

CERPO

Centro de Referencia Perinatal Oriente

Facultad de Medicina, Universidad de Chile



Seminario Genética

Cardiopatías genéticas

Ximena Marques J.

Programa de especialización

Medicina Materno Fetal

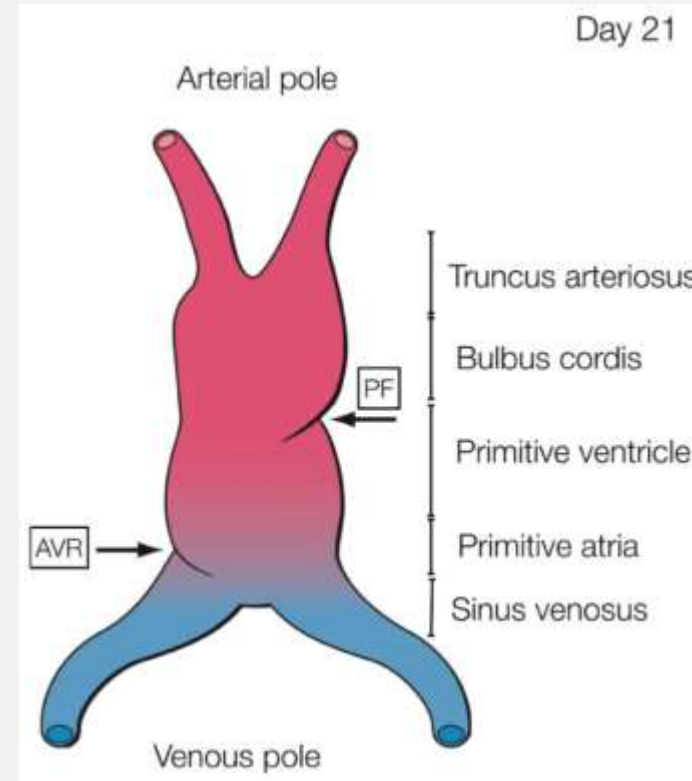
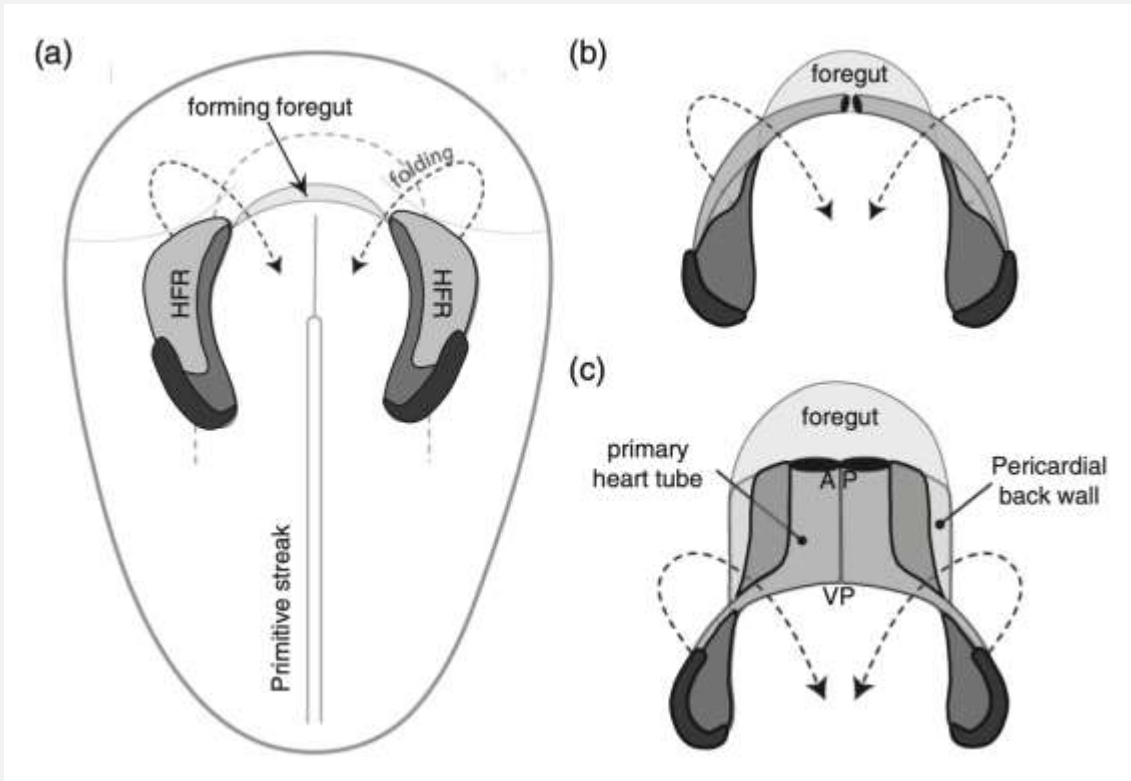
Tutor Catherine Díaz

Hoja de Ruta



- Embriología
- Epidemiología - Etiología
- Cardiopatías sindrómicas: fenotipo prenatal y cardiopatías asociadas a:
 - Aneuploidías
 - CNV
 - SNV
 - Otros

Formación del tubo cardíaco primitivo



Aorta y Tronco Pulmonar

Región lisa de VD – Cono Arterial
Región Lisa de VI – vestíbulo Ao

Región trabeculada de VD y VI

Región trabeculada AD y AI

Región Lisa de AD
Sinus Venarum (VP)
Seno coronario

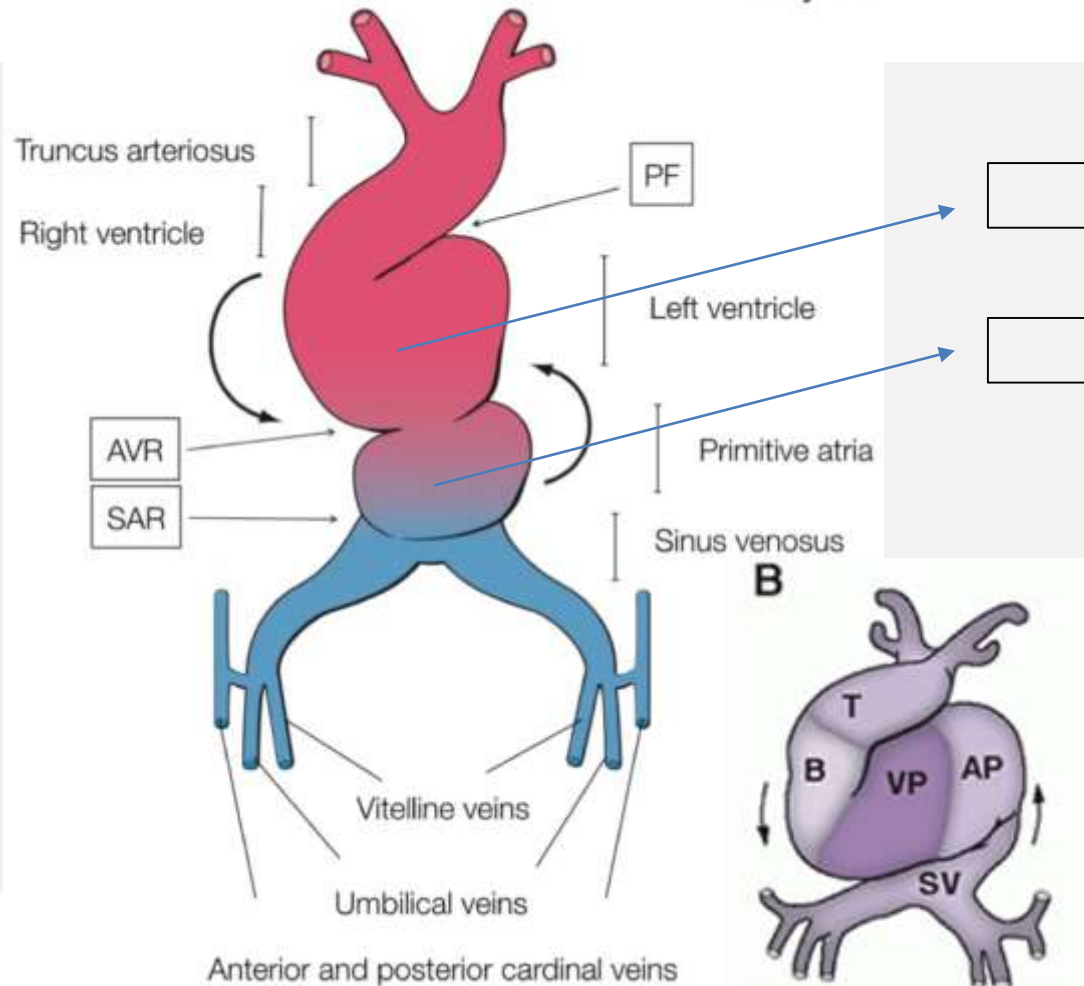
El desarrollo cardíaco se inicia durante la gastrulación al final de la 2da semana del desarrollo (Carnegie 7)

Plegamiento - Septación



Day 28

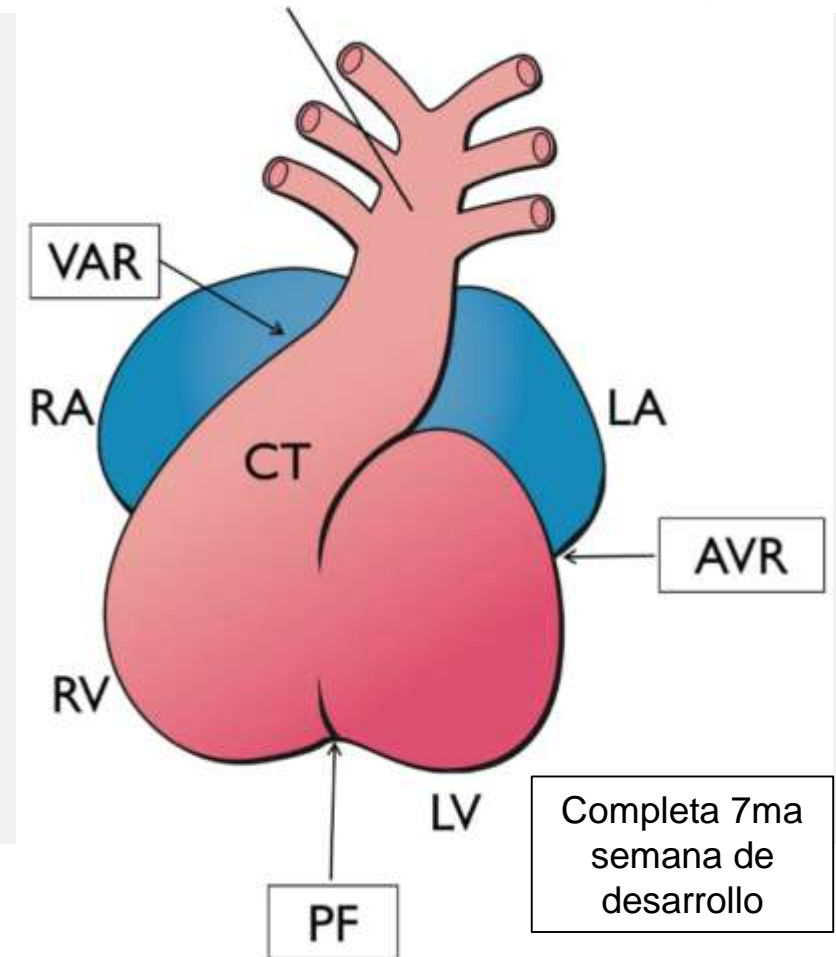
Day 23



Abajo - Derecha

Arriba - Izquierda

Aortic sac

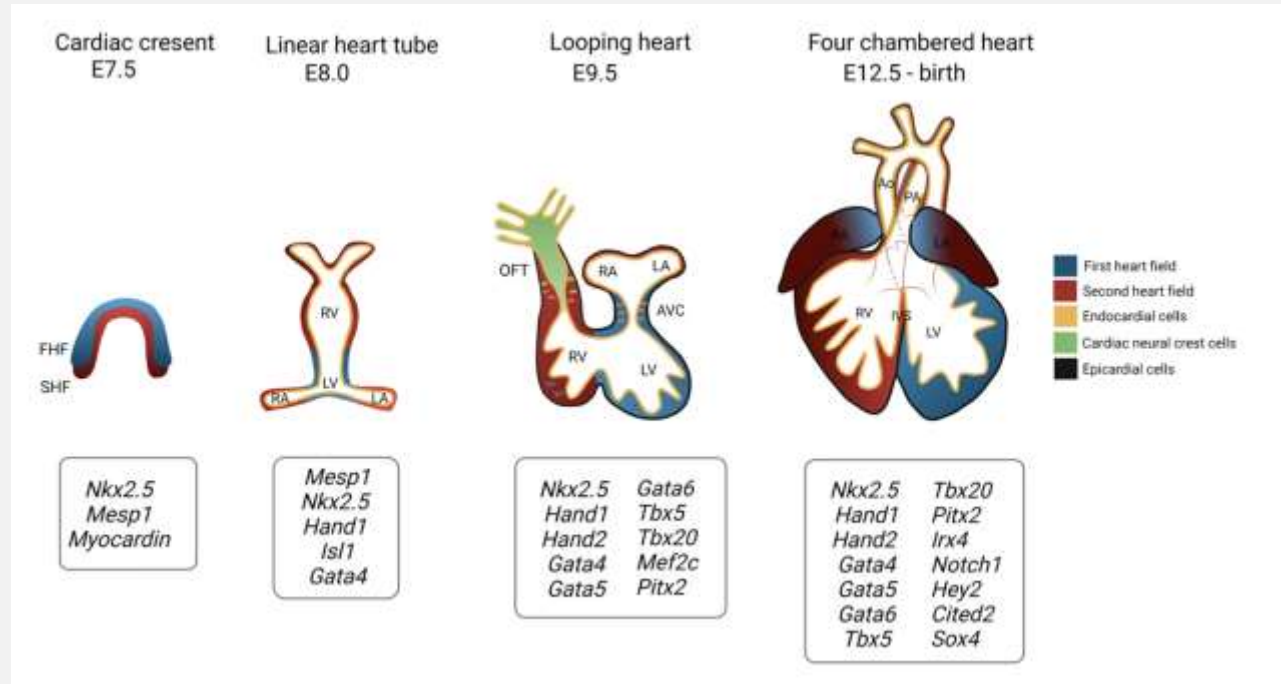
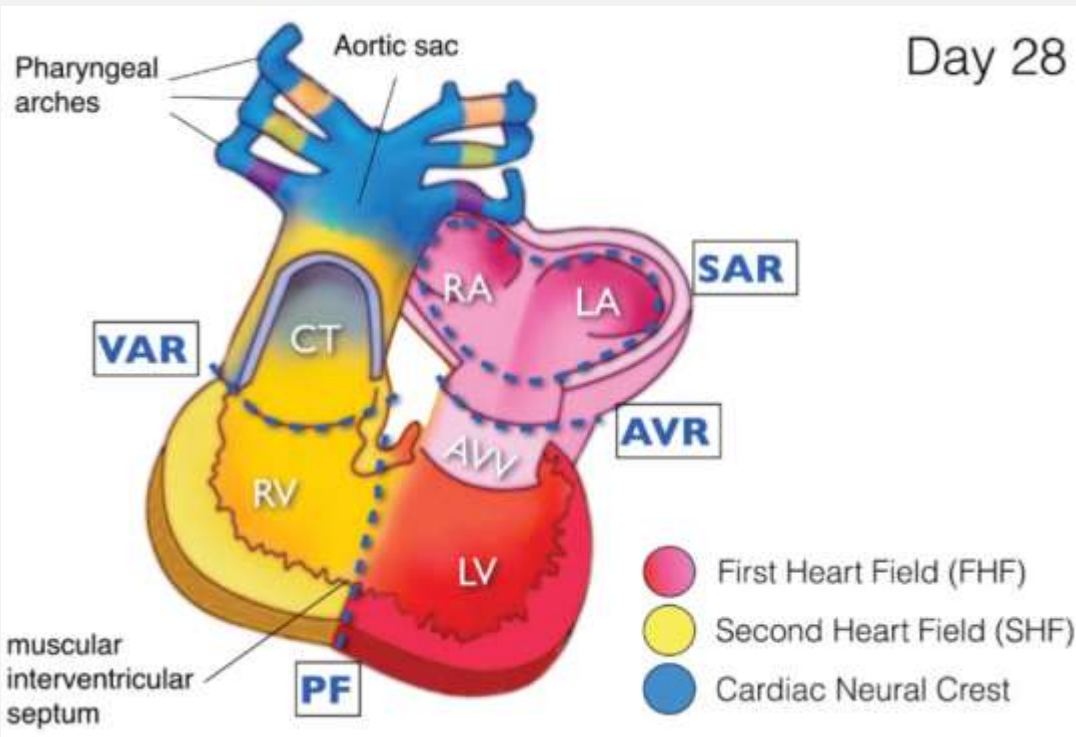


Completa 7ma semana de desarrollo

Al comienzo de la 4ta semana de desarrollo (EC)10 el tubo recto comienza su plegamiento

Campos cardíacos

Cresta neural: base del septo atrial, sistema de conducción y tractos de salida



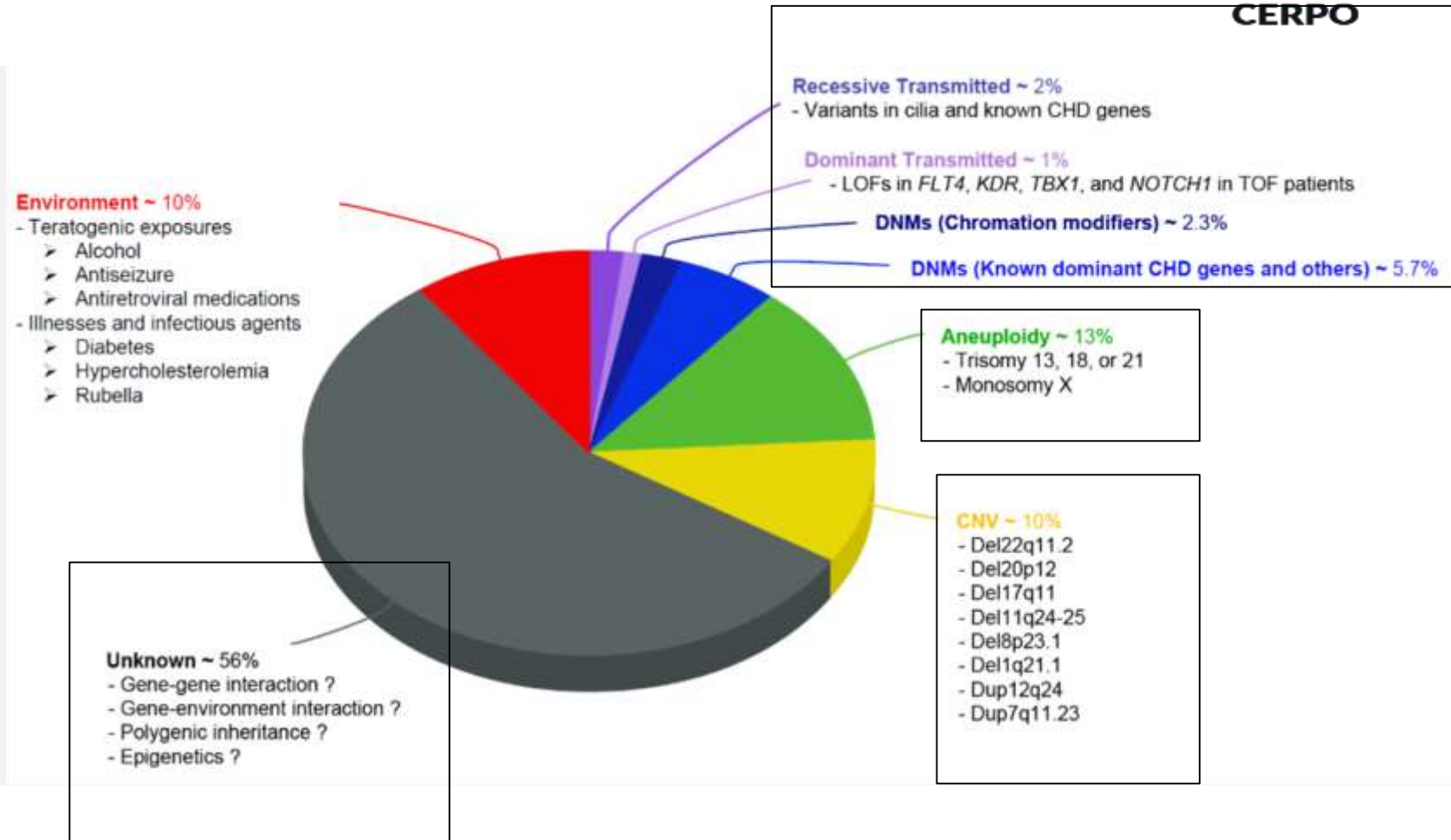
Disrupción de la diferenciación embrionaria y cardiogénesis resulta en CC
Ambos procesos regulados por distintos genes y sus productos

Epidemiología



CERPO

- Las CC afectan al 1% de los RNV.
- Primeros estudios de recurrencia familiar 16% vs 1-2% (Dr. Ruth Whittemore. Yale)
- Grandes estudios poblaciones NGS.



Aneuploidías

Trisomía 21
Trisomía 18
Trisomía 13
Síndrome de Turner
Síndrome Cat Eye

Trisomías 21,18 y 13



	Trisomía 21	Trisomía 18	Trisomía 13
Prevalencia	3:1000 NV	1:6000 NV	1:10.000 NV
Etiología	<ul style="list-style-type: none"> • 47,XY,+21 • No disyunción de los cromosomas homólogos (66%) o 	<ul style="list-style-type: none"> • 47,XY,+ 18 - 90% • Traslocación 18. • Trisomía 18 en mosaico (47XY,+18/46,XY). 	<ul style="list-style-type: none"> • 47,XY,+ 13 - 80% • Translocación Robertsoniana Desbalanceada 45,XY,t(13;14)(q10;q10) • Trisomia 13 en mosaico (47,XY,+13/46,XY)
Trisomía 21 libre (47, XX,+ 21)	95%		
Traslocación Robertsoniana	3-4%		
Mosaicismo (47,XX,+21/46,XX)	1-2%		
Trisomía 21 parcial	<1%		

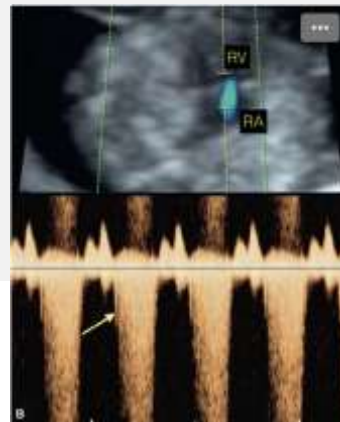
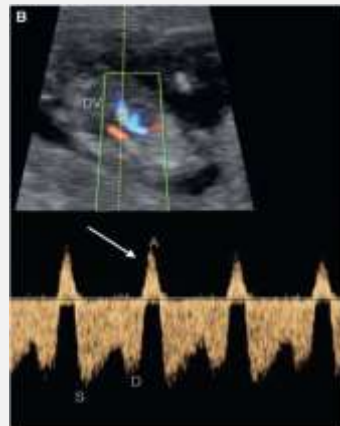
Fenotipo Prenatal

Table 6.1 • Biochemical and Sonographic Features of Trisomies 21, 18, and 13

NT Mixture Model	Euploid	Trisomy 21	Trisomy 18	Trisomy 13
CRL-independent distribution, %	5	95	70	85
Median CRL-independent NT, mm	2.0	3.4	5.5	4.4
Median serum free β -hCG, MoM	1.0	2.0	0.2	0.5
Median serum PAPP-A, MoM	1.0	0.5	0.2	0.3
Absent nasal bone, %	2.5	60	53	45
Tricuspid regurgitation, %	1.0	55	33	30
Ductus venosus reversed A-wave, %	3.0	66	58	55

NT, nuchal translucency; CRL, crown-rump length; β -hCG, β -human chorionic gonadotropin; MoM, multiple of the median; PAPP-A, pregnancy-associated plasma protein A.

From Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. *Prenat Diagn.* 2011;31:7–15; copyright John Wiley & Sons, with permission.

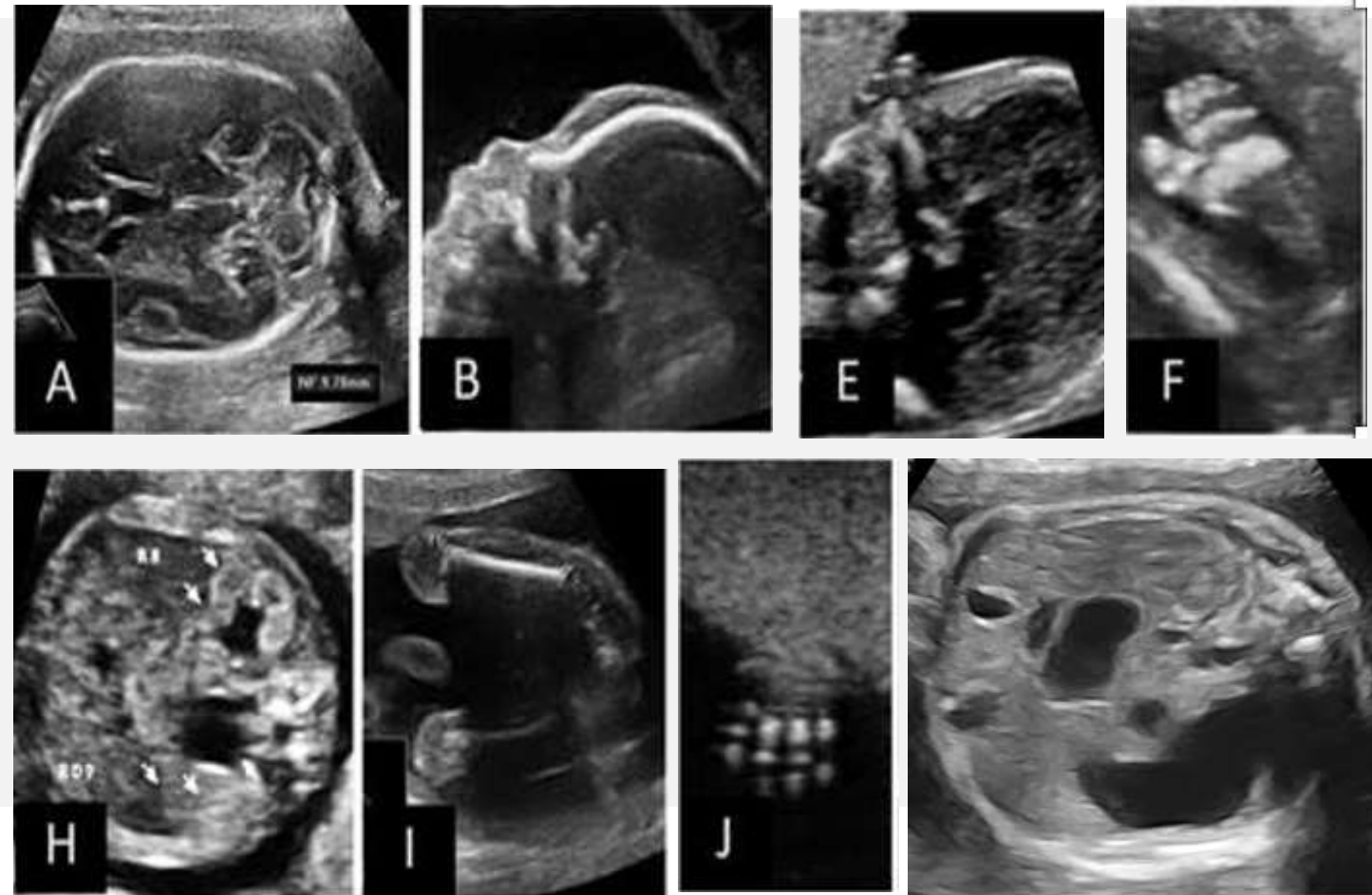


Marcadores de
1er Trimestre

Fenotipo Prenatal



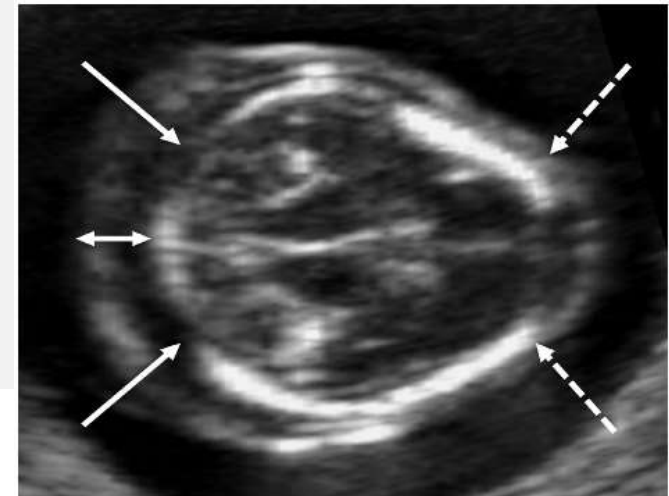
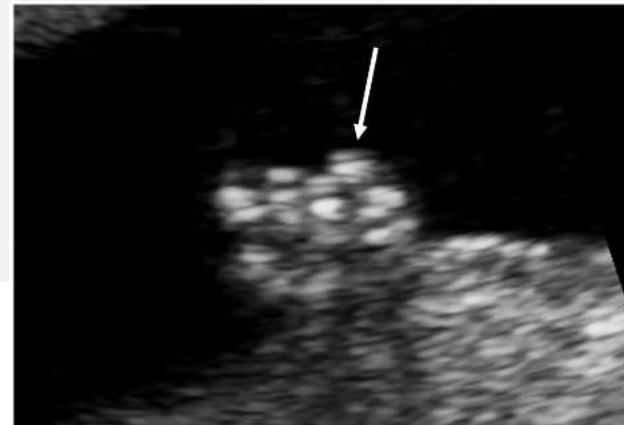
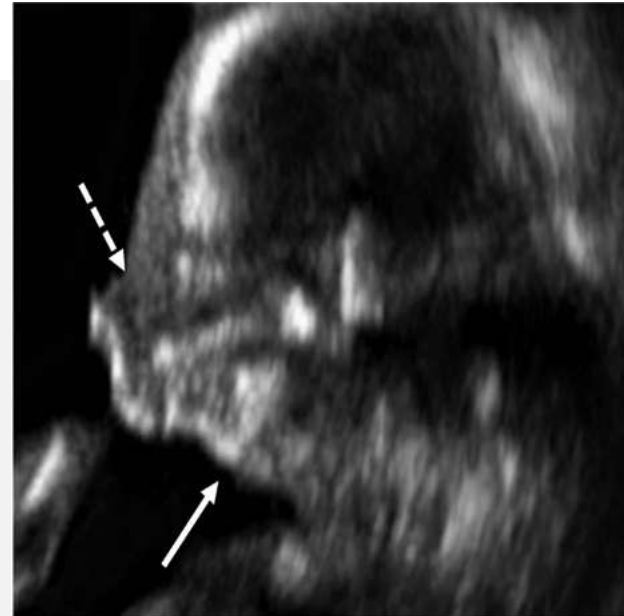
Aneuploidía	Trisomía 21
Patrón de alteraciones	Hipoplasia nasal Aumento del pliegue nucal y espesor prenasal Defectos cardíacos Foco cardíaco ecogénico Ventriculomegalia leve Atresia duodenal Intestino hiperecogénico Hidronefrosis leve Fémur corto Pie en sandalia Clinodactilia



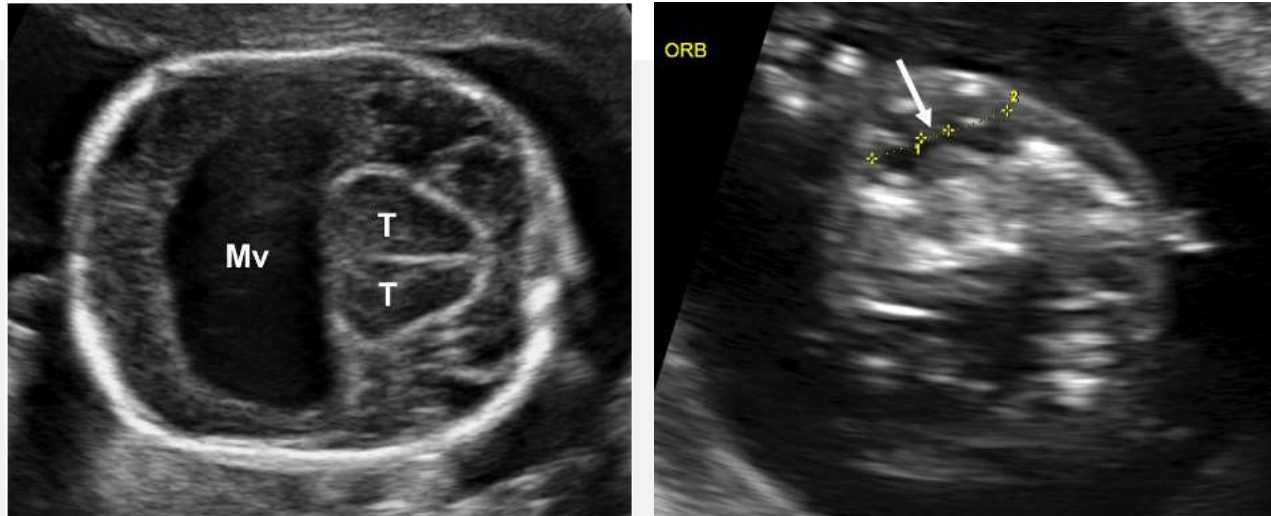
Fenotipo Prenatal



Aneuploidía	Trisomía 18
Patrón de alteraciones	Cráneo en fresa Quistes de plexo coroideo Ausencia del cuerpo calloso Megacisterna Magna Hendidura facial Micrognatia Edema nuczal Defectos cardíacos Hernia diafragmática Atresia esofágica Onfalocele AUU Intestino hiperécogénico Mielomeningocele RCIU Huesos largos cortos Dedos superpeuestos Pie en mecedora



Fenotipo Prenatal



Aneuploidía	Trisomía 13
Patrón de alteraciones	Holoprosencefalia Microcefalia Anomalías faciales Anomalías cardíacas Riñones grandes hiperecogénicos Onfalocele Polidactilia postaxial

Trisomías: Cardiopatías Congénitas



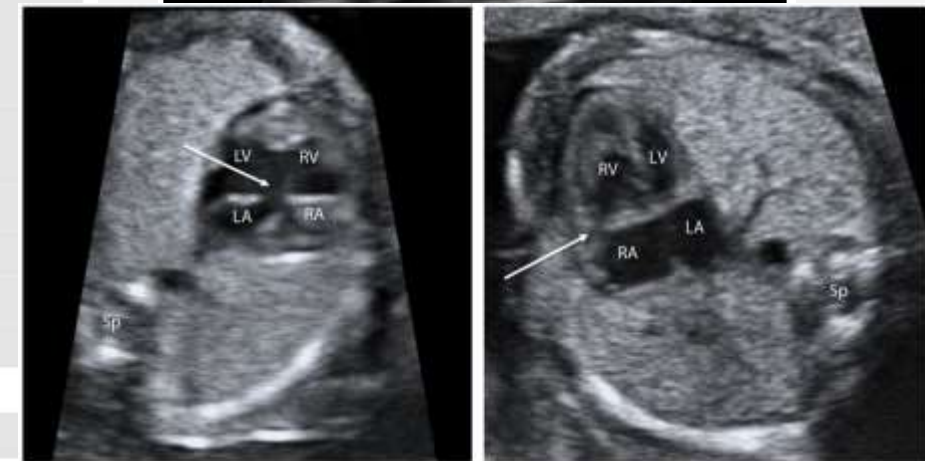
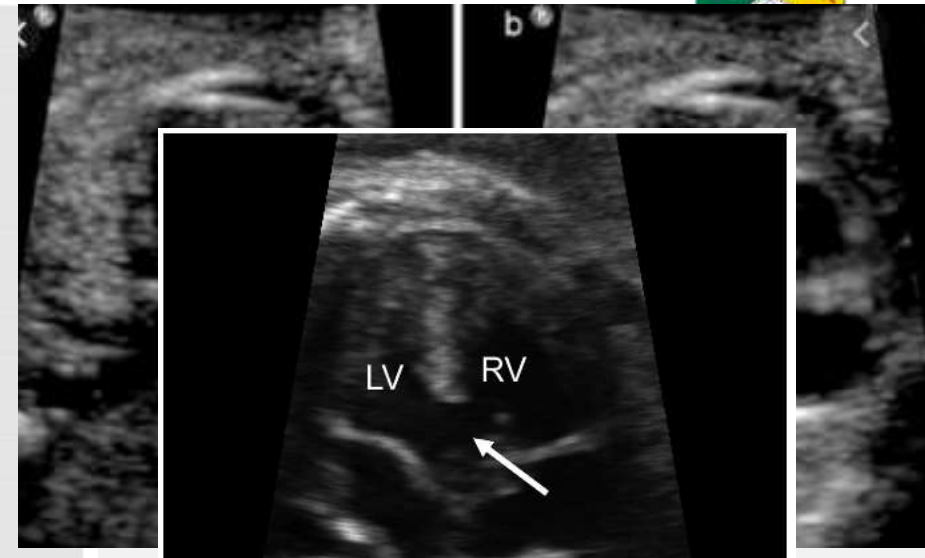
TABLE 1 Congenital heart defects (CHDs) in autosomal aneuploidy syndromes

Syndrome	Trisomy 13	Trisomy 18	Trisomy 22	Trisomy 21 (Down syndrome)
References	Musewe, Alexander, Techima, Smallhorn, & Freedom, 1990 Wylie et al., 1994; Lin et al., 2007 Polli et al., 2014 Kosiv, Gossett, Bai, & Collins, 2017 Domingo, Carey, Eckhauser, Wilkes, & Menon, 2019	Van Praagh et al., 1989 Musewe et al., 1990 Balderston, Shaffer, Washington, & Sondheimer, 1990 Baty et al., 1994; Crider, Olney, & Cragan, 2008 Savva, Walker, & Morris, 2010 Kosiv et al., 2017	Abdelgadir, Nowaczyk, & Li, 2013; Kehinde et al., 2014	Bergstrom et al., 2016; Pfitzer et al., 2018; Freeman et al., 2008 Lange, Guenther, Busch, Hess, & Schreiber, 2007; de Graaf et al., 2015
Prevalence of syndrome per 10,000 livebirths	1.4	1.2–2.3	NA	12.6
^a Frequency at birth of CHDs in syndrome	^b ≥ 80%	≥ 90%	75–100%	50%



TABLE 1 Congenital heart defects (CHDs) in autosomal aneuploidy syndromes

Syndrome	Trisomy 13	Trisomy 18	Trisomy 22	Trisomy 21 (Down syndrome)
Types of CHDs				
Laterality defects	Rare	Rare	Not reported	Rare
Conotruncal, all	25–50%	25–50%	5–25%	Rare
D-TGA		Rare		
Other	Rare	Rare	Not reported	Rare
L-transposed great arteries				
Single ventricle				
Single ventricle physiology	20–30%			
Septal defects, all	25–50%		50–75%	5–25%
ASD, secundum	85%	50–75%		
VSD, membranous	40–50%	≥ 90%		
VSD, muscular				
VSD, canal-type				
VSD, malalignment				
PDA	50–60%	85%		
AVSD	10%	10%	Rare	25–50%
AVSD, complete				5–25%
ASD, primum				
TAPVC	Rare	Rare	Not reported	
Valve defects	Polyvalvar dysplasia	Polyvalvar dysplasia	5–25%	Rare
	75%	75–100%		



Síndrome de Turner

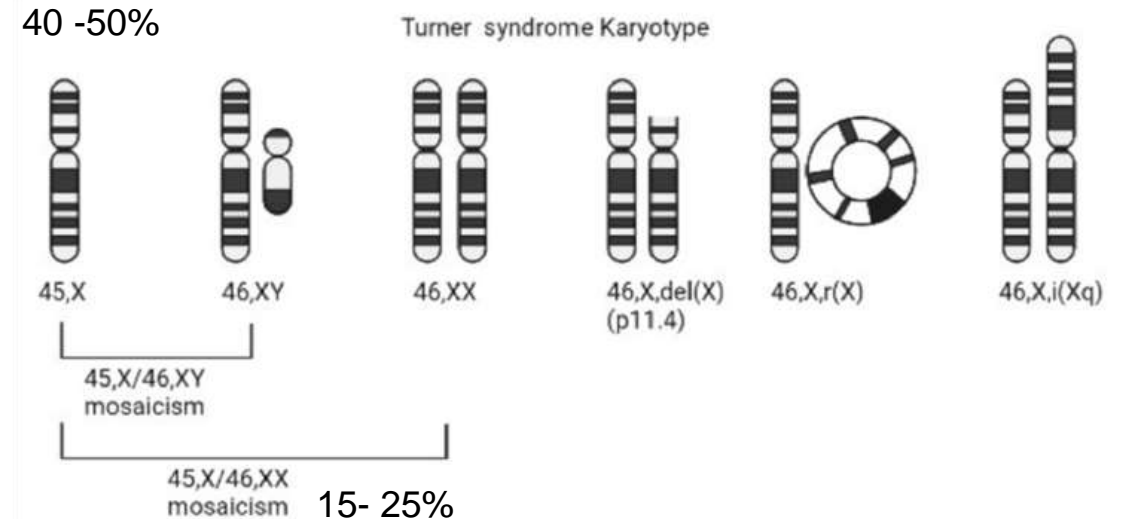


Prevalencia de 1: 2000 a 2500 mujeres nacidas vivas

Etiología: La pérdida parcial o total del 2do cromosoma sexual.

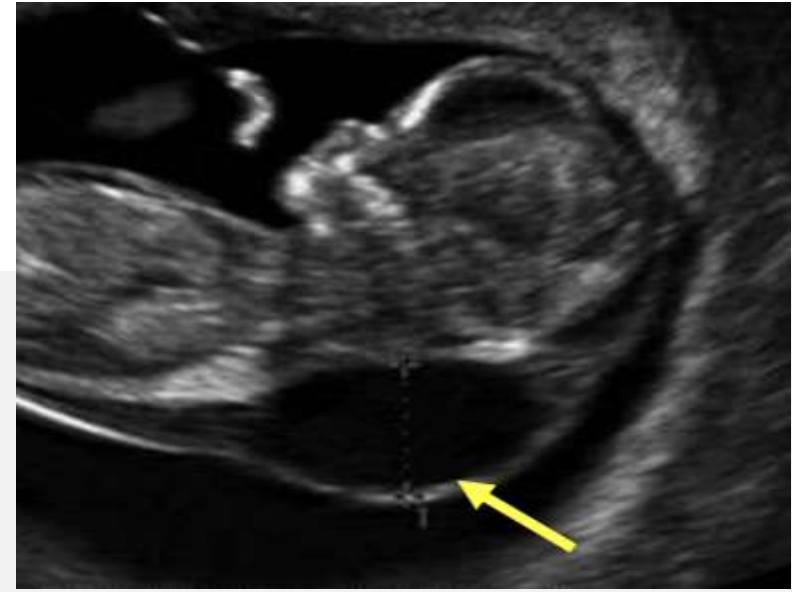
- No disyunción en la meiosis paterna.
- No disyunción mitótica postcigótica

El riesgo del síndrome de Turner no cambia con la edad materna



Fenotipo prenatal

- 1er T TN aumentada. – mediana 8 mm sobre la media normal – Taquicardia 50% - RCF precoz leve
- Higroma quístico 20% corresponde a sd Turner.



Fenotipo prenatal



- Edema Generalizado
- Derrame pleural leve
- Ascitis
- Riñón en herradura
- Anomalías cardíacas



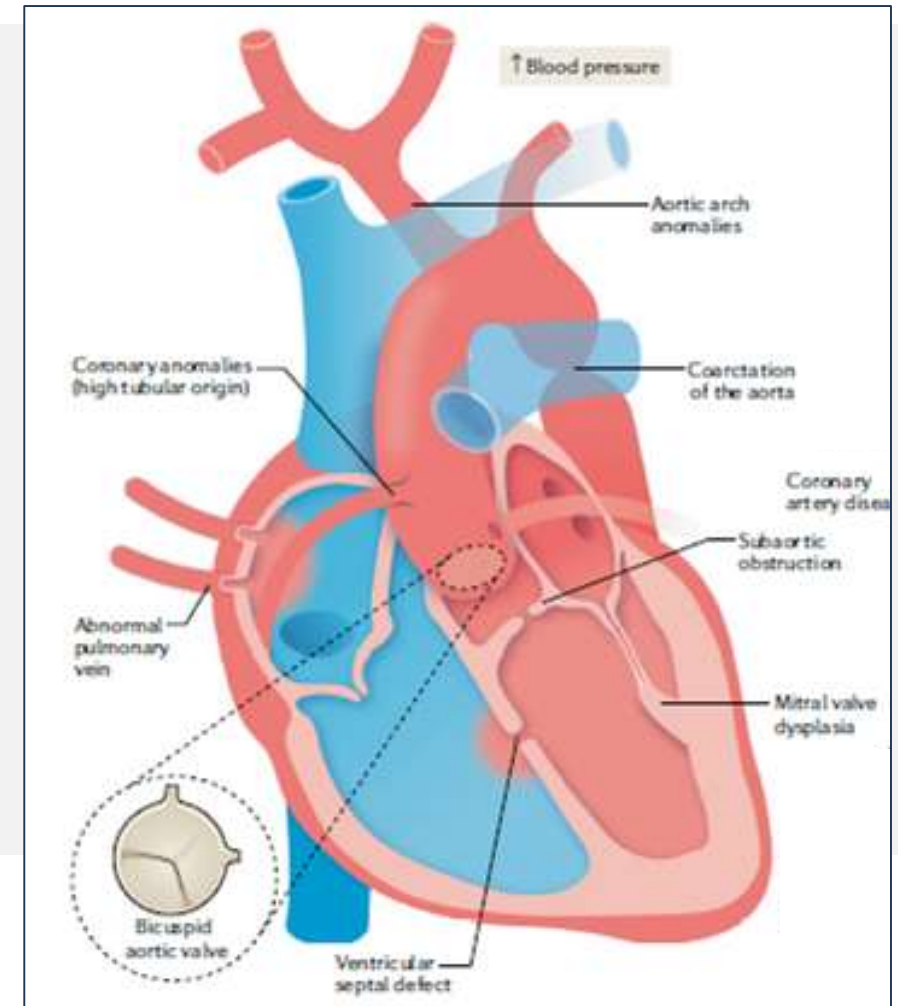
Liau J, Romine L, Kory LA, et al. Simplifying the ultrasound findings of the major fetal chromosomal aneuploidies. *Curr Probl Diagn Radiol.* 2014

Sd. Turner: Cardiopatías



- Afectan a un 26-50% de las pacientes.
- Principal causa de mortalidad precoz.
- **Defectos congénitos izquierdos**

- Válvula aórtica bicúspide 25%
- Anomalías coronarias
- Drenaje pulmonar anómalo parcial 15-25%
- Anomalías del arco aórtico
- Aorta Bovina
- CoAo
- Displasia Mitral
- SVIH



Sd. Turner: Cardiopatías

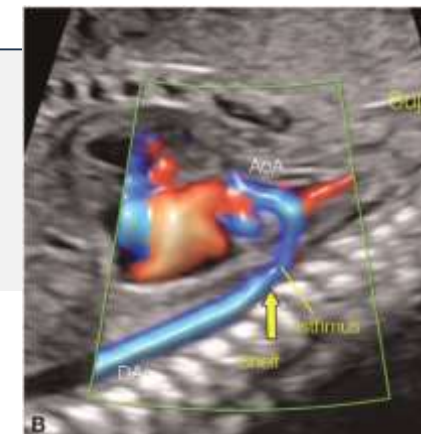
Table 1

Prevalence of congenital heart diseases in patients with Turner syndrome.

Congenital heart disease	Fuchs M et al. (2019) [10]	Donadille B et al. (2012) [30]	Kim H et al. (2011) [24]	Loscalzo M et al. (2005) [31]	Ho V et al. (2004) [22]	Pooled total
Bicuspid aortic valve (n [%])	102 (32)	49 (21)	20 (39.2)	27 (21)	N/R	198 (27)
Coarctation of aorta (n [%])	43 (14)	16 (6.9)	8 (15.7)	16 (12)	10 (12)	93 (12)
Persistent left superior vena cava (n [%])	24 (8)	6 (2.5)	4 (7.8)	N/R	11 (13)	45 (6)
Anomalous pulmonary vein (n [%])	18 (6)	2 (0.9)	8 (15.7)	N/R	11 (13)	39 (5)
Others (n [%])	22 (7)	124 (52)*	16 (31.4)#	N/R	42 (49)#	204 (30)

N/R – not reported; * – minor malformations.

– elongation of the transverse aortic arch.



CAT EYE



Prevalencia: 1:150.000

Etiología: invdup(22pter-q11) - tetrasomía parcial del cr.22

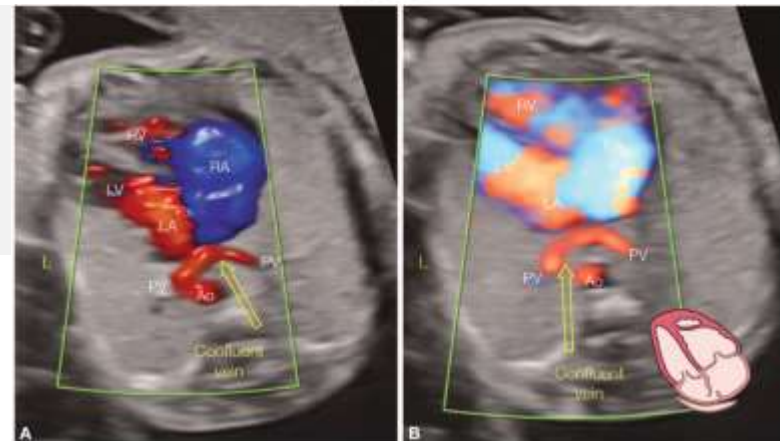
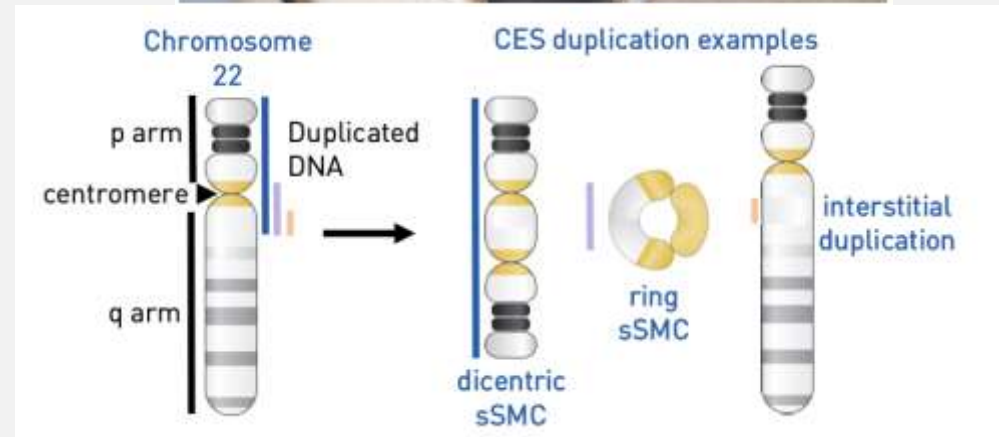
Herencia Autosómica Dominante

Tríada clásica:
Coloboma del iris
Malf. Auriculares
Malformaciones anales

Anomalías Cardíacas

60%

RVPAT
Interrupción del arco
aórtico



Diagnóstico

- QF – PCR
- Cariograma convencional (BVC – AMCT)
- aCGH



CNV

Síndrome de Microdelección 22q11.2
Síndrome de Williams

Síndrome microdelección 22q11.2



- Prevalencia 1 en 2000 a 6000 RNV – 1 en 300 a 1000 fetos
- Segundo síndrome de microdelección más frecuente en humanos
- Hombres y mujeres afectados por igual
- Etiología: deleción heterocigota en 22q11.2
- Microdelección 1.5–3 Mb (2.54 Mb)
- Herencia autosómica dominante
- 90% de los casos son de novo

* 602054

T-BOX TRANSCRIPTION FACTOR 1; TBX1

Alternative titles; symbols

T-BOX 1

HGNC Approved Gene Symbol: [TBX1](#)

Cytogenetic location: [22q11.21](#) Genomic coordinates (GRCh38): [22:19,756,703-19,783,593](#) (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype View Clinical Synopsis	Phenotype MIM number	Inheritance	Phenotype mapping key
22q11.21	Conotruncal anomaly face syndrome	217095		3
	DiGeorge syndrome	188400	AD	3
	Tetralogy of Fallot	187500	AD	3
	Velocardiofacial syndrome	192430	AD	3

Fenotipo Prenatal

Received: 3 July 2017 | Revised: 14 February 2018 | Accepted: 15 February 2018

DOI: 10.1002/ajmg.a.38665

ORIGINAL ARTICLE

WILEY AMERICAN JOURNAL OF medical genetics A

Expanding the fetal phenotype: Prenatal sonographic findings and perinatal outcomes in a cohort of patients with a confirmed 22q11.2 deletion syndrome

- 42 casos con evaluación prenatal y confirmación pre (28/42) o postnatal (14/42).
- 81% deleción estándar LCR22A – LCR22D
- 95% presentó una CC
- 90% existían anomalías extracardíacas

TABLE 3 Prenatal extracardiac findings associated with the fetal phenotype of 22q11.2

Central nervous system	38% (16/42)
Asymmetric lateral ventricles	31% (5/16)
Prominent cavum septum pellucidum	37.5% (6/16)
Mega cisterna magna	12.5% (2/16)
Neural tube defect	25% (4/16)
Gastrointestinal	9.5% (4/42)
Tracheoesophageal fistula (one with associated imperforate anus)	50% (2/4)
Umbilical cord hernia	25% (1/4)
Umbilical Vein Varix	25% (1/4)
Genitourinary	17% (7/42)
Dilated renal pelvis/pyelectasis	71% (5/7)
Bilateral ureterocele	14% (1/7)
Unilateral multicystic dysplastic kidney	14% (1/7)
Pulmonary	7% (3/42)
Congenital diaphragmatic hernia	67% (2/3)
Congenital cystic adenomatoid malformation	33% (1/3)
Craniofacial dysmorphism	21% (9/42)
Bilateral cleft lip/palate	10% (1/10)
Small ears	60% (6/10)
Micrognathia	10% (1/10)
Hypotelorism	10% (1/10)
Bulbous nose	10% (1/10)
Skeletal	19% (8/42)
Bilateral talipes	25% (2/8)
Anomalous vertebrae	50% (4/8)
Pectus carinatum	12.5% (1/8)
Short long bones	12.5% (1/8)
Small/hypoplastic thymus	26% (11/42)
Polyhydramnios	31% (13/42)
Single umbilical artery	2% (1/42)

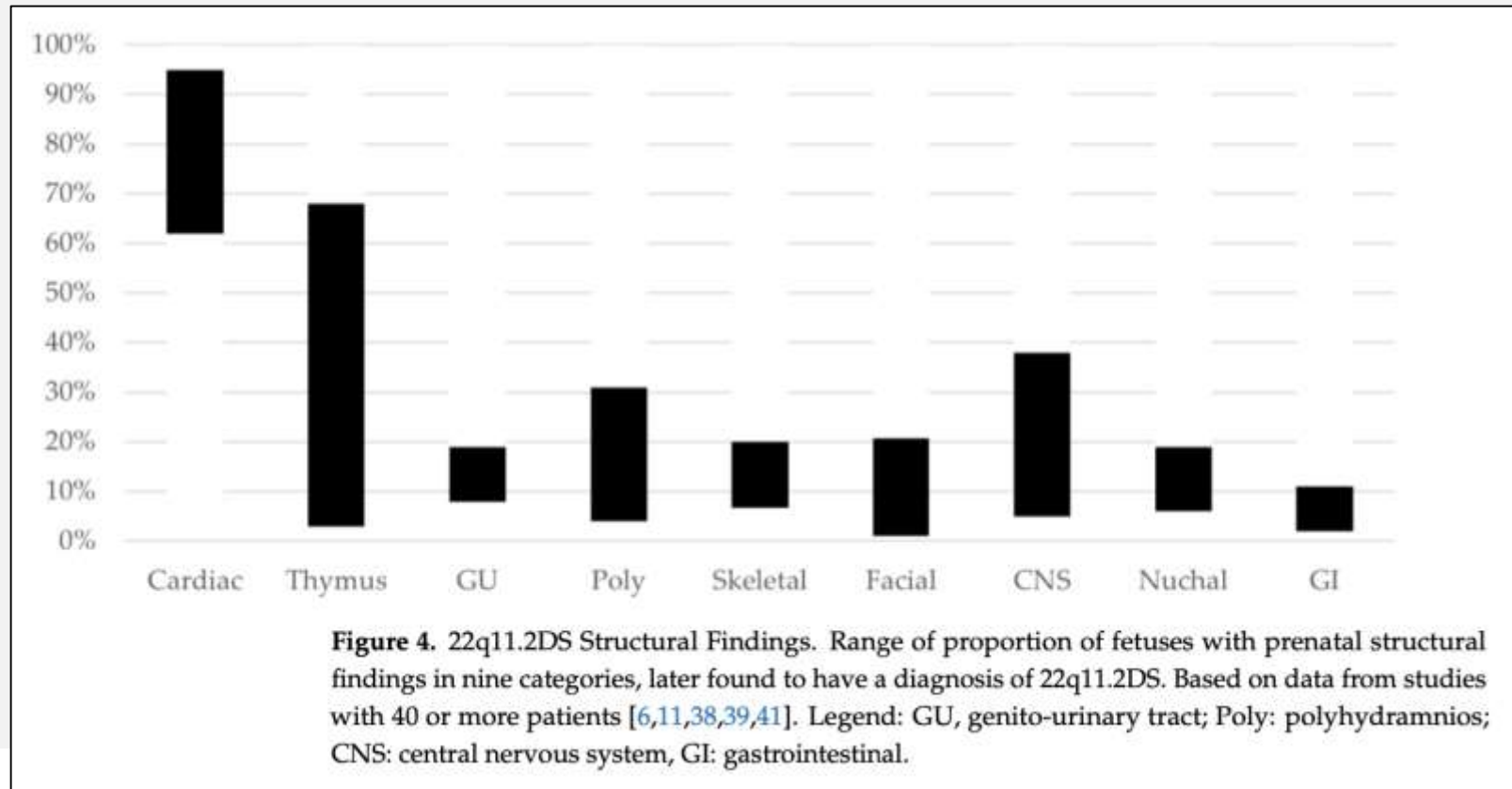
Cranial dysmorphism represents nine individual cases. One case had both hypertelorism and small ears.

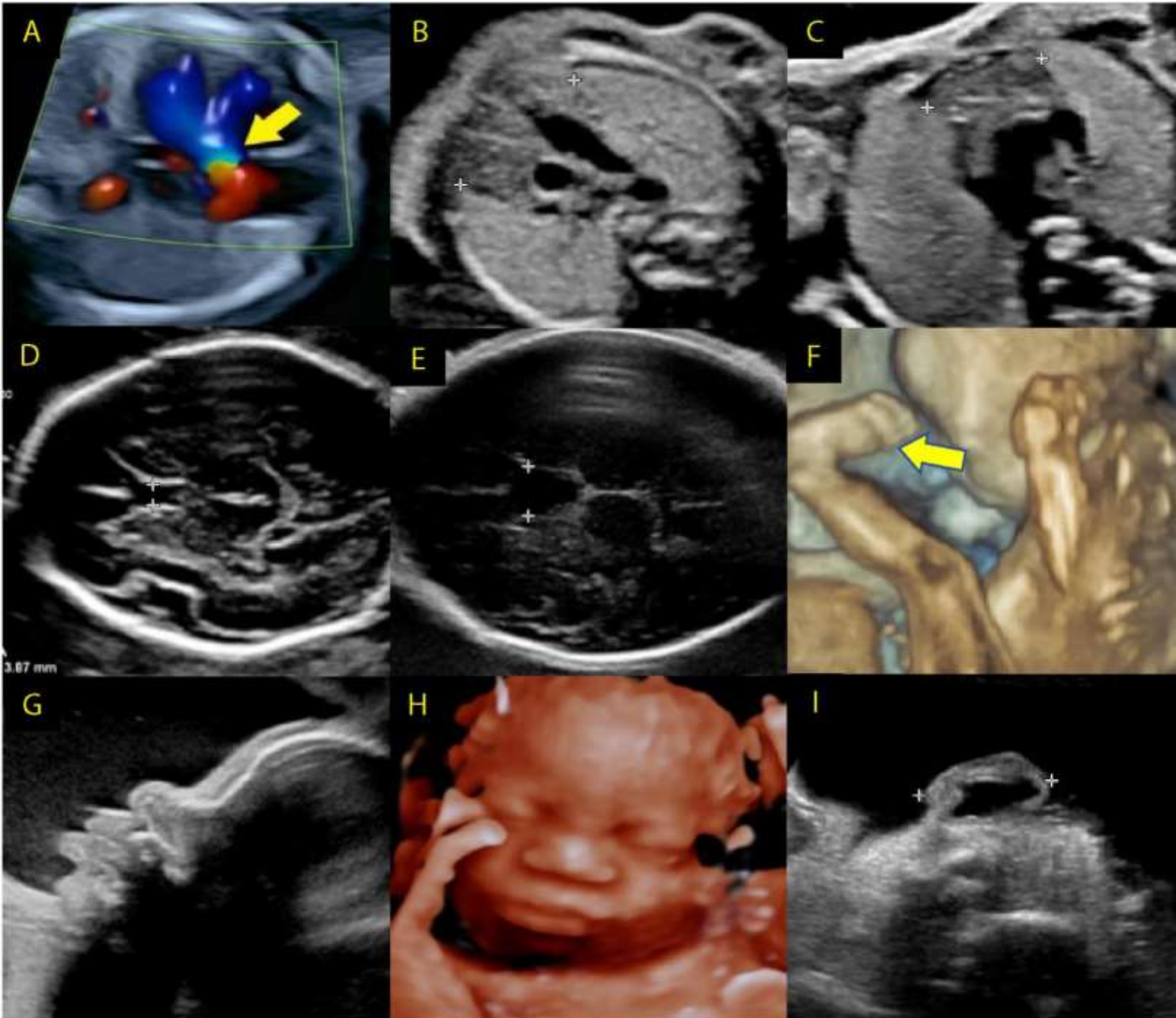


Fenotipo Prenatal



- Hipoplasia o aplasia del timo S90% E 98% VPP 81,8%
- Anomalías esqueléticas: Talipes equinovaro 20%
- Anomalías craneofaciales: 1-21%. Orejas pequeñas, labio – paladar hendido, hipotelorismo, nariz bulbosa, hueso nasal hipoplásico, micrognatia.
- RCF: riesgo aumentado 6 veces



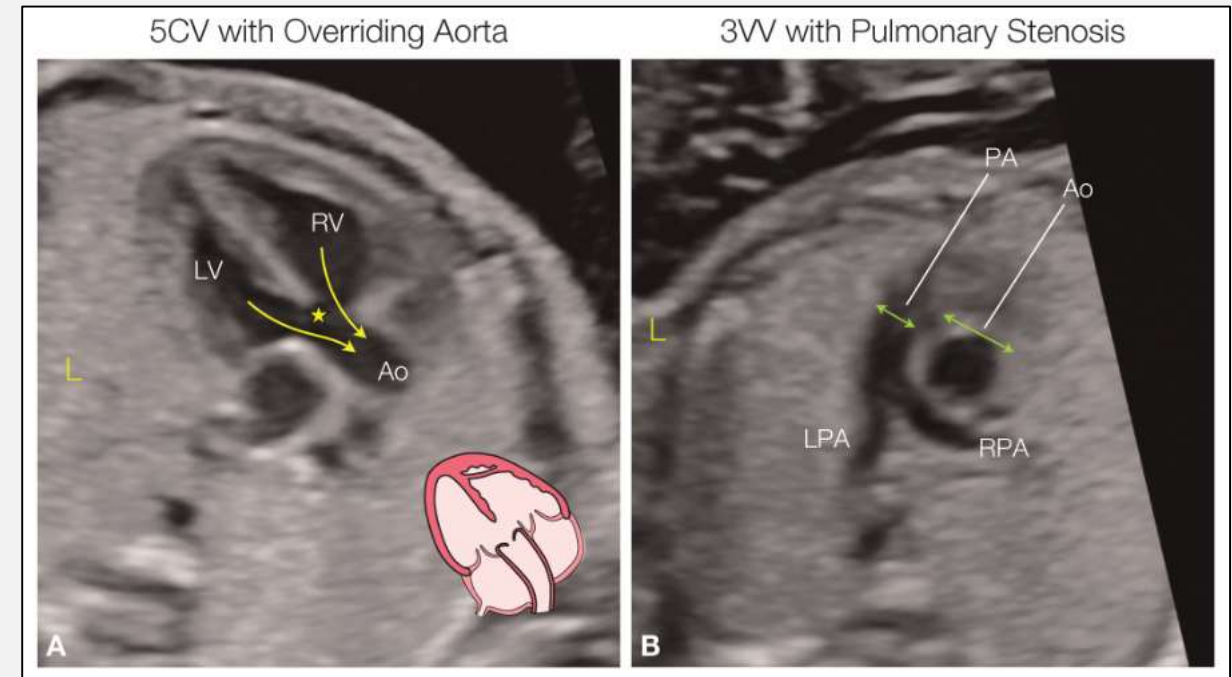


Síndrome microdelección 22q11.2: Cardiopatías

- CC reportadas series prenatales 76-100%.
- Categoría más frecuentemente asociada: defectos conotruncales.

TABLE 2 Cardiac diagnoses associated with the fetal phenotype of 22q11.2

Tetralogy of Fallot	21% (9/42)
Tetralogy of Fallot with pulmonary atresia	21% (9/42)
Interrupted aortic arch	24% (10/42)
Truncus arteriosus	17% (7/42)
VSD	7% (3/42)
Vascular ring	5% (2/42)
HLHS variant	2% (1/42)



Síndrome microdelección 22q11.2: Cardiopatías

APVS: Three-Vessel View in Grayscale

APVS: Three-Vessel View in Color Doppler

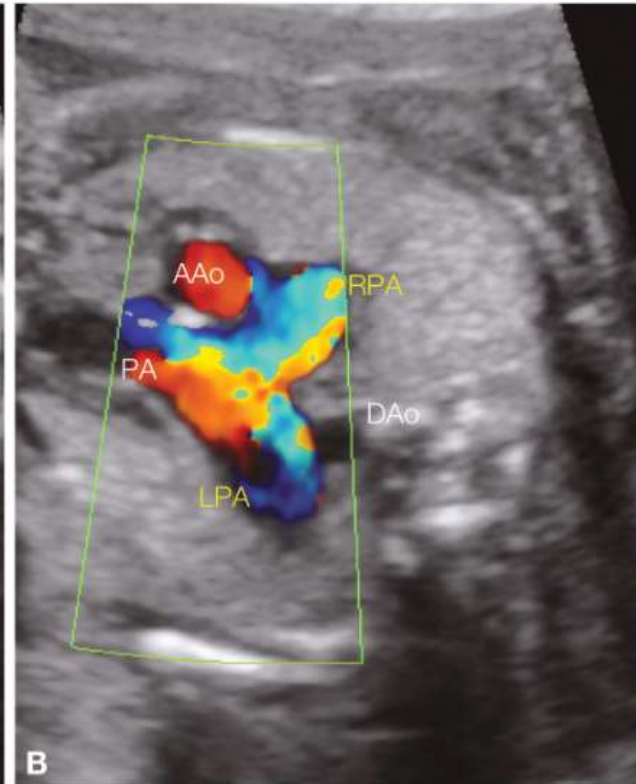
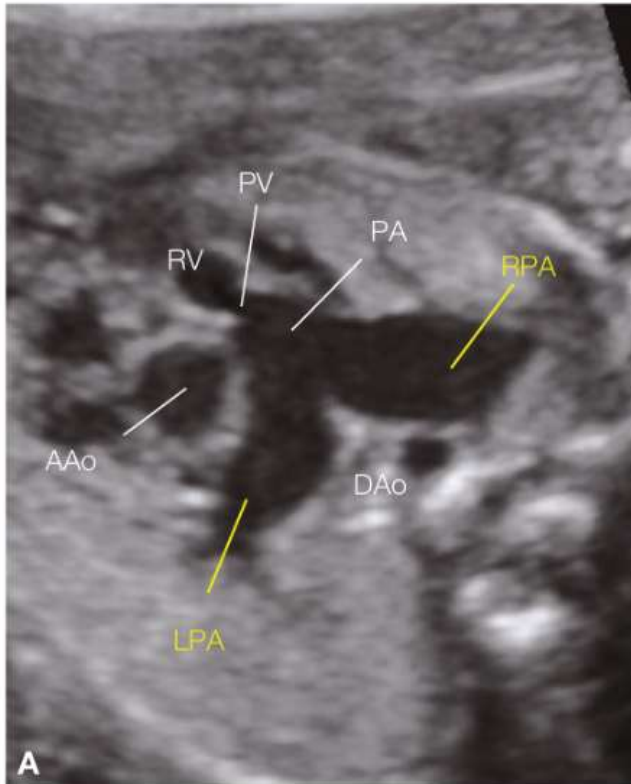


TABLE 2 Frequency of 22q11.2 deletion in cardiac patients^a

Cardiac malformation	Range of estimated frequency (%)
Interrupted aortic arch type B	50-89
Truncus arteriosus	34-41
Tetralogy of Fallot	8-35
Conoventricular septal defect	7 ^b
Isolated aortic arch anomaly	5-24 ^c
Double outlet right ventricle	<1 ^d
Transposition of the great arteries	<1 ^d

^aAverage frequency presented. In all cases, frequency will be higher in the presence of an aortic arch anomaly as compared to normal left-sided aortic arch with normal branching pattern.

^bFrequency increases from 5% to 29% with a normal aortic arch versus arch anomaly, respectively.

^cReflects findings on published fetal data (~5%) versus single post-natal study (24%).

^d22q11.2 deletion only seen in cases with aortic arch anomalies in one study.

Síndrome de Williams



- Prevalencia: 1/7000 RNV
- Etiología: Microdelección de 1,55 - 1,8 Mb en cr. 7q11.23
- Herencia Autosómica Dominante

Desorden multisistémico caracterizado por:
Alteraciones cardiovasculares y endocrinas
Características faciales típicas
Discapacidad intelectual y cognitiva
Hipersociabilidad



ELN – codifica la proteína elastina.
SNV patogénicas en *ELN* típicamente se asocian con Estenosis Ao
Supravalvular

Fenotipo Prenatal



TABLE 3 Fetal ultrasound features of fetuses with 7q11.23 microdeletion.

	Total (40)	
IUGR	28	70.0%
SFFL/SFB	10	25.0%
Hypoplastic/absent nasal bone	3	7.5%
Increased nuchal translucency	2	5.0%
Cardiovascular defects	12	30.0%
Echogenic intracardiac focus	1	2.5%
Single umbilical artery	2	5.0%
Polyhydramnios	7	17.5%
Abnormality of skull size/shape	3	7.5%
Protruding tongue	6	15.0%
Duodenal atresia	1	2.5%
Small stomach	1	2.5%
Omphalocele	1	2.5%
Urinary tract abnormalities	2	5.0%
Buried penis	2	5.0%
Gyration delay	1	2.5%
Aplasia/Hypoplasia of the corpus callosum	1	2.5%
Fetal choroid plexus cysts	1	2.5%

Abbreviations: IUGR, intrauterine growth retardation; SFFL, short fetal femur length; SLB, short long bone.

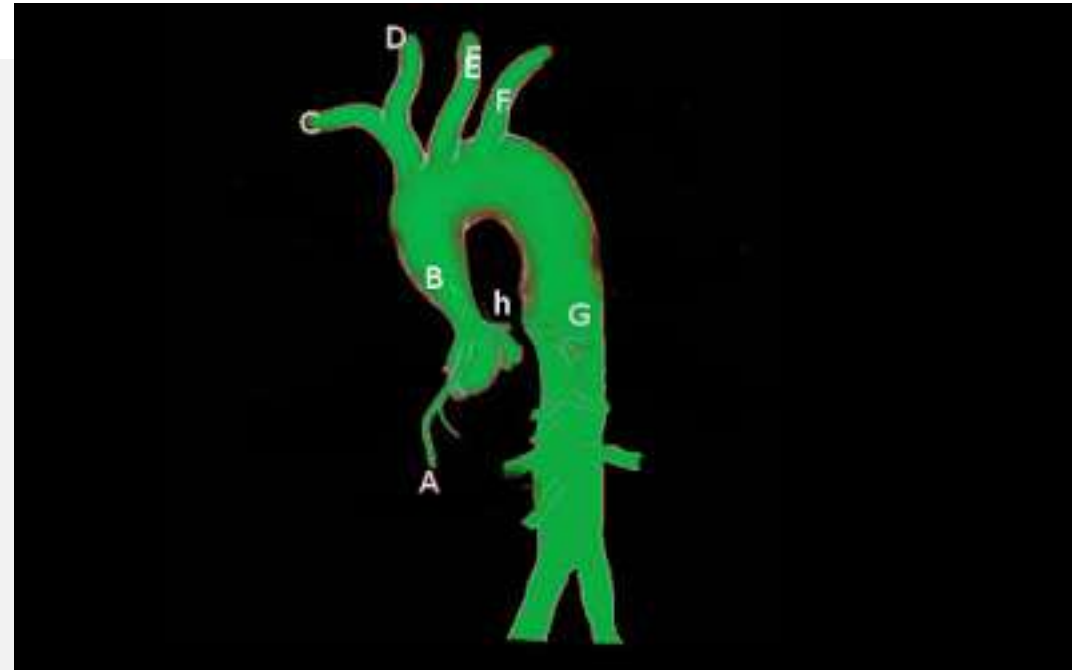
40 fetos
24 casos de novo



Síndrome de Williams: Cardiopatías



- Las alteraciones Cardiovasculares de la haploinsuficiencia de ELN incluyen:
- Estenosis Ao Supravalvular
- Estenosis arterial pulmonar periférica
- Estenosis pulmonar
- Estenosis Ao
- Coartación Ao
- Válvula Aórtica bicúspide
- Defectos septales



Serie fetal

Lesiones obstructivas izquierdas: 11/14

Arco Ao Hipoplásico 6/14

SVAS 3/14 □ 2 diagnóstico postnatal

Diagnóstico



- FISH
- MLPA – Panel 21 Microdeleciones
- CMA

SNV

Síndrome CHARGE
Síndrome de Noonan
Síndrome de Alagille
Síndrome de Holt Oram
Síndrome de Rubinstein Taybi
Síndrome Hidroletal

Síndrome CHARGE



- Prevalencia: 1/10.000
- Etiología: Mutaciones de novo gen *CHD7*
- helicasa cromodominio unión a DNA 7 o deleción.
- Herencia Autosómica Dominante
- Caracterizado por un patrón de anomalías congénitas.

CHARGE

C oloboma

H Heart defects

A atresia choanae

R RCF

G Genital hipoplasia

E Ear anomalies or deafness



Anomalías N. craneales
Defectos vestibulares
Labio o paladar hendido
Anomalías traqueoesofágicas
Anomalías cerebrales
Anomalías renales

Síndrome CHARGE: Cardiopatías



- Prevalencia 74%

TABLE 1 Spectrum of congenital heart disease in CHARGE syndrome versus all congenital heart disease

Primary classification (modified from Botto, Lin, Riehle-Colarusso, Malik, & Correa, 2007)	CHARGE syndrome			All CHD		
	Literature review (# patients)	Corsten-Janssen et al., 2013 (# patients)	Total (# patients)	% of all CHD	Prevalence per 1,000	% of all CHD
Conotruncal	88	54	142	33.6	0.876	10.2
Atrioventricular Septal defect	22	26	48	11.3	0.290	3.4
Right ventricular outflow tract malformation	19	20	39	9.2	0.805	9.3
Septal defect	55	58	113	26.7	4.512	52.4
Left ventricular outflow tract malformation	20	23	43	10.2	0.886	10.3
PDA	15	19	34	8.0	1.004	11.7
Complex single ventricle	2	1	3	0.7	0.093	1.1
Abnormal pulmonary venous return	0	1	1	0.2	0.144	1.7
Number with congenital heart disease	221	202	423	100		

Adapted from Liu, Chen, et al. (2019)

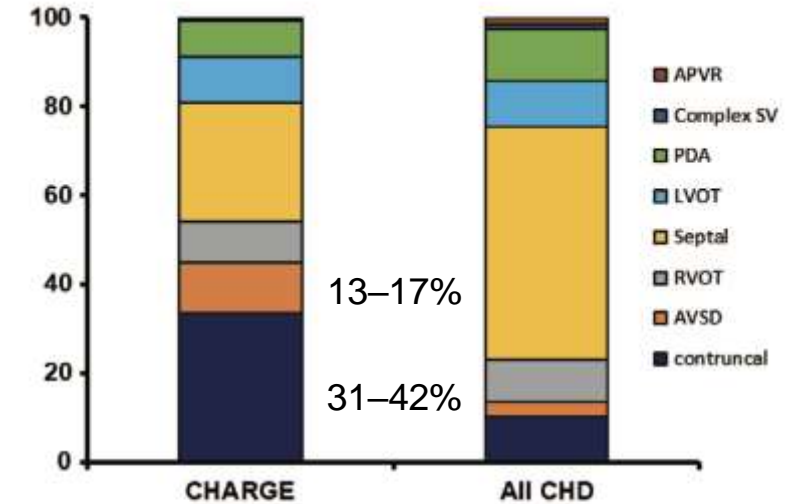


FIGURE 1 Spectrum of congenital heart disease in CHARGE syndrome compared to all congenital heart disease. Conotruncal defects and atrioventricular septal defects (AVSDs) are over-represented in CHARGE compared to all congenital heart disease from Table 1. There are fewer isolated septal defects, similar degree right ventricular outflow tract (RVOT), left ventricular outflow tract (LVOT), isolated patent ductus arteriosus (PDA), complex single ventricles (SV), and anomalous pulmonary venous return (APVR)

Van Ravenswaaij-Arts CM, Hefner M, Blake K, et al. CHD7 Disorder. 2006 Oct 2 [Updated 2022 Sep 29]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.

Meisner JK. Congenital heart defects in CHARGE: The molecular role of CHD7 and effects on cardiac phenotype and clinical outcomes. *Am J Med Genet C Semin Med Genet.* 2020

Síndrome de Noonan



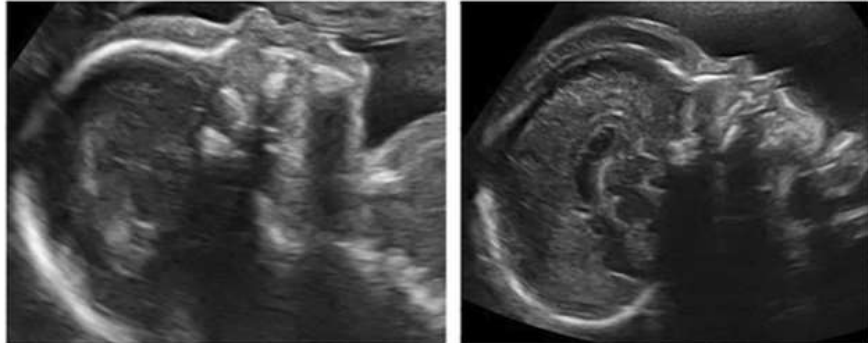
Table 1. Molecular Genetic Testing Used in Noonan Syndrome (NS)

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
<i>BRAF</i>	<2% ⁶	100%	Unknown ⁷
<i>KRAS</i>	<5% ⁸	100%	Unknown ⁷
<i>LZTR1</i>	~8% ⁹	100%	Unknown ⁷
<i>MAP2K1</i>	<2% ¹⁰	100%	Unknown ⁷
<i>MRAS</i>	<1% ¹¹	100%	Unknown ⁷
<i>NRAS</i>	<1% ¹²	100%	Unknown ⁷
<i>PTPN11</i>	50% ¹³	Nearly 100%	Rare duplication, ¹⁴ diagnosis of NS questioned ¹⁵
<i>RAF1</i>	5% ¹⁶	Nearly 100%	1 reported case w/a duplication, ¹⁷ diagnosis of NS questioned ¹⁵ ; 1 reported case of a deletion ¹⁸
<i>RASA2</i>	Unknown ¹⁹	100%	Unknown ⁷
<i>RIT1</i>	5% ¹⁶	100%	Unknown ⁷
<i>RRAS2</i>	<1% ²⁰	100%	Unknown ⁷
<i>SOS1</i>	10%-13% ²¹	100%	Unknown ⁷
<i>SOS2</i>	~4% ²²	100%	Unknown ⁷

- Prevalencia 1:1000 – 2500
- Etiología: variantes patogénicas en genes de la vía RAS/MAPK
- Trastorno autosómico dominante .
- Fenotipo variable, penetrancia completa

Fenotipo Prenatal

(D) Prominent forehead and skin edema



Fetus 5 : 21+5 WG

Fetus 6 : 26 WG

(E) Hypertelorism



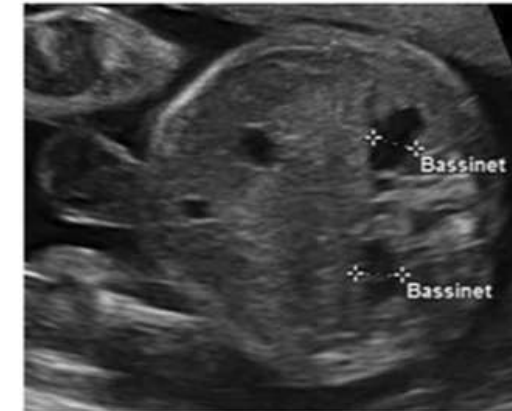
Fetus 6 : 22 WG

Fetus 6 : 26 WG

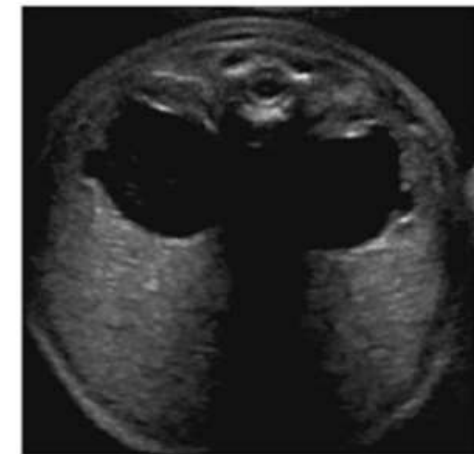
Table 3 Cohort 2: prenatal ultrasound findings in fetuses with normal chromosomal microarray and analysed for rasopathy using next generation sequencing panel

Prenatal findings	Total (n (%))	Mutation positive (n (%))	Mutation negative (n (%))	P-value
Increased NT/cystic hygroma in first trimester*	166/193 (86)	23/25 (92)	143/168 (85)	0.282
Persistent NT	61/193 (32)	16/25 (64)	45/168 (27)	0.000
Jugular lymph sacs	24/193 (12)	12/25 (43)	12/168 (7)	0.000
Hydrops fetalis	26/193 (13)	14/25 (56)	12/168 (7)	0.000
Pleural effusion	32/193 (17)	11/25 (44)	21/168 (13)	0.000
Ascites	8/193 (4)	3/25 (12)	5/168 (3)	0.069
Cardiac anomalies	34/193 (18)	12/25 (48)	22/168 (13)	0.000
Renal anomalies	10/193 (5)	4/25 (16)	6/168 (4)	0.027
Polyhydramnios	7/193 (4)	4/25 (16)	3/168 (2)	0.006
Other anomalies	32/193 (17)	9/25 (36)	23/168 (14)	0.009

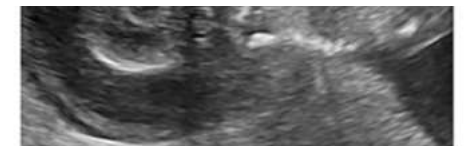
*Excluding nuchal fold, which is measured at approximately 20 weeks of gestation.
NT, nuchal translucency.



Fetus 5 : 21+5 WG



Fetus 6 : 26 WG



Fetus 11 : 14+1 WG

Stuurman KE, Joosten M, van der Burgt I, et al. Prenatal ultrasound findings of rasopathies in a cohort of 424 fetuses

Lamouroux A. Extending the prenatal Noonan's phenotype by review of ultrasound and a

Síndrome de Noonan: Cardiopatías

TABLE 2 Spectrum of cardiac abnormalities in Noonan syndrome

No cardiovascular disease		10-16%
Congenital heart disease	Pulmonary valve stenosis	25-71%
	Atrial septal defect	4-57%
	Ventricular septal defect	1-14%
	Atrioventricular canal defect	1-13%
	Mitral abnormalities	2-17%
	Aortic coarctation	2-9%
	Patent ductus arteriosus	1-6%
	Tetralogy of Fallot	1-4%
	Other cardiovascular	Hypertrophic cardiomyopathy
	Arterial aneurysms	<1%

Data obtained from 12 cohorts of patients with a clinically established NS diagnosis, with $n \geq 20$: (Burch et al., 1993; Ishizawa, Oho, Dodo, Katori, & Homma, 1996; Marino, Digilio, Toscano, Giannotti, & Dallapiccola, 1999; Bertola et al., 2000; Tartaglia et al., 2002; Sarkozy et al., 2003; Shaw, Kalidas, Crosby, Jeffery, & Patton, 2007; Sznajder et al., 2007; Smpokou, Tworog-Dube, Kucherlapati, & Roberts, 2012; Colquitt & Noonan, 2014; Li, X et al., 2019).

La frecuencia de CC se estima en 50-80%



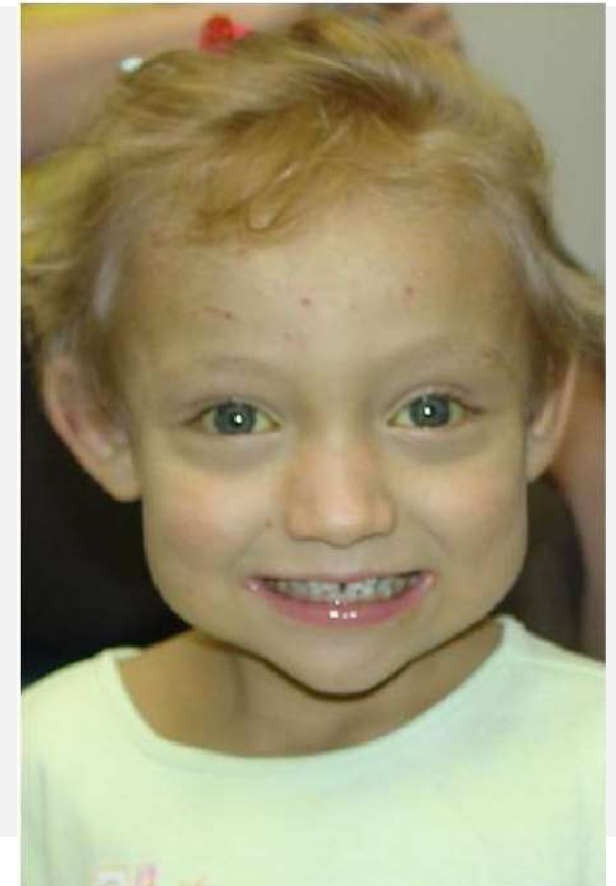
Síndrome de Alagille



- Prevalencia: 1-30000 a 1 – 50000.
- Etiología: 30-50% variante patogénica heredada – 50-70% de novo en JAG1 o NOTCH2.
- Herencia autosómica dominante con expresión variable.
- Desorden multisistémico: Colestasia, defectos cardíacos (arterias pulmonares), vertebras en mariposa, anomalías oftalmológicas, dismorfias faciales.

Table 2. Features of Alagille Syndrome

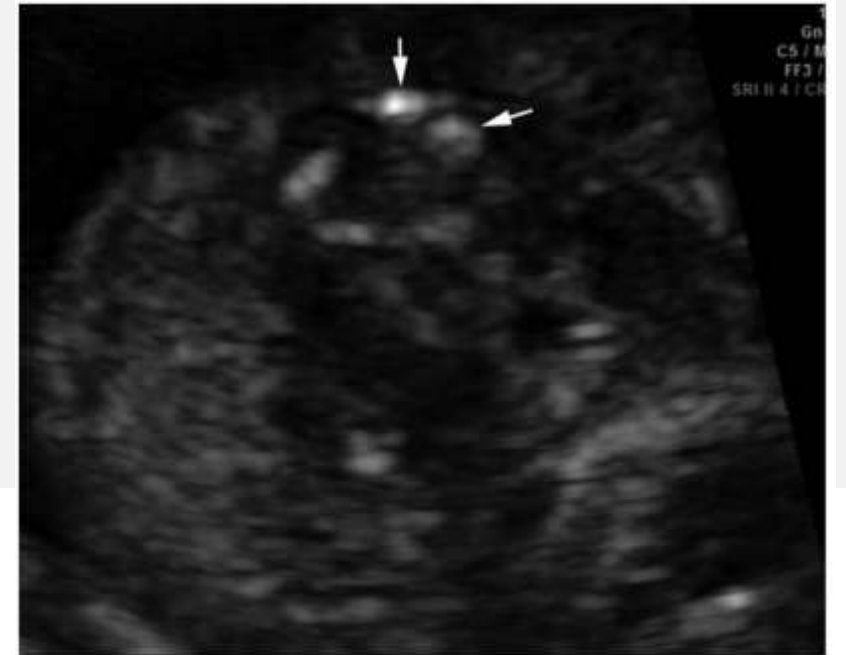
Feature	% of Persons w/Feature	Comment
Hepatic abnormality incl: bile duct paucity; conjugated hyperbilirubinemia; chronic cholestasis characterized by pruritus, xanthomas & fat-soluble vitamin deficiencies; & end-stage liver disease	≤100%	
Cardiac malformation	90%-97%	Most common cardiovascular malformations incl pulmonary stenosis & tetralogy of Fallot
Posterior embryotoxon	78%-89%	
Renal disease	39%	
Vertebral anomalies	33%-93%	
Characteristic facies	77%-97%	



Fenotipo Prenatal

TABLE 1
Features of Prenatally Diagnosed Alagille Syndrome

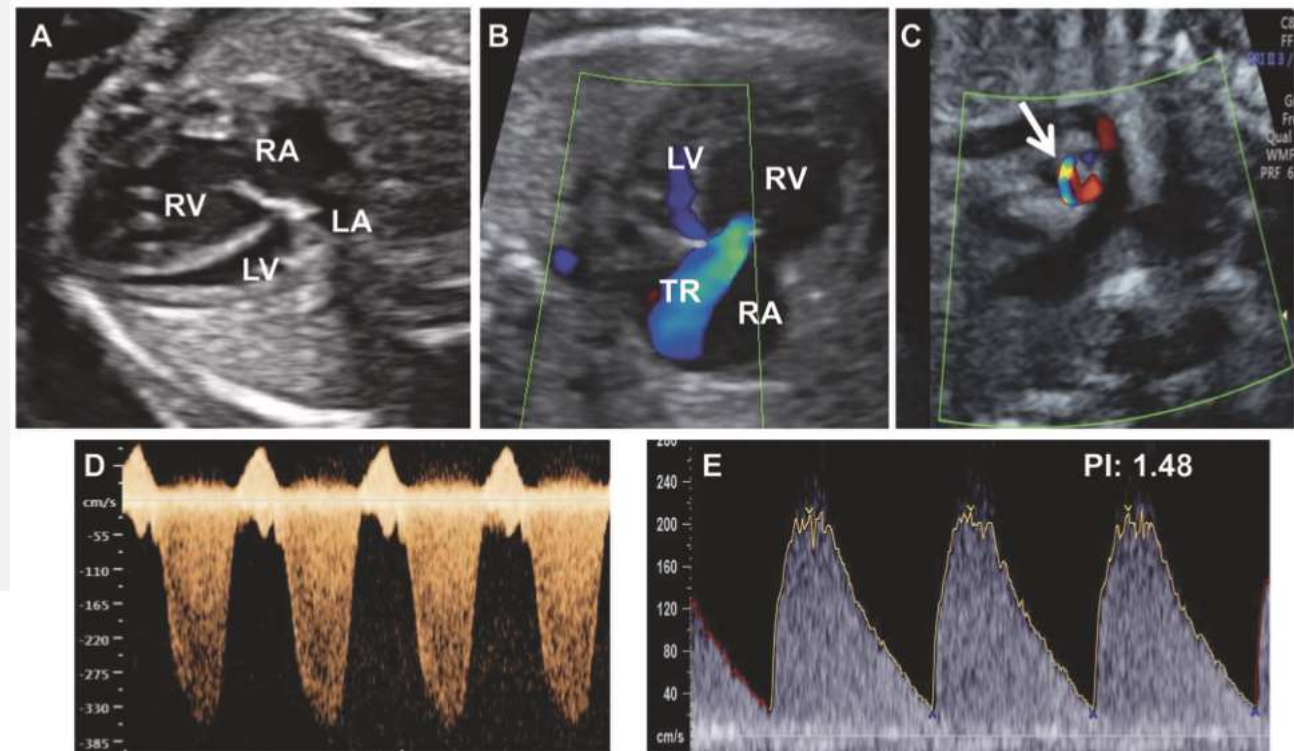
Reference	Affected Parent	Method of Diagnosis	Gestational Age at Ultrasound	Sonographic Findings	Delivery	Outcome and Other Findings
Witt ²	Mother	DNA at 12 weeks	-	-	ETOP	-
Antsaklis ¹	Mother	Post partum physical examination	24 ^{5/7}	IUGR ascites polyhydramnios	ETOP	Intrahepatic cholestasis Facies pulmonary stenosis
Albayram ³	Mother	Prenatal ultrasound	21 ^{4/7}	Pulmonary stenosis, prominent stomach, IUGR (28 weeks)	35 ^{5/7} weeks vaginal delivery	Death day of life, 5 postoperative complications-heart surgery
Ghidini ⁴	No	Post partum physical examination	21 ^{5/7}	Thoracic hemivertebrae, T12/L1 kyphoscoliosis, Tetralogy of Fallot Nonvisualized gallbladder	ETOP	Two-vessel cord, paucity of bile ducts, bilobed left lung, fused T12/L1,L2 vertebrae
Current case	Father	Prenatal ultrasound	20 ^{0/7}	Hemivertebrae, Butterfly vertebrae, two-vessel cord, prominent chin	39 weeks vaginal delivery	Asymmetrical aortic valve



Síndrome de Alagille: Cardiopatías

- La vasculatura pulmonar es la más frecuentemente comprometida.
- Estenosis Pulmonar 67%.
- Tetralogía de Fallot es el defecto complejo más frecuente 7%-16%.
- Otras:
- VSD, ASD, Estenosis Ao, CoAo.

2 casos reportados de constricción idiopática del ductus arterioso.



Holt Oram – Displasia atrio digital



- Prevalencia 1:100.000
- Etiología: Variantes patogénicas heterocigotas en *TBX5*.
- 85% de Novo
- Herencia Autosómica Dominante

Table 1. Molecular Genetic Testing Used in Holt-Oram Syndrome

Gene ¹	Method	Proportion of Probands with a Pathogenic Variant ² Detectable by Method
<i>TBX5</i>	Sequence analysis ³	>70% ⁴
	Gene-targeted deletion/duplication analysis ⁵	<1% ⁶

- Malformaciones extremidades superiores, de predominio radial o preaxial
- Anomalías huesos carpales presente en todos los individuos
- Malformaciones cardíacas
- Alteraciones de la conducción cardíaca: Bradicardia sinusal, bloqueo AV, FA

Unilateral/bilateral
Pulgares ausentes/focomelia
Longitud desigual – aplasia o hipoplasia radio
Fusión de huesos carpales
Oposición anormal del pulgar – pulgar 3 falanges

Holt Oram – Displasia atrio digital



Holt Oram: Cardiopatías



- Prevalencia : 75% - en su mayoría defectos septales

Ultrasound Obstet Gynecol 2014; 43: 475–476
Published online 3 March 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.13238

Unexplained right atrial enlargement may be a sign of Holt–Oram syndrome in the fetus

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Received: 8 May 2023 | Revised: 9 June 2023 | Accepted: 16 June 2023

DOI: 10.1002/pd.6399

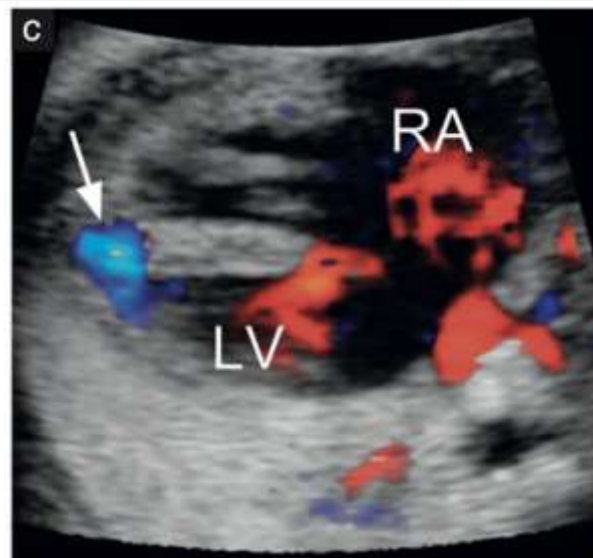
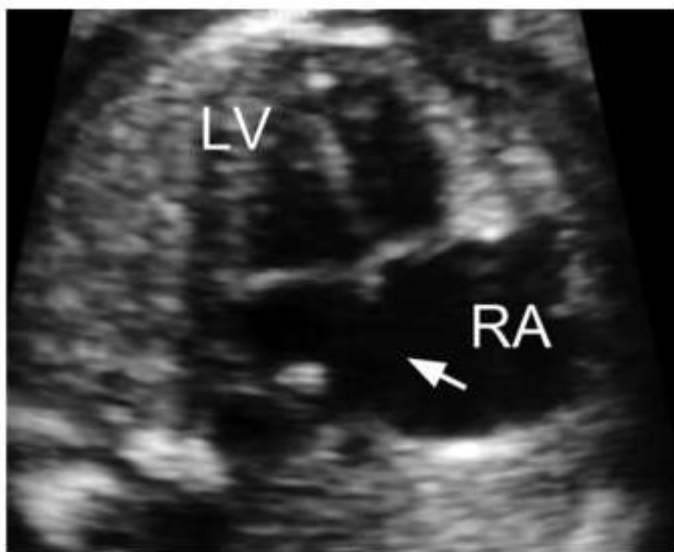
Pulgar izquierdo hipoplásico –
ausencia del primer
metacarpiano

PRENATAL
DIAGNOSIS WILEY

GENOTYPE:PHENOTYPE REPORT

A rare case of isolated right atrial enlargement and TBX5 mutation associated with Holt–Oram syndrome

Sandra D. Kikano | Wubishet Belay | Ann Kavanaugh-McHugh



Pulgar
bífido



Pulgar hipoplásico
Ausencia primer
metacarpiano

Rubinstein Taiby



Prevalencia 1:100.000 a 125.000

Etiología: Mutaciones de novo en *CREBBP* y *EP300*

Herencia autosómica dominante

Riesgo de recurrencia empírico 1%

Table 1. Molecular Genetic Testing Used in Rubinstein-Taybi Syndrome

Gene ^{1, 2}	Proportion of RSTS Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant ³ Detectable by Method	
		Sequence analysis ⁴	Gene-targeted deletion/duplication analysis ⁵
<i>CREBBP</i>	50%-60% ⁶	~80%	~20% ⁷
<i>EP300</i>	8%-10% ⁸	>99%	<1% ⁹
Unknown ¹⁰	~30%	NA	



- Características faciales distintivas
- Déficit Intelectual
- Pulgar y hallux anchos y angulados
- Adicionales: anomalías oculares, defectos cardíacos, anomalías renales, criptorquidea.

Fenotipo Fetal

SHORT REPORT

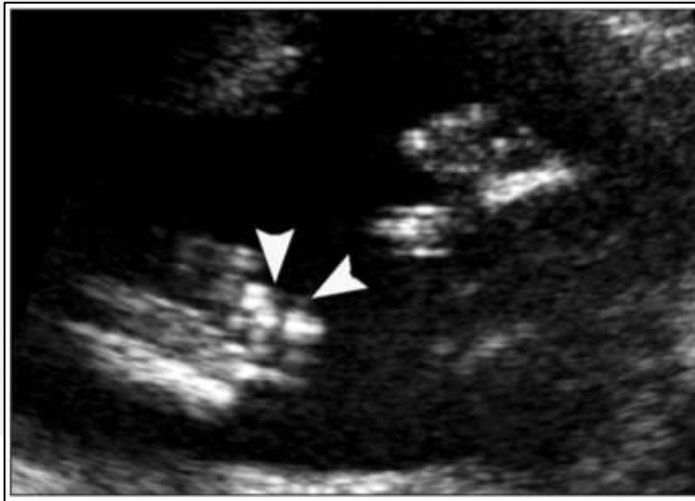
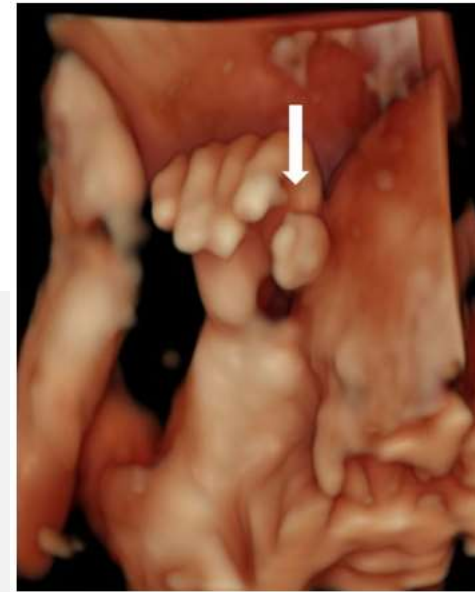
WILEY

Fetal phenotype of Rubinstein-Taybi syndrome caused by *CREBBP* mutations

Julien Van-Gils¹ | Sophie Naudion¹ | Jérôme Toutain¹ | Gwenaëlle Lancelot¹ |
Tania Attié-Bitach² | Sophie Blesson³ | Bénédicte Demeer⁴ | Bérénice Doray⁵ |
Marie Gonzales⁶ | Jelena Martinovic² | Sandra Whalen⁷ | Laurence Taine¹ |
Benoit Arveiler^{1,8} | Didier Lacombe^{1,8} | Patricia Fergelot^{1,8}

9 casos con diagnóstico prenatal con mutaciones en gen *CREBBP*

RCF y PHA en 56% (5/9) y 33% (3/9).



Rubinstein Taiby: Cardiopatías



- Cardiopatías congénitas ocurren en aproximadamente 1/3 de los individuos
- ASD, VSD
- DAP
- CoAo
- Estenosis Pulmonar
- Válvula Ao bicúspide
- Estenosis Aórtica
- Anillos vasculares
- Anomalías de la conducción

Síndrome Hidroletal



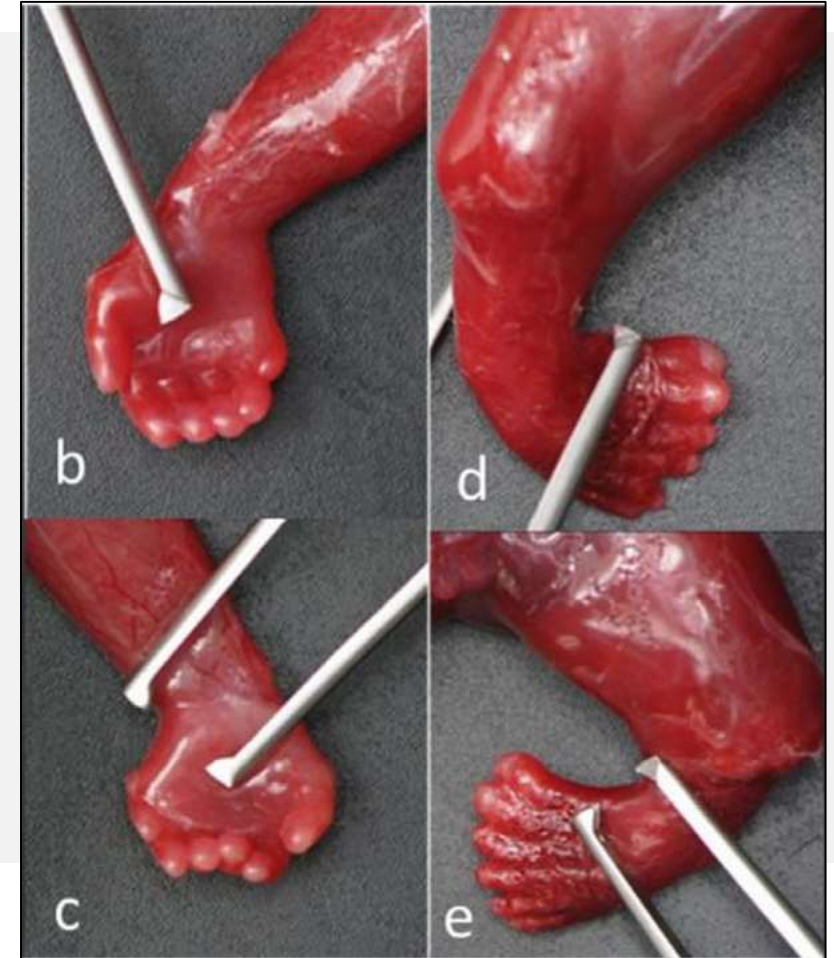
(HLS) (OMIM #236680)

- Síndrome perteneciente al grupo de las ciliopatías
- Polihidroamnios – Hidrocefalia - letalidad
- Presente principalmente en familias de origen finlandés.
- La incidencia anual en Finlandia se estima en 1/20.000.
- El SHL está causado por mutaciones en los genes *HYLS1* (11q24.2) y *KIF7* (15q26.1)
- Herencia autosómica recesiva



Fenotipo y Cardiopatías

- Micrognatia
- Fisura labiopalatina
- Polidactilia preaxial en manos y postaxial en pies
- Halluz duplex
- Hidrocefalia – agenesia de estructuras de la línea media
- Pie equinovaro
- 50% Defecto del septum AV



Diagnóstico



- Gen único
- Panel
- Exoma
- Genoma



Otros

VACTERL

- Asociación que involucra múltiples anomalías congénitas.
- 1:20.000
- Causa heterogénea – esporádica

VACTERL
Vertebrae
Anal atresia
Cardiac Defects
Trachea
Esophagus
Renal - Urinary
Limbs

3 componentes
diagnóstico

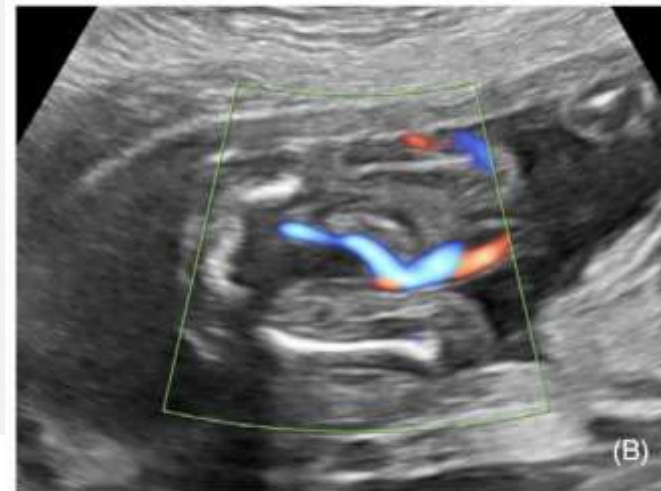
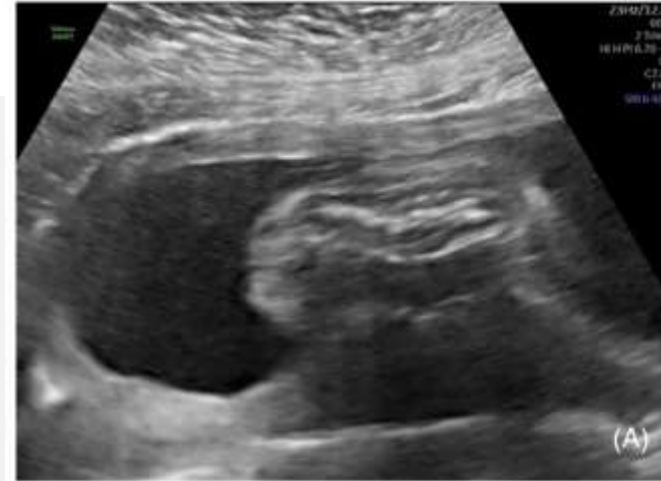


FIGURE 1 Ultrasound diagnosis of VACTERL association:
(A) Lumbo-sacral scoliosis; (B) single umbilical artery

VACTERL



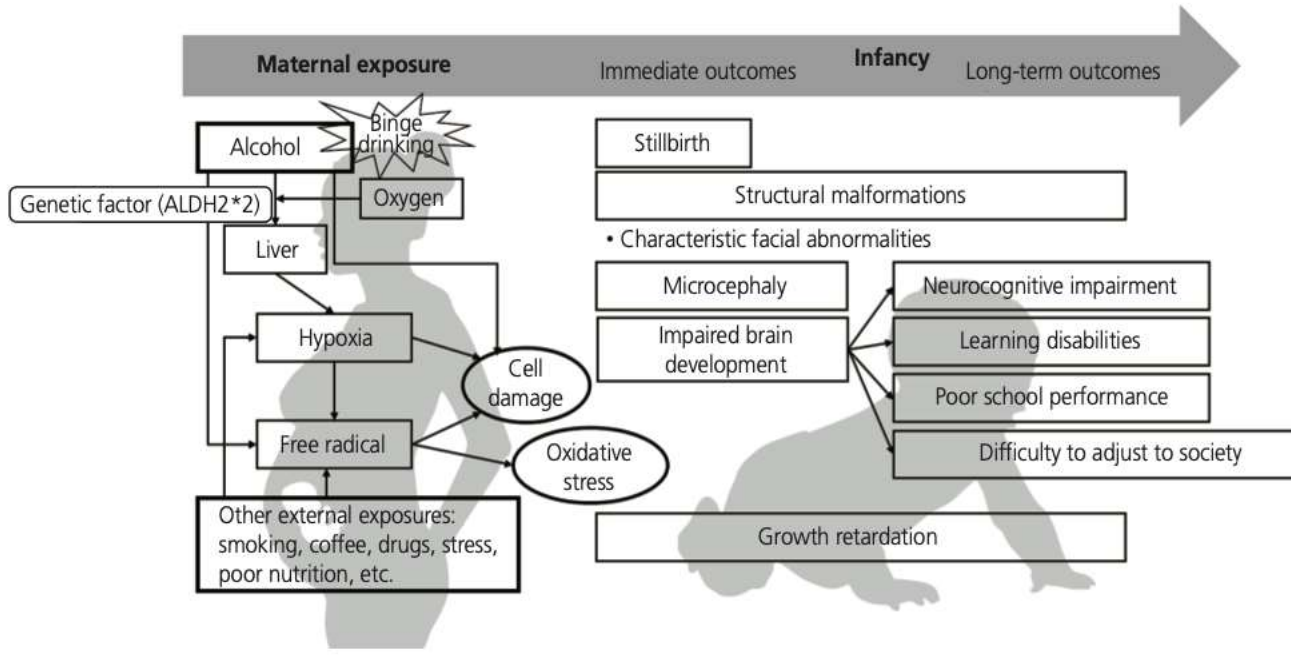
Table 5. Distribution of the different congenital anomalies according to the current study and the literature

Component feature	Major features (total group of VACTERL patients, N = 397), N (%)	Major features (STRICT-VACTERL, N = 213), N (%)	Major and minor features (total group of VACTERL patients, N = 397), N (%)	Major and minor features (STRICT-VACTERL, N = 213), N (%)	Husain et al. ¹³ (N = 36), N (%)	Solomon et al. ⁸ (N = 60), N (%)	Botto et al. ¹² (N = 286), N (%)	Khoury et al. ³ (N = 50), N (%)
V	131 (33%)	95 (45%)	261 (66%)	137 (64%)	29 (81%)	47 (78%)	190 (66%)	18 (36%)
A	247 (62%)	148 (70%)	259 (65%)	150 (70%)	22 (61%)	33 (55%)	236 (83%)	20 (40%)
C	227 (57%)	144 (68%)	253 (64%)	151 (71%)	30 (83%)	48 (80%)	136 (48%)	40 (80%)
TE	247 (62%)	144 (68%)	247 (62%)	144 (68%)	25 (69%)	31 (52%)	168 (59%)	12 (24%)
R	202 (51%)	122 (57%)	267 (67%)	150 (70%)	22 (61%)	43 (72%)	231 (81%)	41 (82%)
L	98 (25%)	63 (30%)	125 (32%)	72 (34%)	18 (50%)	28 (47%)	111 (39%) ^a	34 (68%)

V vertebral anomalies, A anorectal anomalies, C cardiac anomalies, TE tracheo-esophageal anomalies, R renal anomalies, L limb anomalies, NS not shown
^aN = 100 (35%) of the limb anomalies were pre-axial

Component feature	N
Cardiac anomalies	30 (83.33%)
Ventricular septal defect	22
Valvular anomalies	15
Other anomalies	15
Patent foramen ovale	14
Patent ductus arteriosus	13
Cardiomyopathies	12
Atrial septal defect	11
Vascular anomalies	9
Pulmonary anomalies	9
Tetralogy of fallot	6
Aortic anomaly	2
Double outlet right ventricle	2

Síndrome Alcohólico Fetal



- Disminución de la circunferencia craneana – microcefalia
- Alteraciones cuerpo calloso, cerebelo y ganglios basales
- Defectos cardíacos: Prevalencia 2%
- Defectos septales ventriculares y defectos conotruncales

Alcohol induce la apoptosis de las células de la cresta neural a través de daño oxidativo y interrupción de la señalización de SHH.

Enfermedad	Etiología genética	Herencia	Examen diagnóstico	Cardiopatías asociadas
Trisomía 21	47,XY,+21	-	Cariograma	CIA, CIV, Comunicación AV
Trisomía 13	47,XY,+13	-	Cariograma	Defectos septales y conotruncales Ventrículo único
Trisomía 18	47,XY,+18	-	Cariograma	Defectos septales y conotruncales
Monosomía X	45, X	-	Cariograma	Válvula Ao bicúspide Coartación Aortica DVPAP
Sd. Cat Eye	invdup(22pter-q11)	AD	Cariograma	DVPAC
Microdelección 22q11.2	Microdelección heterocigota 1.5–3 Mb en 22q11.2	AD 90% casos de novo	FISH MLPA CMA	Tetralogía de Fallot Interrupción del arco Ao tipo B Tronco arterioso
Síndrome de Williams	Microdelección heterocigota 1,55 - 1,8 Mb en cr. 7q11.23	AD	FISH MLPA CMA	Estenosis Aórtica supra valvular Arco Ao hipoplásico
Síndrome CHARGE	CHD7	AD	Gen único – Panel Exoma Genoma	Cardiopatías Conotruncales Comunicación AV
Síndrome de Noonan	PTPN11 SOS1	AD	Gen único – Panel Exoma Genoma	Estenosis pulmonar Miocardiopatía hipertrófica
Síndrome de Alagille	JAG1 NOTCH2	AD	Gen único – Panel Exoma Genoma	Estenosis Pulmonar Tetralogía de Fallot
Síndrome de Holt Oram	TBX5	AD	Gen único – Panel Exoma Genoma	CIA CIV
Síndrome de Rubinstein Taybi	CREBBP EP300	AD	Gen único – Panel Exoma Genoma	CIA CIV CoAo
Síndrome hidroletal	HYLS1 KIF7	AR	Gen único – Panel Exoma Genoma	Comunicación AV



CERPO

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Ximena Marques J.

Programa de especialización

Medicina Materno Fetal

Tutor Catherine Diaz