómica dominante***
- Mutación heterocigota en gen PTPN11, RAF1, BRAF
- **L:** Lentigos
- **E:** ECG (anomalías de conducción)
- **O:** Ocular (hipertelorismo)
- **P:** Pulmonar (estenosis)
- **A:** Anomalìas genitales
- **R:** Retardo del crecimiento
- **D:** Deafness (Sordera neurosensorial)



Digilio MC, Sarkozy A, de Zorzi A, Pacileo G, Limongelli G, Mingarelli R, Calabrò R, Marino B, Dallapiccola B. LEOPARD syndrome: clinical diagnosis in the first year of life. Am J Med Genet A. 2006 Apr 1;140(7):740-6.

Clínica y diagnóstico:

A. Múltiples léntigos que aparecen durante la infancia.

B. Anomalías cardíacas, retraso crecimiento/estatura baja, deformidad toracica, dismorfia facial

*A + 2B

*3B+ familiar primer grado afectado

Digilio MC, Sarkozy A, de Zorzi A, Pacileo G, Limongelli G, Mingarelli R, Calabrò R, Marino B, Dallapiccola B. LEOPARD syndrome: clinical diagnosis in the first year of life. Am J Med Genet A. 2006 Apr 1;140(7):740-6.

Síndrome cardio-facio-cutáneo (CFC)

- Trastorno **autosómico dominante**, la mayoría se presenta por mutaciones de novo.
- Causado por mutaciones en 4 genes: *BRAF*, *MAP2K1* (*MEK1*) y *MAP2K2* (*MEK2*) y *KRAS.*
- Las principales características incluyen dismorfia craneofacial, cardiopatía congénita (estenosis pulmonar), anomalías dermatológicas, retraso del crecimiento y discapacidad intelectual.

Rauen KA. Cardiofaciocutaneous Syndrome. 2007 Jan 18 [Updated 2023 Feb 9]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1186/

Clínica post natal:

- **Facial:** Cara triangular
- Problemas de **alimentación**: RGE
- **Cutáneo:** Xerosis, uñas dismórficas, cabello escaso
- **Oculares:** Estrabismo, nistagmus, hipoplasia nervio óptico
- **Neurologico:** Hipotonía, alteración cognitiva, convulsiones
- Criptorquidea en hombres

Rauen KA. Cardiofaciocutaneous Syndrome. 2007 Jan 18 [Updated 2023 Feb 9]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1186/

Clínica Prenatal:

Findings in Cardiofaciocutaneous Syndrome:	Current	Literature
Number of Patients	9	69
	PRENATAL FINDINGS	
Congenital Heart Defect	1/9 (11%)[a]	n.d.
Arrhythmia	0/9 (0%)	n.d.
Fetal abdominal circumference >90th centile	2/9 (22%)	2/40 (5%)
Small or absent stomach	n.d.	n.d.
Long bones <5th centile	n.d.	2/40 (5%)
Lymphatic dysplasia	2/9 (22%)[b]	5/42 (12%)
OFC >90th centile	1/9 (11%)	n.d
Polyhydramnios	8/9 (89%)	40/69 (58%)
Renal anomaly	5/9 (55%)[c]	2/40 (5%)

- Cardíaca: Estenosis pulmonar, cardiomiopatía hipertrófica
- Restricción de crecimiento, macrocefalia

Myers A, Bernstein JA. 2014. Perinatal features of the RASopathies: Noonan syndrome, Cardiofaciocutaneous syndrome and Costello syndrome. Am J Med Genet Part A. 9999:1–8

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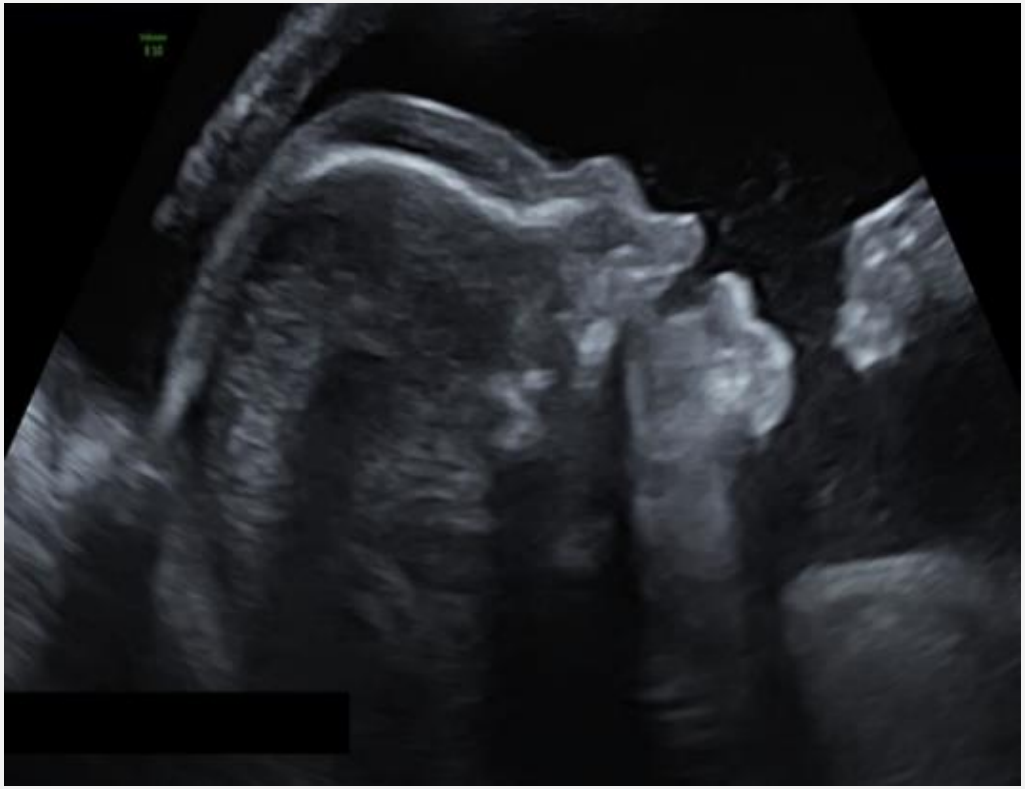
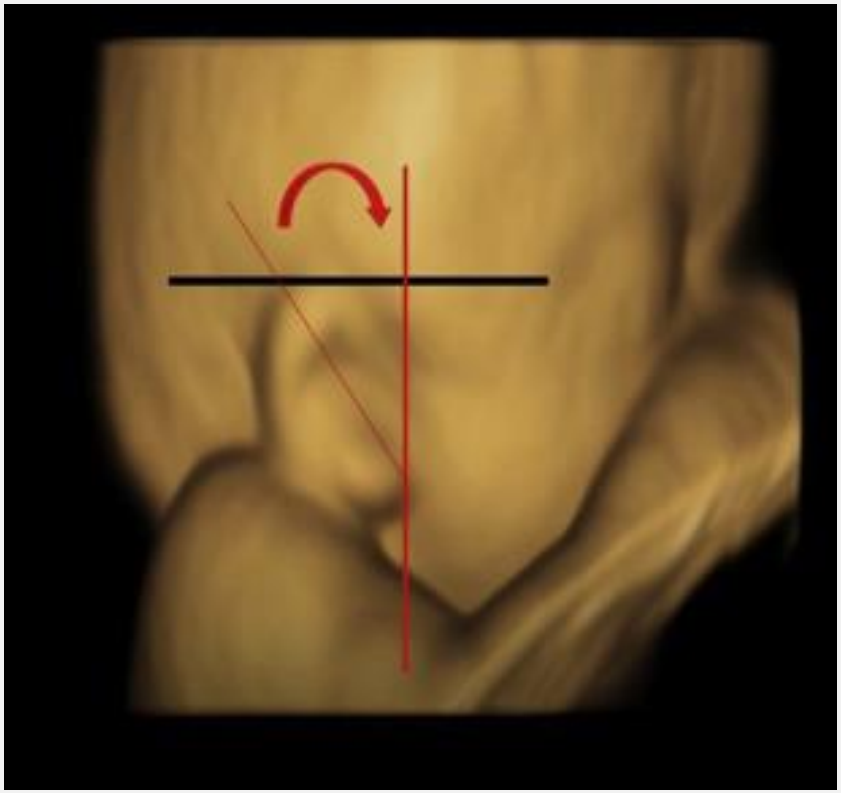
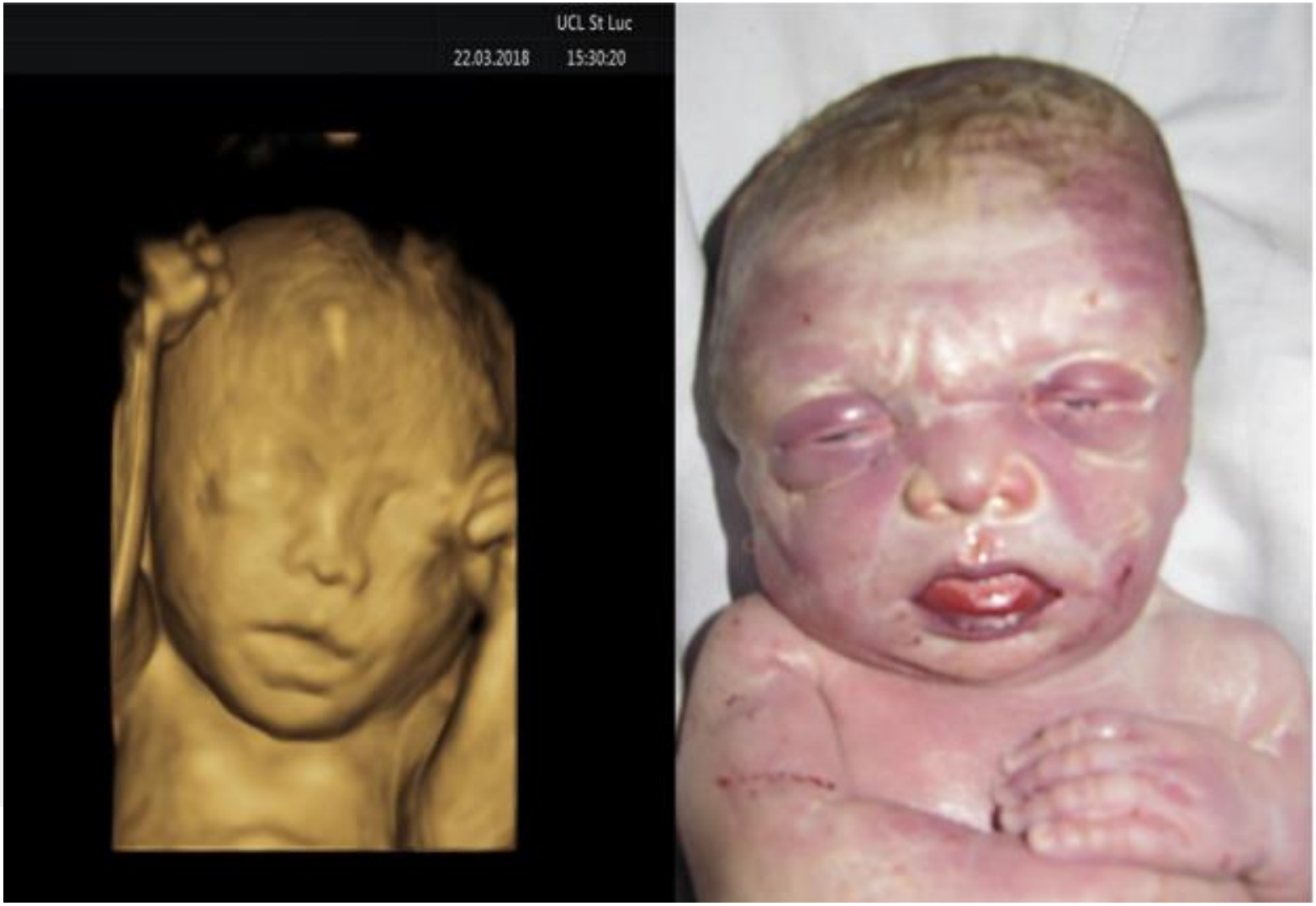




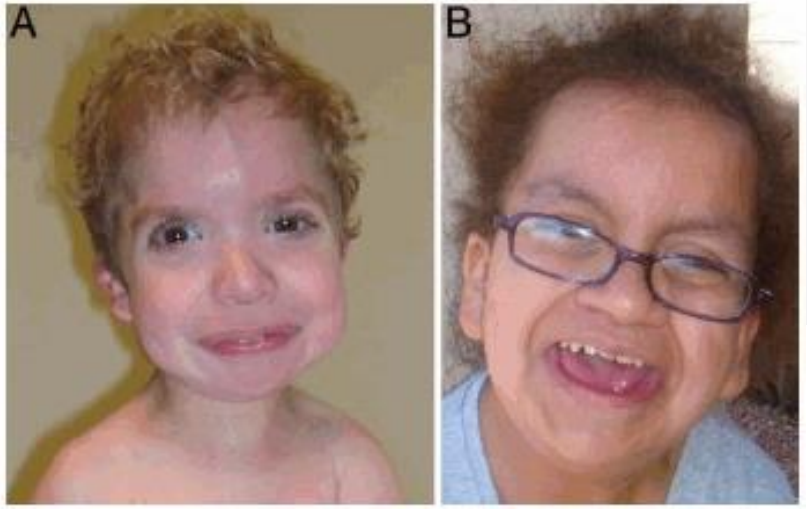
Biard JM, Steenhaut P, Bernard P, Race V, Sznajer Y. Antenatal diagnosis of cardio-facio-cutaneous syndrome: Prenatal characteristics and contribution of fetal facial dysmorphic signs in utero. About a case and review of literature. Eur J Obstet Gynecol Reprod Biol. 2019 Sep;240:232-241.



Biard JM, Steenhaut P, Bernard P, Race V, Sznajer Y. Antenatal diagnosis of cardio-facio-cutaneous syndrome: Prenatal characteristics and contribution of fetal facial dysmorphic signs in utero. About a case and review of literature. Eur J Obstet Gynecol Reprod Biol. 2019 Sep;240:232-241.

Síndrome de Costello (CS)

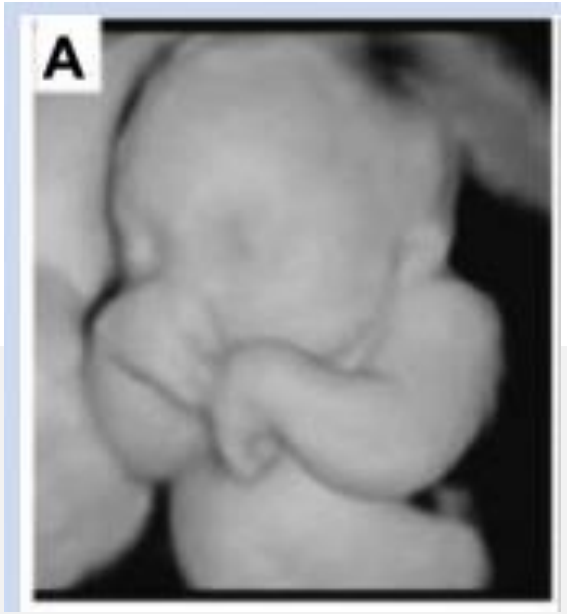
- Enfermedad ***autosómica dominante***
- Causada por mutación en el gen HRAS
- Alto riesgo de desarrollar neoplasias benignas y malignas (15%)
- Afección múltiples órgano

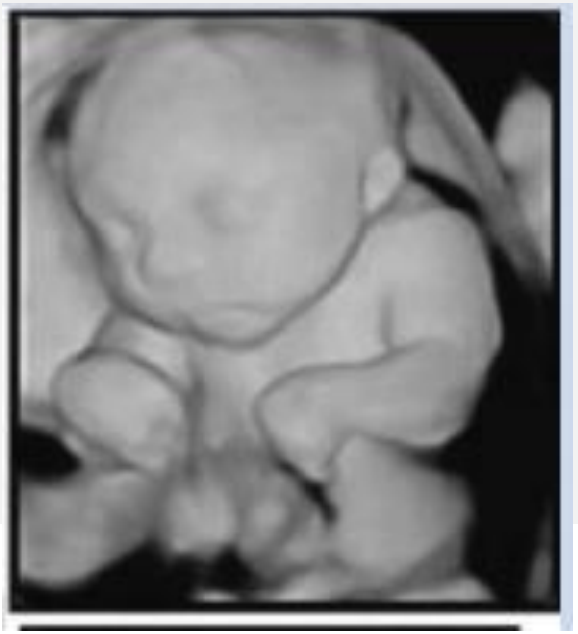


Gripp KW, Rauen KA. Costello Syndrome. 2006 Aug 29 [Updated 2019 Aug 29]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1507/

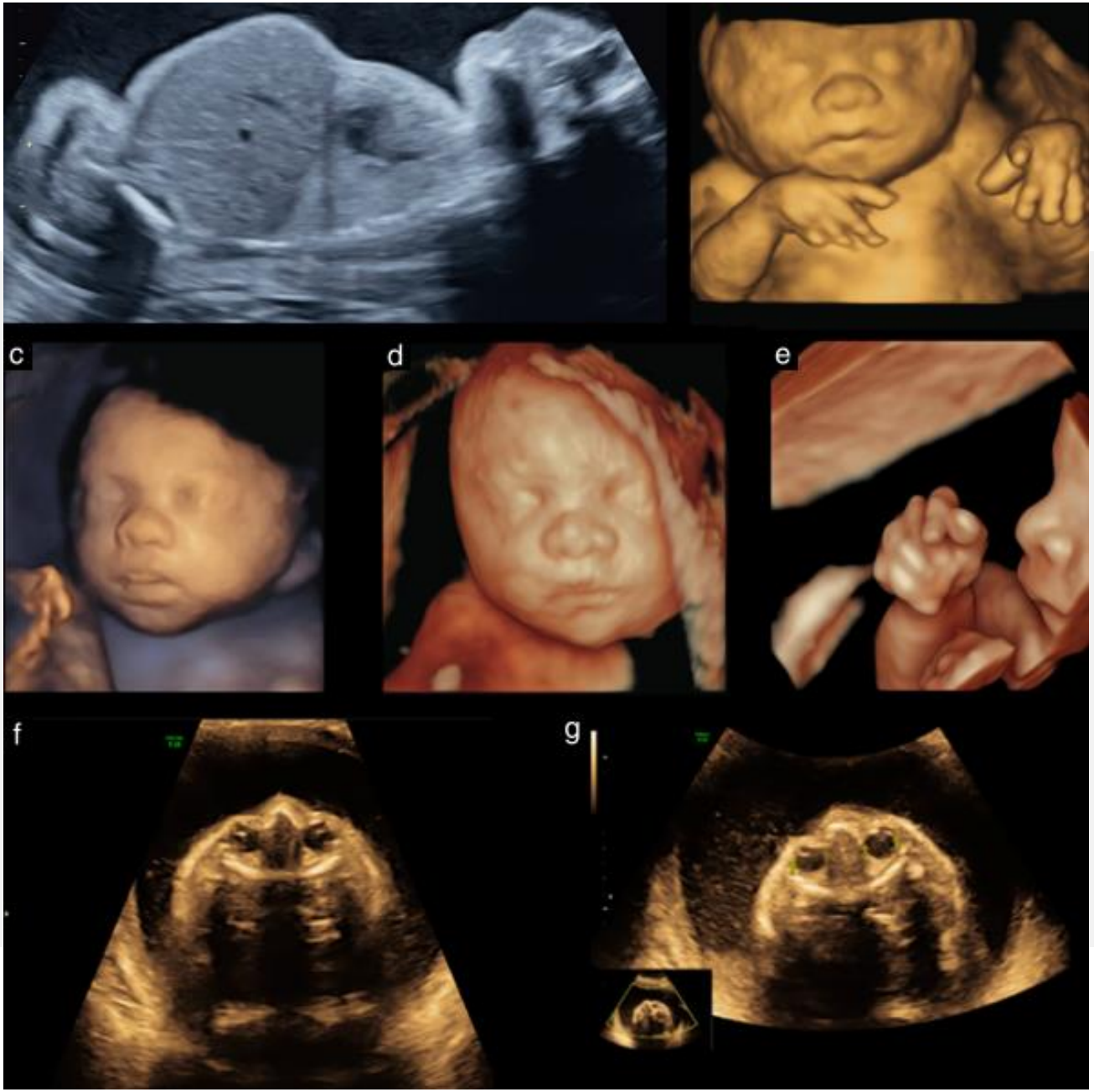
Clínica prenatal:

- Aumento de translucencia nucal
- Polihidroamnios (>90%)
- Desviación ulnar de la muñeca
- Humero y fémur corto
- Taquicardia fetal
- Parto prematuro





Kuniba H, Prenatal diagnosis of Costello syndrome using 3D ultrasonography amniocentesis confirmation of the rare HRAS mutation G12D. Am J Med Genet A. 2009 Feb 15;149A(4):785-7.



CERPO

Schøler Nørgaard M, Mogra R, Pinner J, Kagan KO, Warming Jørgensen M, Gjørup V, Petersen OB, Sandager P, Vogel I. Fetal Costello syndrome: description of phenotype of HRAS exon 1 mutations. Ultrasound Obstet Gynecol. 2020 Feb;55(2):274-275.

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Findings in Costello Syndrome: Current and Literature Cohorts

	Total
Number of Patients	97
Congenital Heart Defect	2/4 (50%)
Arrhythmia	6/17 (35%)
Fetal abdominal circumference >90th centile	5/6 (83%)
Small or absent stomach	5/6 (83%)
Long bones <5th centile	2/6 (33%)
Lymphatic dysplasia	11/16 (69%)
OFC >90th centile	4/10 (40%)
Polyhydramnios	71/97 (73%)
Renal anomaly	5/6 (83%)

Myers A, Bernstein JA. 2014. Perinatal features of the RASopathies: Noonan syndrome, Cardiofaciocutaneous syndrome and Costello syndrome. Am J Med Genet Part A. 9999:1–8

Clínica postnatal:

- Dificultad para la alimentación
- Retraso en el crecimiento
- Estatura baja
- Macrocefalia
- Cabello rizado, escaso y fino
- Rasgos faciales

Figure 1a.

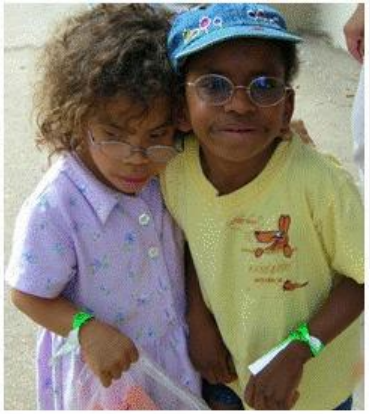
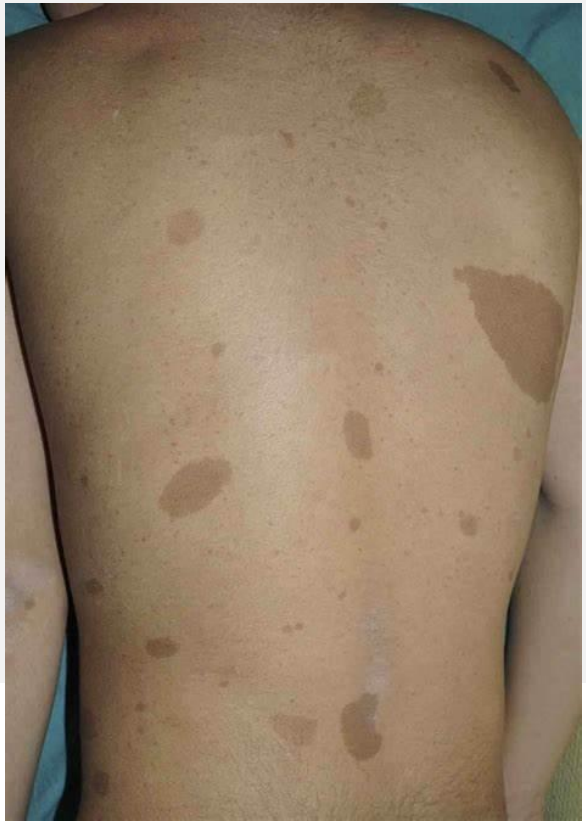


Figure 1b.

Gripp KW, Rauen KA. Costello Syndrome. 2006 Aug 29 [Updated 2019 Aug 29]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1507/

Síndrome de Legius (LS)

- Trastorno **autosómico dominante**
- Causado por mutaciones en el gen *SPRED1*
- *2% de los pacientes NF1 tiene una mutación SPRED1*



Legius E, Stevenson D. Legius Syndrome. 2010 Oct 14 [Updated 2020 Aug 6]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK47312/

Clínica:

- Similar a NF1
- Máculas café con leche, pecas axilares, deterioro neurocognitivo leve, macrocefalia
- Sin neurofibromas, nodulos de Lisch de iris ni tumores del SNC.

Legius Syndrome: Frequency of Select Features

Feature	% of Persons with Feature
Café au lait macules	>99%
Skin freckling	30%-50%
Macrocephaly	20%
Short stature	12%
Neurobehavioral/developmental issues	30%
Multiple lipomas	18%
Pectus deformity	12%
Noonan -like facial features	15%

Legius E, Stevenson D. Legius Syndrome. 2010 Oct 14 [Updated 2020 Aug 6]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK47312/

Diagnóstico:

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Table 2. Diagnostic criteria for Legius syndrome.

A: The diagnostic criteria for Legius syndrome are met in an individual who does not have a parent diagnosed with Legius syndrome if the following CRITERIA are present:

- Six or more café-au-lait macules (Supplementary Fig. 12) bilaterally distributed and no other NF1-related diagnostic criteria except for axillary or inguinal freckling[a]
- A heterozygous pathogenic variant in *SPRED1* with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

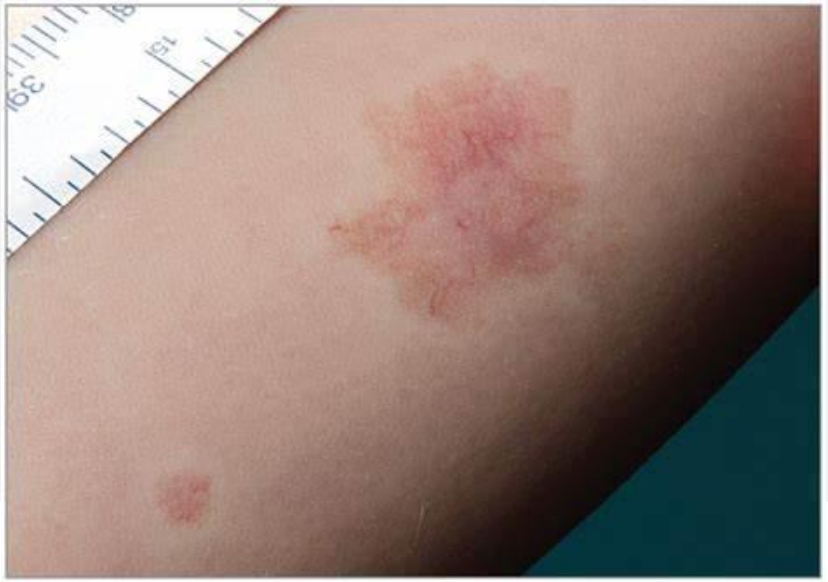
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of Legius syndrome if one or more of the criteria in A are present

[a]The presence of fewer than six café-au-lait spots does not exclude Legius syndrome.

Legius E, Messiaen L, Wolkenstein P,nternational Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC); Huson SM, Evans DG, Plotkin SR. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021 Aug;23(8):1506-1513.

Sindrome de malformación AV por malformación capilar (CM-AVM)

- Trastorno **autosomico dominante**
- Caracterizado por malformaciones A-V multifocales
- Causado por mutación en gen RASA1
- Malformaciones CV:
  -Tetralogía de Fallot
  -Defectos de tabique
  -Anomalías valvulares



-Bayrak-Toydemir P, Stevenson DA. Capillary Malformation-Arteriovenous Malformation Syndrome. 2011 Feb 22 [Updated 2019 Sep 12]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.
-Sibley CD, Ramien ML. Capillary Malformation–Arteriovenous Malformation Syndrome. JAMA Dermatol. 2019;155(6):733.

Genes **2023**, *14*, 549. https://doi.org/10.3390/genes14030549

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genes

MDPI

Article

Prenatal Clinical Findings in *RASA1*-Related Capillary Malformation-Arteriovenous Malformation Syndrome

Emanuele Coccia [1,2], Lara Valeri [1,3], Roberta Zuntini [1], Stefano Giuseppe Caraffi [1,*], Francesca Peluso [1], Luca Pagliai [1], Antonietta Vezzani [1], Zaira Pietrangiolillo [4], Francesco Leo [4], Nives Melli [4], Valentina Fiorini [4], Andrea Greco [5], Francesca Romana Lepri [6], Elisa Pisaneschi [6], Annabella Marozza [7,8], Diana Carli [9], Alessandro Mussa [9], Francesca Clementina Radio [10], Beatrice Conti [11], Maria Iascone [12], Giancarlo Gargano [4], Antonio Novelli [6], Marco Tartaglia [10], Orsetta Zuffardi [13], Maria Francesca Bedeschi [11,†] and Livia Garavelli [1,†]

Clinical Feature	Literature Review Frequency (%) [11,14–27]
Capillary malformations, postnatal findings (skin)	11/15 (73.3%)
Increased fetal nuchal thickness	2/3 (66.7%)
Vascular malformations, including postnatal findings (AVMs and AVFs)	13/20 (65%)
Polyhydramnios	8/21 (38.1%)
Deceased	6/20 (30%)
Cardiac failure	5/20 (25%)
Pleural effusion	5/21 (23.8%)
Non-immune hydrops fetalis	5/21 (23.8%)
Structural cardiac anomalies	4/21 (19%)
Chylothorax	3/20 (15%)
Parkes Weber Syndrome	2/16 (12.5%)
Ascites	2/20 (10%)
In utero drainage/shunt	2/20 (10%)
VGAM	2/20 (10%)
Renal anomalies	2/21 (9.5%)
Pericardial effusion	1/20 (5%)
Basilar artery aneurism	1/20 (5%)

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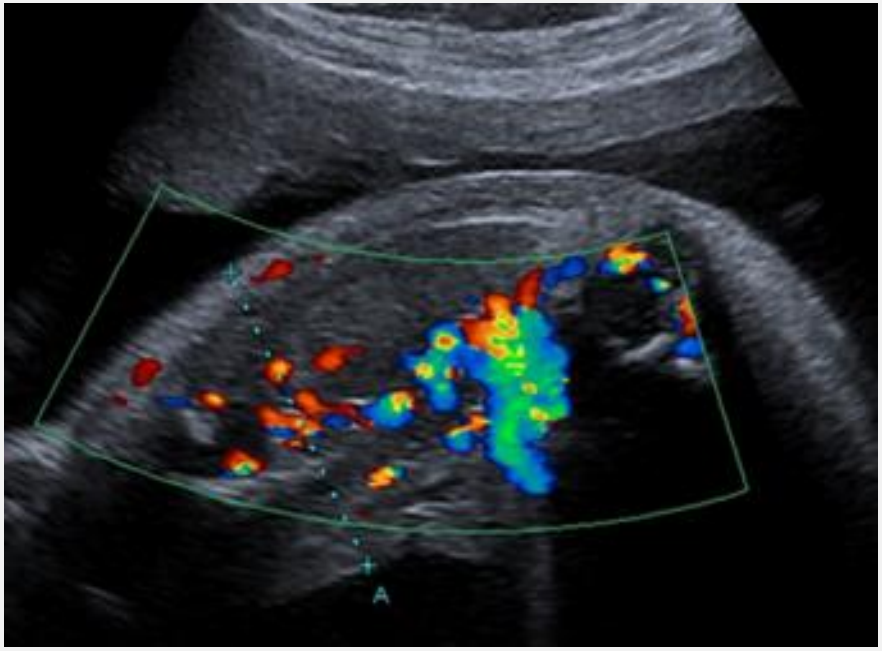
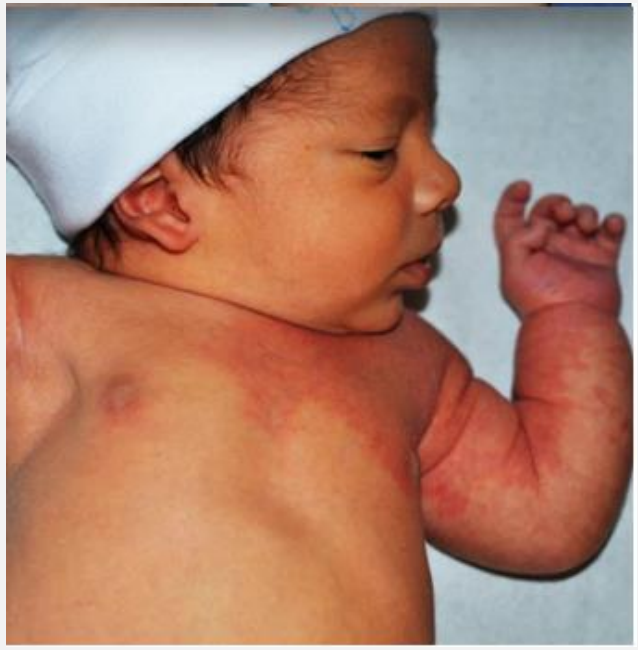
Coccia E, Valeri L, Zuntini R. Prenatal Clinical Findings in *RASA1*-Related Capillary Malformation-Arteriovenous Malformation Syndrome. Genes (Basel). 2023 Feb 22;14(3):549.

Diagnóstico prenatal:



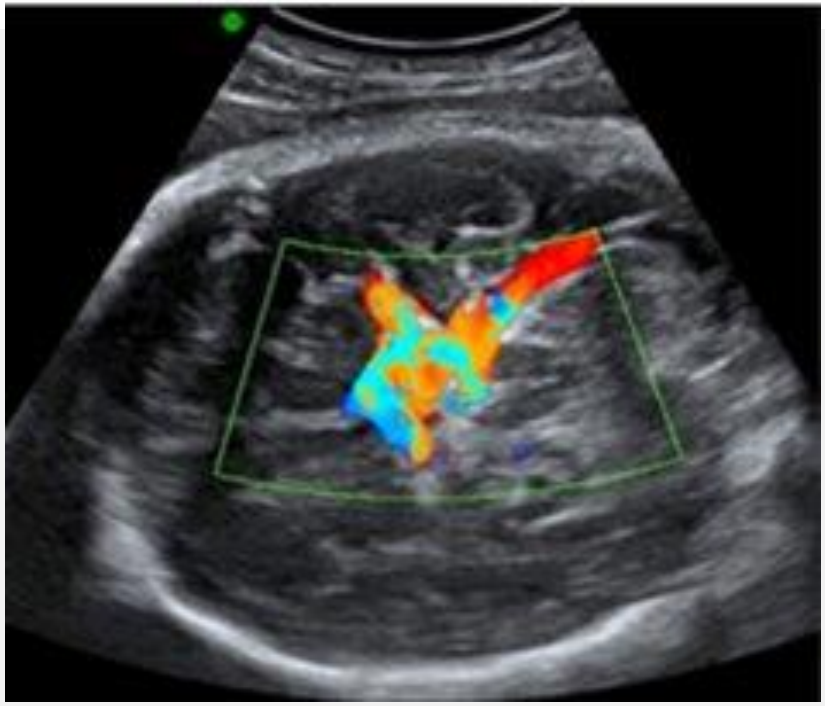


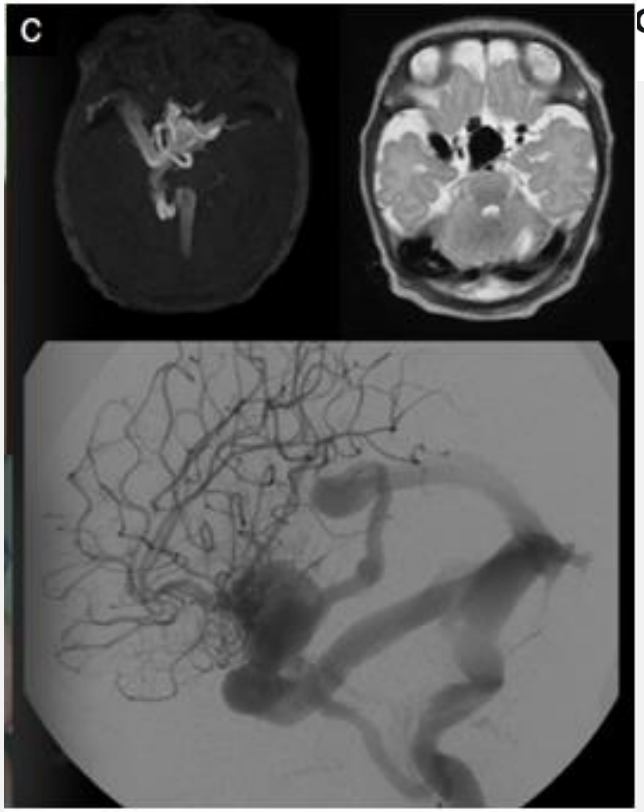
A) Doppler prenatal 32 EG con hipertrofia difusa en brazo izquierdo y flujo difuso que sugieren multiples fistulas AV

B) RN que confirma compromiso de brazo izquierdo

Lacalm A, Fichez A, Broussin B, Abel C, Lacombe D, Guibaud L. Prenatal diagnosis of cerebral and extracerebral high-flow lesions revealing familial capillary malformation-arteriovenous malformation (CM-AVM) syndrome. Ultrasound Obstet Gynecol. 2018 Mar;51(3):409-411.

Diagnóstico prenatal:





A) Doppler prenatal 32 EG con dilatación en polígono de Willis con aumento del flujo venoso (sugiere fistula AV)

B) AngioRNM post natal que confrima fistula AV

Lacalm A, Fichez A, Broussin B, Abel C, Lacombe D, Guibaud L. Prenatal diagnosis of cerebral and extracerebral high-flow lesions revealing familial capillary malformation-arteriovenous malformation (CM-AVM) syndrome. Ultrasound Obstet Gynecol. 2018 Mar;51(3):409-411.

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Facultad de Medicina, Universidad de Chile

Diagnóstico Prenatal Rasopatías

1. Panel Rasopatías
2. Secuenciación exoma
3. Genoma (?)

INVITAE

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Test catalog > Invitae RASopathies and Noonan Spectrum Disorders Panel

Invitae RASopathies and Noonan Spectrum Disorders Panel

Test code: 04151 • 28 genes

✓ Primary panel
28 genes selected

✓ A2ML1	✓ ACTB	✓ ACTG1	✓ BRAF
✓ CBL	✓ HRAS	✓ KAT6B	✓ KRAS
✓ LZTR1	✓ MAP2K1	✓ MAP2K2	✓ MRAS
✓ NF1	✓ NRAS	✓ NSUN2	✓ PPP1CB
✓ PTPN11	✓ RAF1	✓ RASA1	✓ RASA2
✓ RIT1	✓ RRAS	✓ RRAS2	✓ SHOC2
✓ SOS1	✓ SOS2	✓ SPRED1	✓ YWHAZ

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ARTICLE

When to test fetuses for RASopathies? Proposition from a systematic analysis of 352 multicenter cases and a postnatal cohort

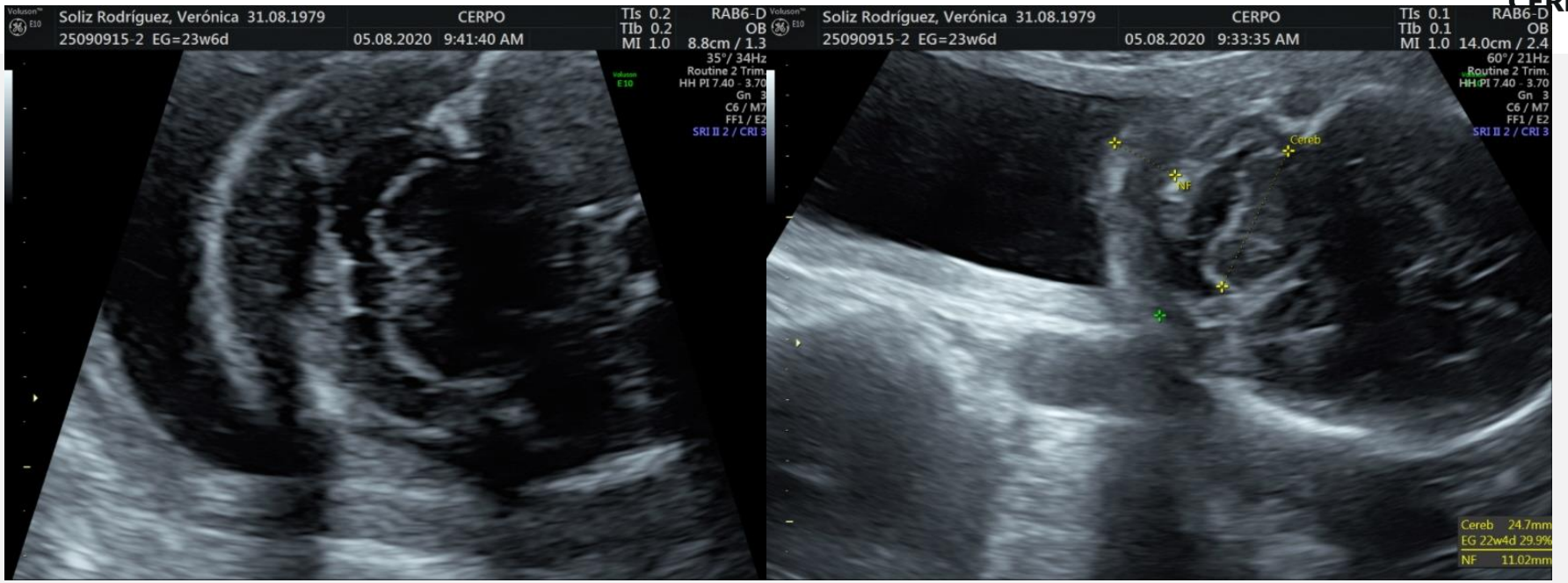
Alexandra Scott[1✉], Niccolò Di Giosaffatte[2], Valentina Pinna[2], Paola Daniele[2], Sara Corno[3], Valentina D'Ambrosio[3], Elena Andreucci[4], Annabella Marozza[5], Fabio Sirchia[6], Giada Tortora[7], Daniela Mangiameli[8], Chiara Di Marco[9], Maria Romagnoli[10], Ilaria Donati[11], Andrea Zonta[12], Enrico Grosso[12], Valeria Giorgia Naretto[12], Gioia Mastromoro[13], Paolo Versacci[14], Francesca Pantaleoni[15], Francesca Clementina Radio[15], Tommaso Mazza[16], Giuseppe Damante[17], Laura Papi[5], Teresa Mattina[8], Antonella Giancotti[3], Antonio Pizzuti[13], Anne-Marie Laberge[1], Marco Tartaglia[15,18✉], Marie-Ange Delrue[1,18] and Alessandro De Luca[2,18✉]

Los hallazgos ecográficos con mayor rendimiento diagnóstico:

1. MCH con o sin defecto cardíaco
2. Derrame pleural/ascitis
3. Hidrops fetal
4. Higroma quístico + otro hallazgo ecográfico
5. Higroma quístico persistente.
6. Pligue nucal + otro hallazgo ecografico

Scott A, Di Giosaffatte N, Pinna V. When to test fetuses for RASopathies? Proposition from a systematic analysis of 352 multicenter cases and a postnatal cohort. Genet Med. 2021 Jun;23(6):1116-1124.

Caso CERPO



Paciente derivada a CERPO por TN aumentada
Cariograma (cordocentesis): 46 XY

RNPT 35 semanas AEG, SDR, Papiloma preauricular izquierdo, sd dismórfico en estudio. Sd Noonan.

¿Porqué el estudio pre natal?

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- Screening de otros órganos comprometidos de forma dirigida
- Consejería parental
- Predecir pronóstico post natal
- Preparación para el momento del parto
- Ley "IVE"

Enfermedad Genética	Etiología Genética	Herencia	Examen Genético	Signos Prenatales
Sindrome de Noonan	BRAF, KRAS, LZTR1, MAP2K1, MRAS, NRAS, PTPN1, RAF1, RASA2, RIT1, RRAS2, SOS1, SOS2	Autosómico Dominante Gen LZTR1también puede ser Autosómico Recesivo	Panel Genético Exoma	Higroma quístico, Estenosis Pulmonar, CIA, Miocardiopatía Hipertrófica, Ptosis, Micrognatia, Hipertelorismo
Neurofibromatosis 1	NF1	Autosomica Dominante	Panel Rasopatía Exoma Genoma	Neurofibroma plexiforme, estenosis pulmonar
Sd Leopard	PTPN11, RAF1, BRAF	Autosomica dominante	Panel Rasopatía Exoma Genoma	Estenosis pulmonar, RCIU, hipertelorismo
Sd Cardio facio cutáneo	BRAF, MAP2K1 (MEK1), MAP2K2 (MEK2) y KRAS	Autosómica dominante	Panel Rasopatía Exoma Genoma	Estenosis pulmonar, MCPH, RCIU, macrocefalia, PHA
Sd Costello	HRAS	Autosómica dominante	Panel Rasopatía Exoma Genoma	Aumento TN, PHA, húmero y fémur corto, tquicardia fetal, desviación ulnar de muñeca, cardiopatía congénita
Sd Lefius	SPRED 1	Autosomica dominante	Panel Rasopatía Exoma Genoma	RCIU, macrocefalia
Sd malformacion AV por malformacion capilar (CM AVM)	RASA 1	Autosómico dominante	Panel Rasopatía Exoma Genoma	Tetralogía fallot, defectos tabique, anomalías valvulares, malformaciones AV

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Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Seminario Genética: Rasopatías. Sospecha prenatal

Dra Alejandra Plaza Rasjido
Dra Catherine Diaz Sanhueza

Programa Especialización Ginecología y Obstetricia
Facultad de Medicina, Universidad de los Andes
Agosto 2023