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

Microdeleciones comunes 22q11.2 y 1p36

Dr. Jorge Mocarquer Tapia

Programa de Especialización Medicina Materno Fetal
Facultad de Medicina, Universidad de Chile
Mayo 2023

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Deleción 22q11.2
Defectos cardiacos y extracardiacos

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Introducción

- 1965
- Dr. Angelo DiGeorge describió niños con hipoparatiroidismo y ausencia de timo
- Posteriormente se añadió cardiopatía congénita

- 1980
- Aparente deleción heterocigota de 22q11.2

- 1990
- ISH identifica deleciones submicroscópicas de 22q11.2

McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Definición

- Microdeleción

- Pérdida de material cromosómico, que comprende, en la mayoría de los casos entre 1 a 3 millones de pares de bases de DNA, las cuales no pueden ser detectadas por análisis cromosómico convencional.

- Haploinsuficiencia

- Situación en la cual la proteína producida por una sola copia de un gen normal, no es suficiente para garantizar una función normal

Tabla 1. Síndrome por microdelecion

Síndrome	Región cromosómica deletada
Williams-Beuren*	(7q11.23)
Prader-Willi*	(15q11-13)
Angelman*	(15q11-13)
Smith Magenis*	(17p11.2)
Miller-Dieker*	(17p13.3)
DiGeorge*	(22q11.2)
Wolf-Hirschhorn	(4p16.3)
Cri du Chat	(5p15)
Rubinstein-Taybi	(16p13.3)
Kallmann	(Xp22.3)
Ictiosis	(Xp22.3)

*Sondas para estudio FISH disponibles actualmente en nuestro país.

Sindrome de microdeleción 22q11.2

- 0,7 a 3 Mb
- Características fenotípicas

DiGeorge

Velocardiofacial

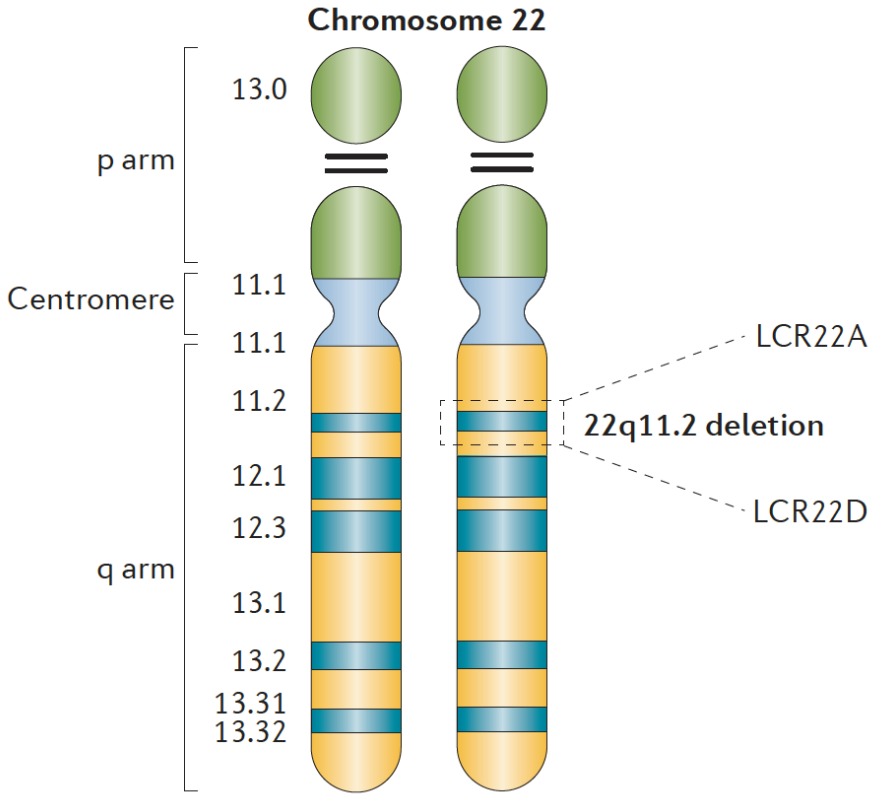
Anomalía facial y Conotruncal

Autosómico dominante Opitz G/BBB

Sedlackova

Cardiofacial de Cayler

CATCH 22



McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Presentación clínica heterogenea

Una misma condición con una **etiología común**

- 2° causa más frecuente de anomalía cardiaca congénita y retraso en el desarrollo
- Causa más común de anomalías sindrómicas que involucran el paladar
- Anomalías inmunes, endocrinas, genitourinarias, neurológicas y psiquiátricas

McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Epidemiología

- Microdeleción más común 1:3000 a 1:6000
- 90 a 95% *de novo*
- Incidencia prenatal es mayor (1:400)
- 1:100 en fetos con malformación estructural mayor
- Afecta por igual a ambos sexos
- Alta mortalidad infantil (4%)

	22q11.2
Frequency	1/4000
Length of DNA deletion	3 Mb or 1.5 M
Clinical Phenotype	
Congenital heart disease (CHD) [a]	75%
Immune deficiency (thymic hypoplasia) [b]	50–70%
Hypocalcemia (hypoparathyroidism)	35%
Dysmorphic craniofacial features	50%
Developmental delay	50%
Renal anomalies	14%
Skeletal defects	60%
Learning problems	70%
Psychiatric disorders [c]	30%
Gastrointestinal abnormalities	30%
Digital malformations (polydactyly)	30%

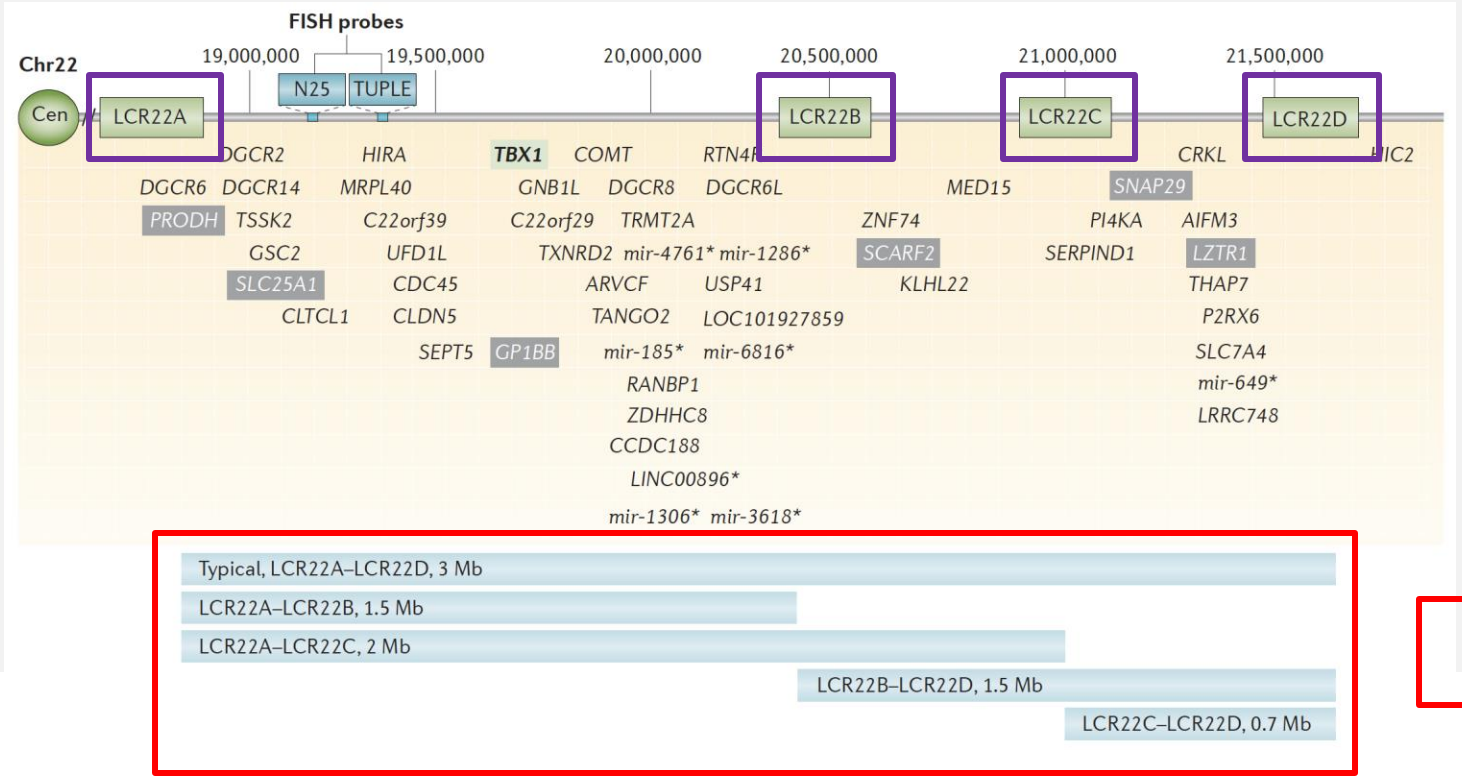
Grati FR, et al. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenat. Diagn.* 2015;35:801–809

Mecanismo

96% idénticas

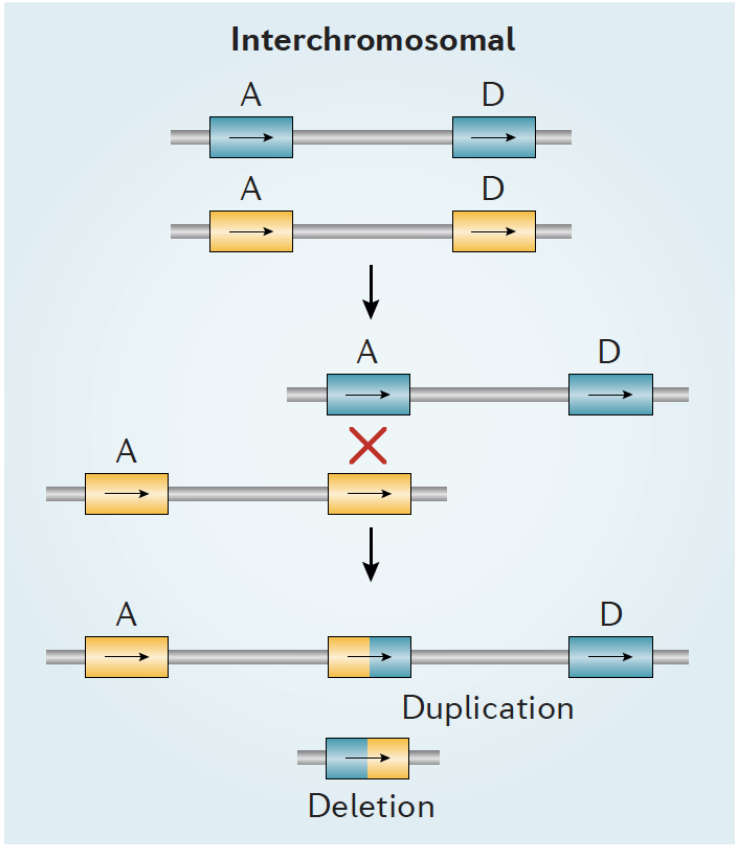
Mayor probabilidad de errores en meiosis

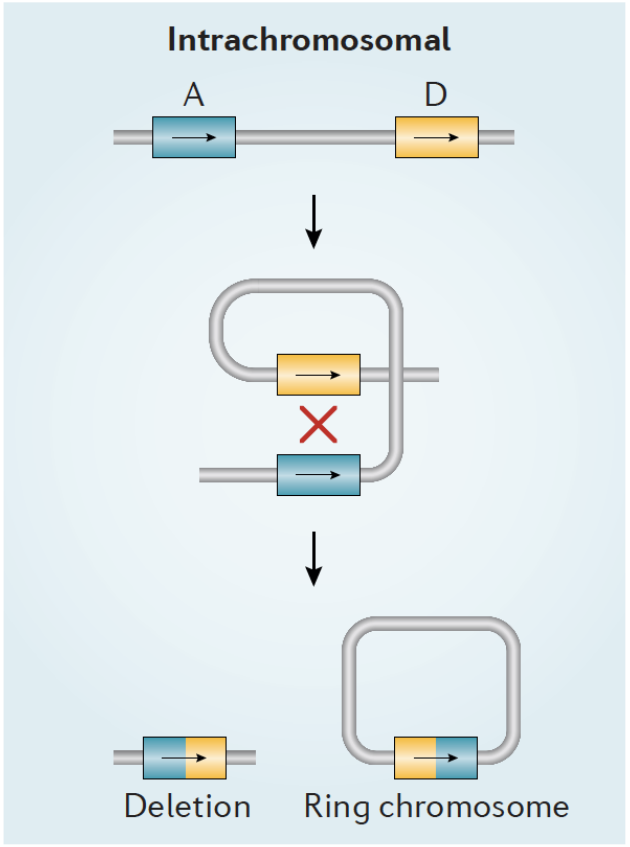
Intercambio meiótico desigual



Deleciones

Mecanismo





Recombinación homologa no alélica entre LCR22A y LCR22D

Mismo mecanismo en deleciones mas pequeñas

LCR22A-LCR22B LCR22A-LCR22C

Deleciones distales generan menos manifestaciones fenotipicas

LCR22B-LCR22D LCR22C-LCR22D

Estas ultimas se heredan con mayor frecuencia

McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Región 22q11.2

90 genes

46 codifican para proteínas

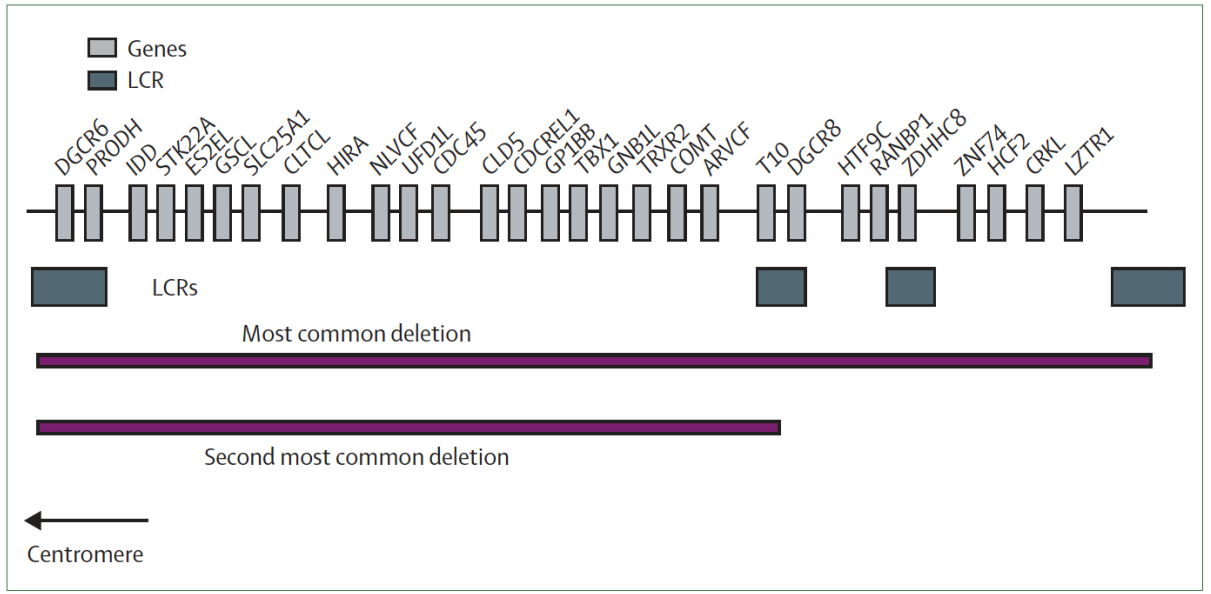
7 codifican para microRNA

10 para RNA no codificante

27 seudogenes

De mayor interés

TBX1



McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Gen TBX1

Haploinsuficiencia provoca disminución de proliferación de células endodérmicas en arcos branquiales

Anomalías cardiacas, timo y paratiroides

FGF8

FGF10

Crecimiento celular y posible rol en migración cresta neural

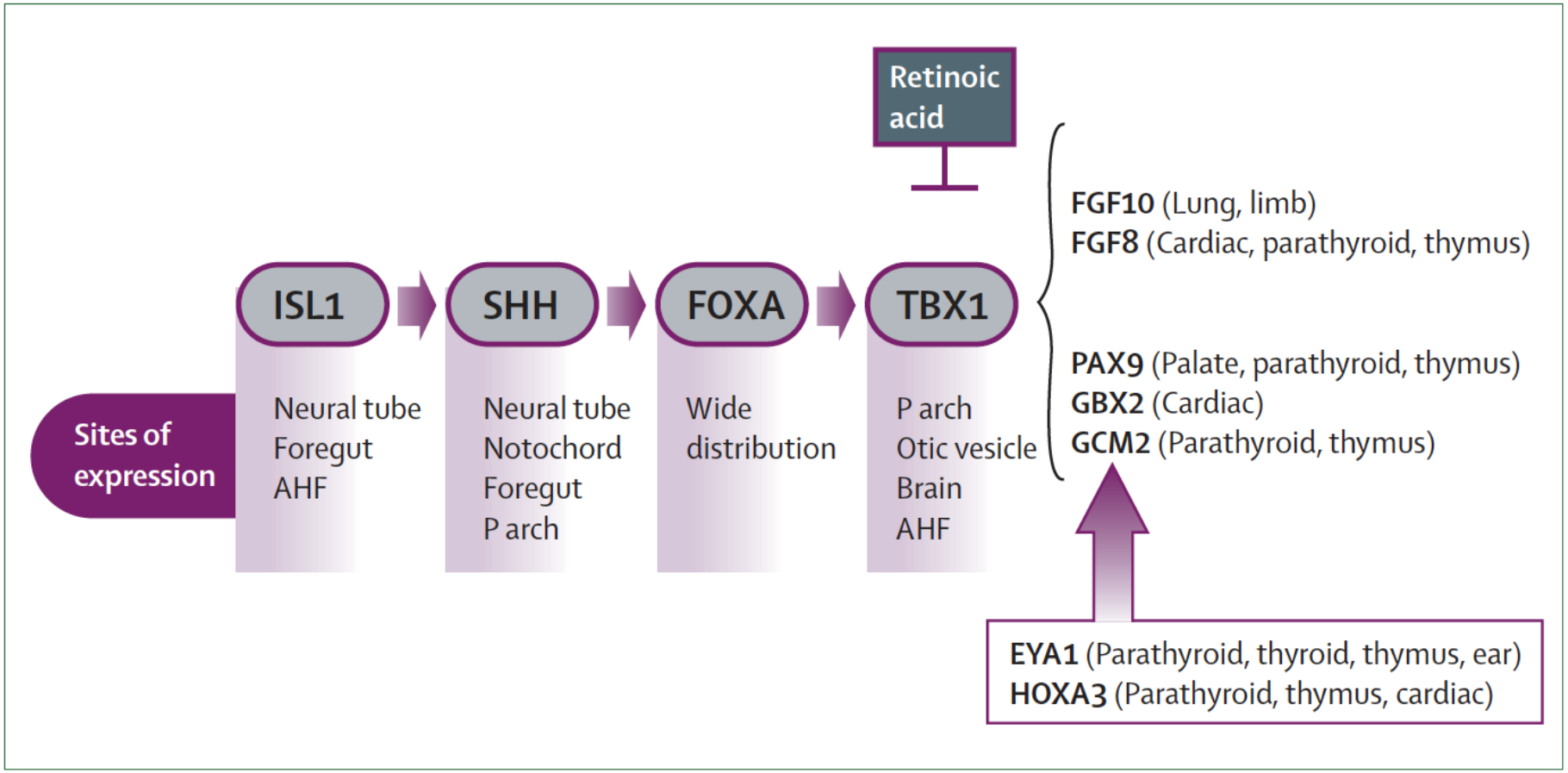
MYF5

MYOD1

Regulan desarrollo de músculos branquiomericos

Kobrynski, L. J., & Sullivan, K. E. (2007). Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. In *www.thelancet.com*

Gen TBX1

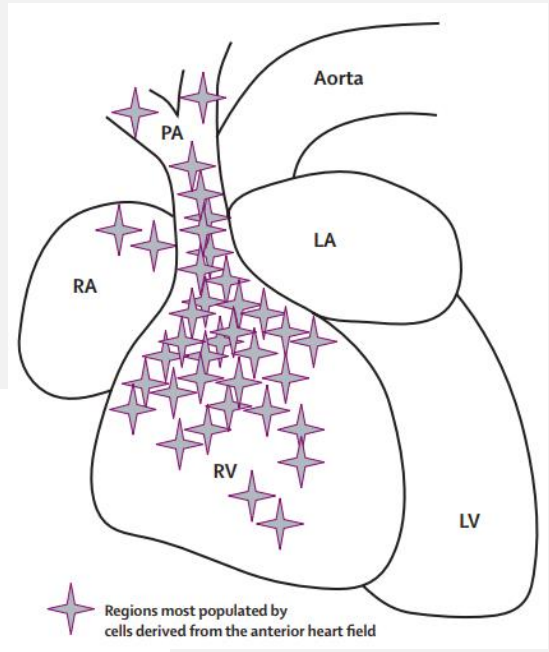


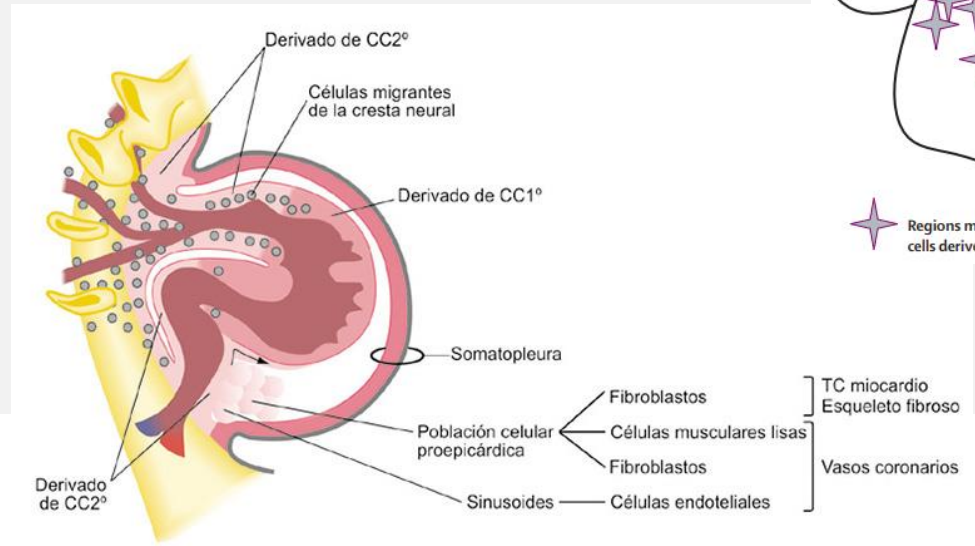
Factores de transcripción que regulan el desarrollo del timo y paratiroides

Kobrynski, L. J., & Sullivan, K. E. (2007). Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. In *www.thelancet.com*

TBX1

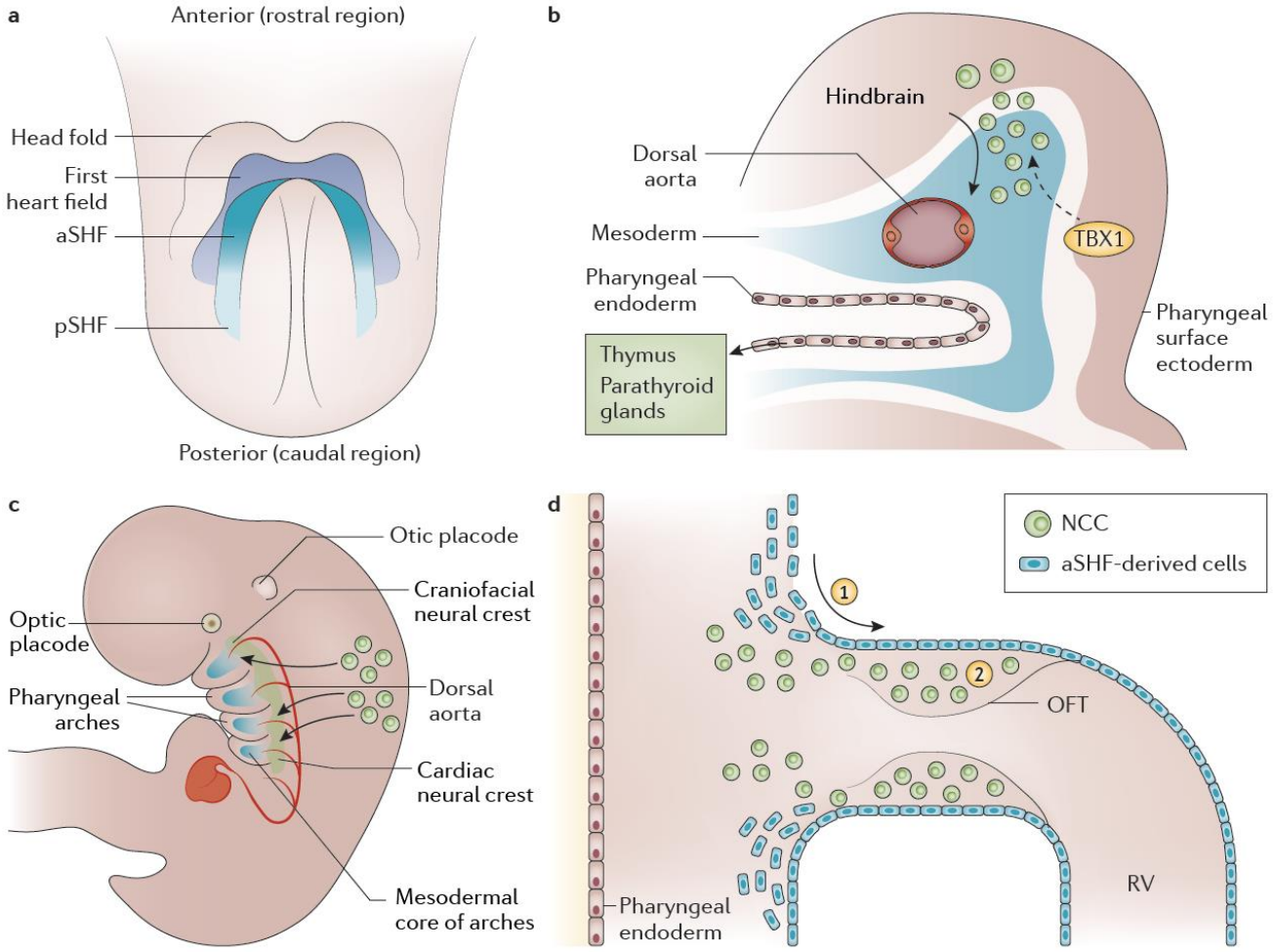
- Se expresa en células del campo cardiaco 2°
  - Da origen a tractos de salida y VD
- Se expresa en parénquima cerebral

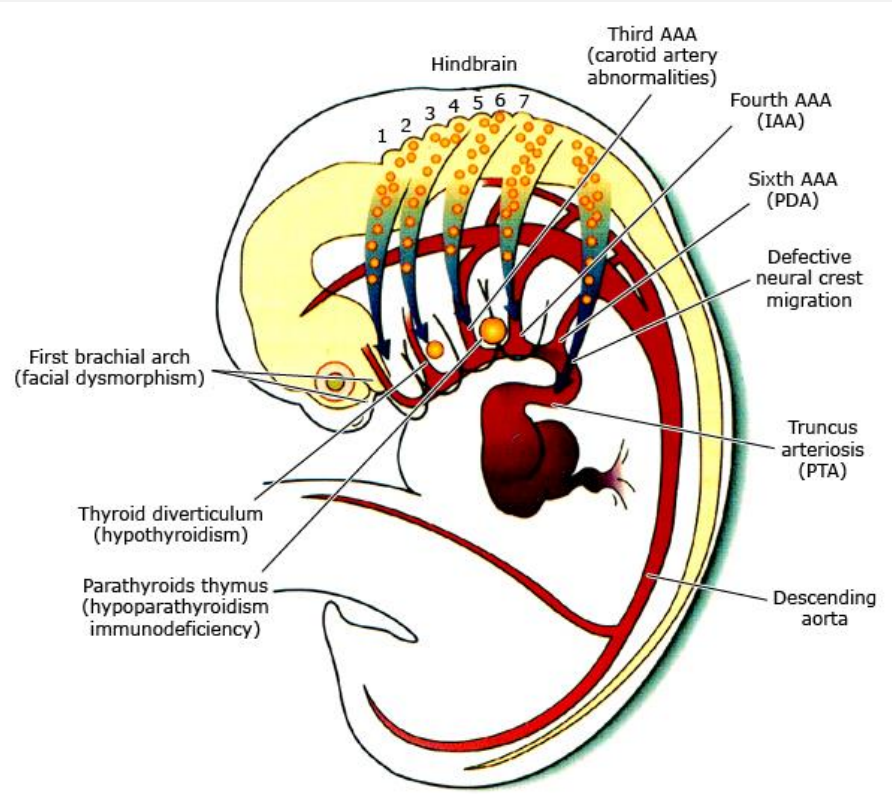




Sullivan K. E. (2019). Chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. *Immunolog. Rev.* 287, 186–201. 10.1111/imr.12701

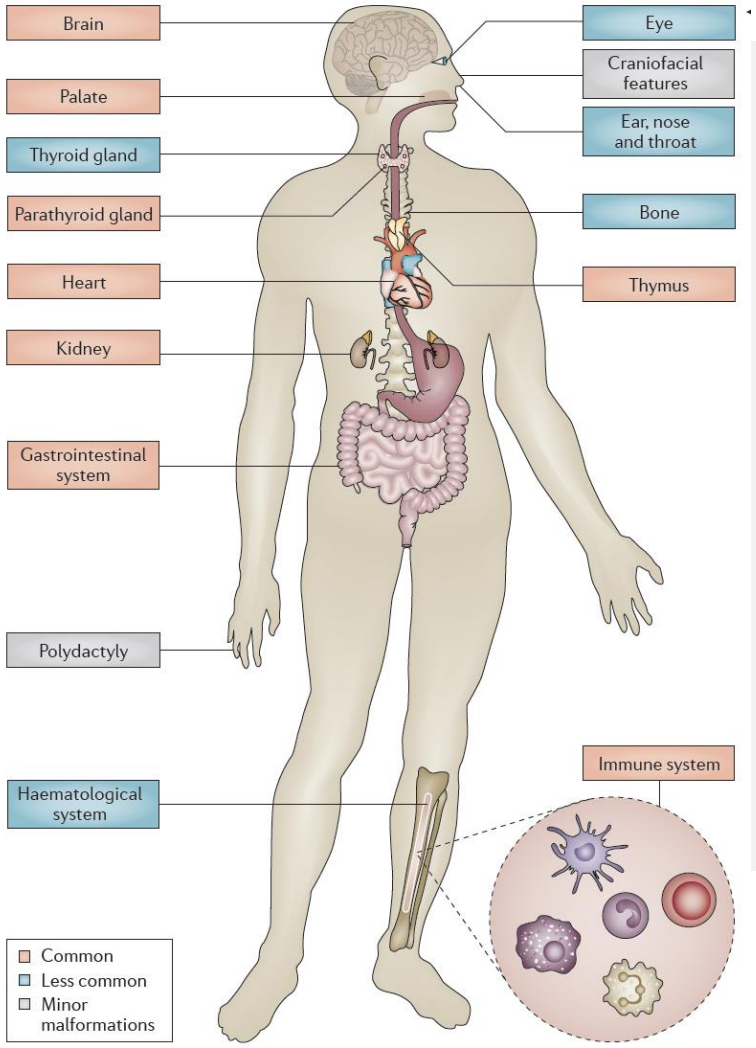
Aspectos del desarrollo





McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Manifestaciones clínicas



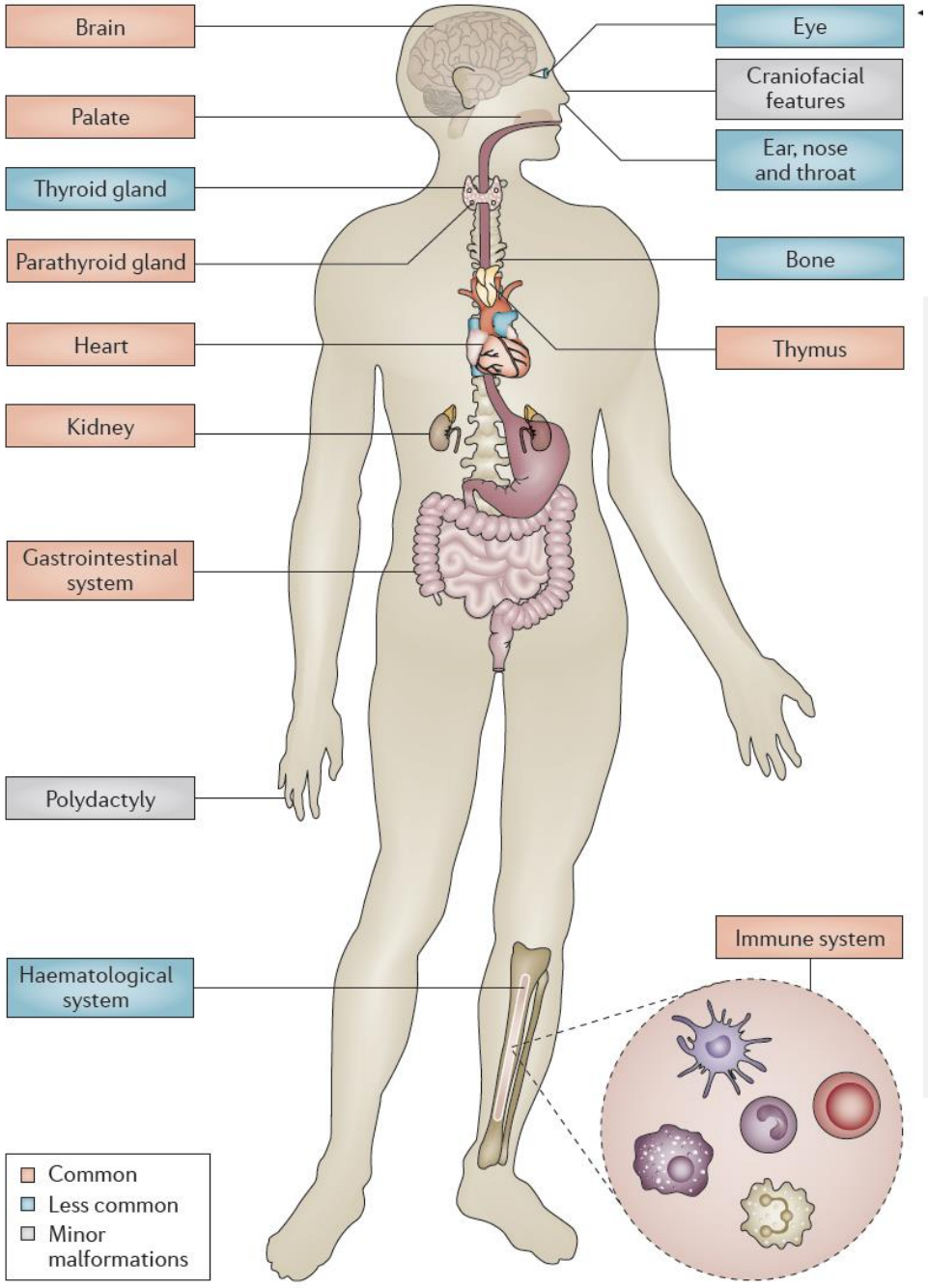
	Level of attention Low		Level of attention High
Birth	Calcium	Feeding	Cardiac
1 year	Cardiac	Feeding	Development
2 years	Feeding	Infection	Development
3 years	Infection	Behaviour	Development
Early school age years	Infection	Behaviour	Cognitive
Teenagers	Infection	Behaviour	Cognitive
Adults	Infection	Psychiatric	Employment

Figure 5: **Change in health concerns with age**

McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

TABLE 1 Clinical findings in patients with chromosome 22q11.2 deletion syndrome

Cardiac anomalies	49%-83%
Tetralogy of Fallot	17%-22%
Interrupted aortic arch	14%-15%
Ventriculoseptal defect	13%-14%
Truncus arteriosus	7%-9%
Endocrine	60%
Hypocalcemia	50%
Growth hormone deficiency	4%
Palatal anomalies	69%-100%
Cleft palate	9%-11%
Submucous cleft palate	5%-16%
Velopharyngeal insufficiency	27%-92%
Bifid uvula	5%
Renal anomalies	36%-37%
Absent/dysplastic	17%
Obstruction	10%
Reflux	4%
Ophthalmologic abnormalities	7%-70%
Tortuous retinal vessels	58%
Posterior embryotoxon (anterior segment dysgenesis)	69%
Neurologic	8%
Cerebral atrophy	1%
Cerebellar hypoplasia	0.4%
Dental: Delayed eruption, Enamel hypoplasia	2.5%
Skeletal abnormalities	17%-19%
Cervical spine anomalies	40%-50%
Vertebral anomalies	19%
Lower extremity anomalies	15%
Speech delay	79%-84%
Developmental delay in infancy	75%
Developmental delay in childhood	45%
Behavior/psychiatric problems	9%-50%
Attention deficit hyperactivity disorder	25%
Schizophrenia	6%-30%



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Anomalías cardiovasculares

Generalmente evidentes en periodo perinatal y es la manifestación que permite la sospecha

Anomalías conotruncales — 60 %

- Tetralogía de Fallot
- Tronco arterioso
- Arco aórtico interrumpido tipo B

+

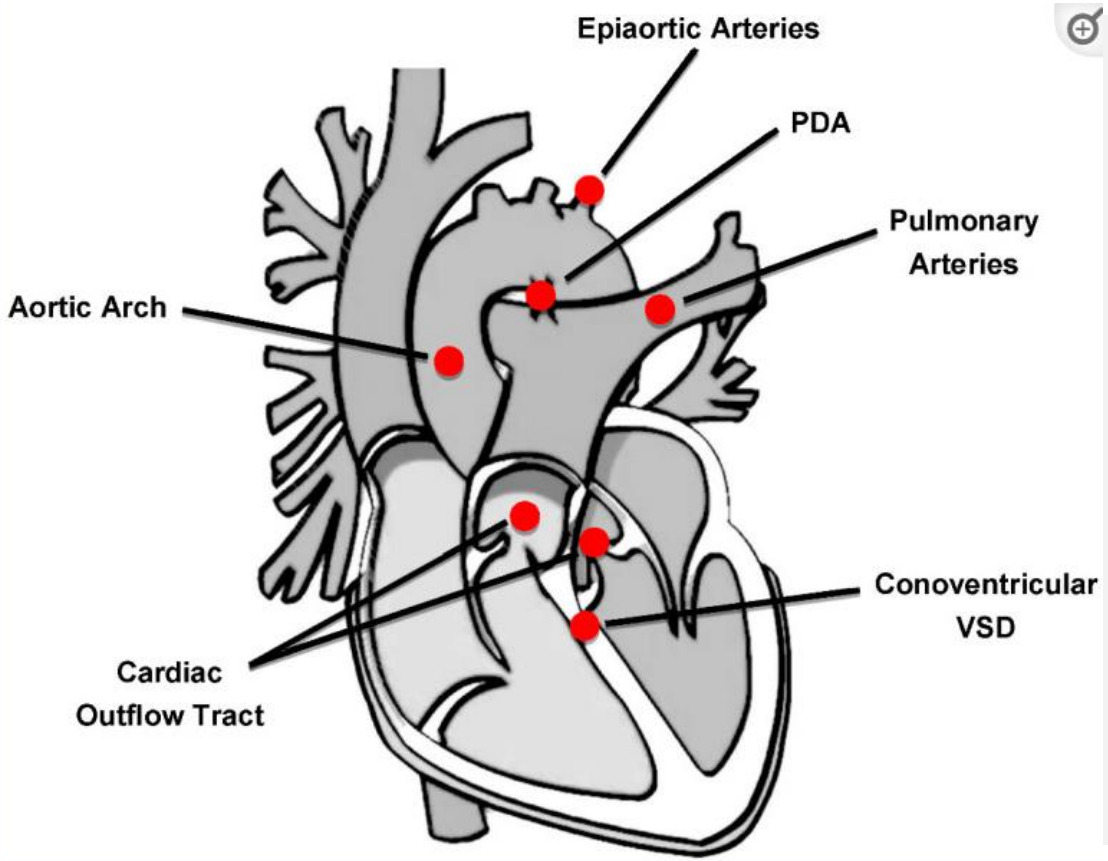
Anomalías arco aórtico y/o arteria pulmonar — 40 %

- Doble arco aórtico
- ARSA

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)

VSD = ventricular septal defect; HLHS = hypoplastic left heart syndrome.

Principal causa de muerte
87%



Cardiac Finding	% of Affected Individuals
Ventricular septal defect	23%
Tetralogy of Fallot (TOF) [1]	18%
Aortic arch anomalies [2]	14%
Interrupted aortic arch (IAA)	11%
Atrial septal defect	10%
Pulmonary atresia	6%
Truncus arteriosus (TA)	4%
Patent ductus arteriosus	6%
Bicuspid aortic valve	3%
Pulmonary stenosis	2%
Other	1%

Inmunodeficiencia

Hipoplasia del timo

↓ Producción de linfocitos T

75% de pacientes pediátricos

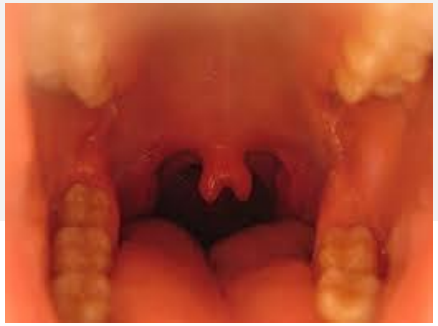
Manifestación heterogénea

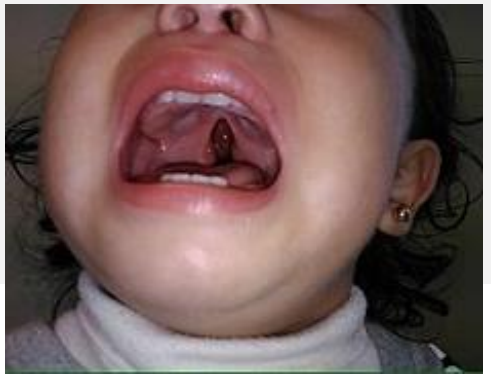
- Infecciones crónicas
- Baja respuesta a vacunas
- Deficiencia de IgA
- Alergia-asma
- Enfermedades autoinmunes

McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Anomalías del paladar

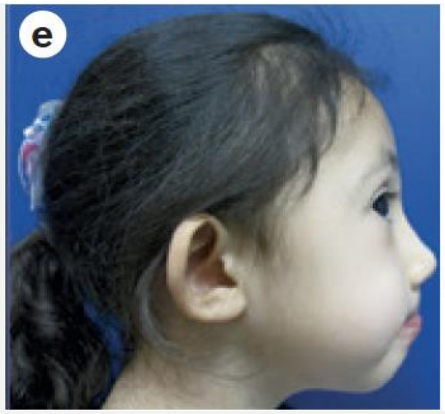
- 11% Fisura Labio-palatina
- 1 a 2% fisura de paladar o labio
- 65% Manifestaciones leves que podrían requerir intervención

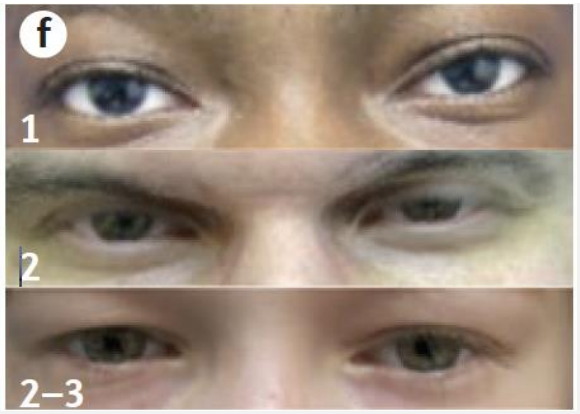


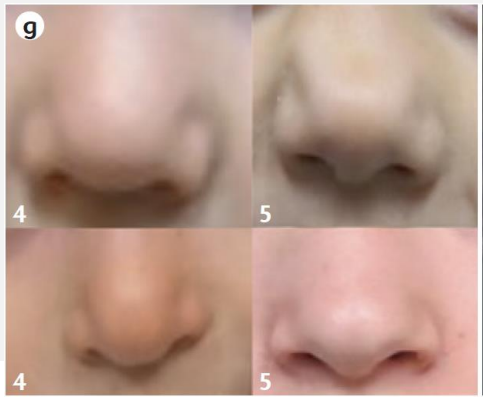


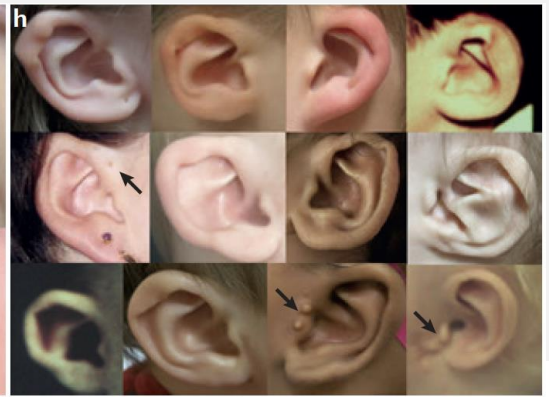
McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Características craneofaciales









McDonald-McGinn, D. M et al (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, *1*(1), 15071. https://doi.org/10.1038/nrdp.2015.71

Alteraciones endocrinas

- 50-65% Hipoparatiroidismo
  - Hipocalcemia
  - Tetania, convulsiones, estridor, Fatiga
- 20% Hipotiroidismo
- 5% Déficit de hormona del crecimiento

Otras anomalías

- 30% Trastornos de deglución
  - Gastrostomía
  - RGE, Dismotilidad esofágica, vómitos, constipación.
  - Ano imperforado, malrotación intestinal, Fístula traqueo-esofágica, Hirschsprung
- 1/3 Anomalías Genitourinarias
  - Agenesia renal uni o, displasia renal, doble sistema, hidronefrosis, cbilateralriptorquidia, hipospadia, ausencia de utero

Retraso en el desarrollo

70% de los niños no hablan o dicen muy pocas palabras a los 2 años de vida

La inteligencia en niños y adolescentes tiene distribución normal, pero el CI promedio es de 70

Se ha observado una caída de 7 puntos en el CI entre los 8 y 24 años de edad

Trastornos psiquiátricos

- Aumento de prevalencia de trastorno de ansiedad, Déficit Atencional, TEA
- 25% Esquizofrenia
- 1 de cada 100 a 200 pacientes con EQZ tienen deleción 22q11.2
- **Factor de riesgo genético más importante para EQZ**

Manejo

Manejo

System/Concern	Evaluation	Comment
Cardiology	Eval by cardiologist incl chest x-ray, EKG, & echocardiogram	Chest MRI may be required if a vascular ring is suspected.
ENT	• Clinical evaluation of the palate • Consider assessment of carotid arteries prior to surgical procedures involving the pharynx. • Consider effects on speech prior to adenoidectomy.	• To screen for palatal anomalies that may affect feeding & speech development • Consider pre- & postoperative sleep studies when performing pharyngeal procedures.
Gastroenterology	Assessment for feeding problems (e.g., gastroesophageal reflux, difficulty w/sucking/swallowing, advancing feeds, addition of textured foods, vomiting) & constipation	Assessment for anatomic differences as needed
Immunology	CBC w/differential	• A ↓ absolute lymphocyte count necessitates eval of T- & B-cell subsets & referral to immunologist. • Immunologic eval; may incl flow cytometry, immunoglobulins, & T-cell function

Manejo

Hematology	Eval by hematologist in those w/history of ↑ bruising/bleeding	Consider assessment of platelet volume & function prior to surgical procedures.
Endocrine	• Serum ionized calcium • Intact parathyroid hormone	• To assess for hypoparathyroidism • Endocrinology eval if abnormal
	TSH & free T4	To evaluate for hypo- & hyperthyroidism
	Growth assessment	Referral to endocrinologist for those w/height <2nd centile for growth hormone deficiency eval
Ophthalmology	Ophthalmology eval	At the time of diagnosis
Audiology	Audiology eval	At the time of diagnosis
Neurology	Neurology eval	If seizures are suspected
Development	Speech & language assessment	• By age 1 yr • Referral to early intervention
Psychiatry	Eval by psychologist or psychiatrist	• In those w/anxiety, mood disorder, behavioral differences, or frank psychosis • In teens & adults: incl assessment for at-risk behaviors.

Manejo

Musculoskeletal	Chest x-ray	To evaluate for thoracic vertebral anomalies
	Cervical spine x-rays (6 views: flexion, extension, AP, lateral, open mouth, skull base)	In all persons age >4 yrs (age at which cervical spine becomes ossified) & prior to hyperextension of the neck during surgical procedures &/or athletic pursuits (e.g., tumbling)
Nephrology	Renal ultrasound exam	
Other	Consultation w/clinical geneticist &/or genetic counselor	

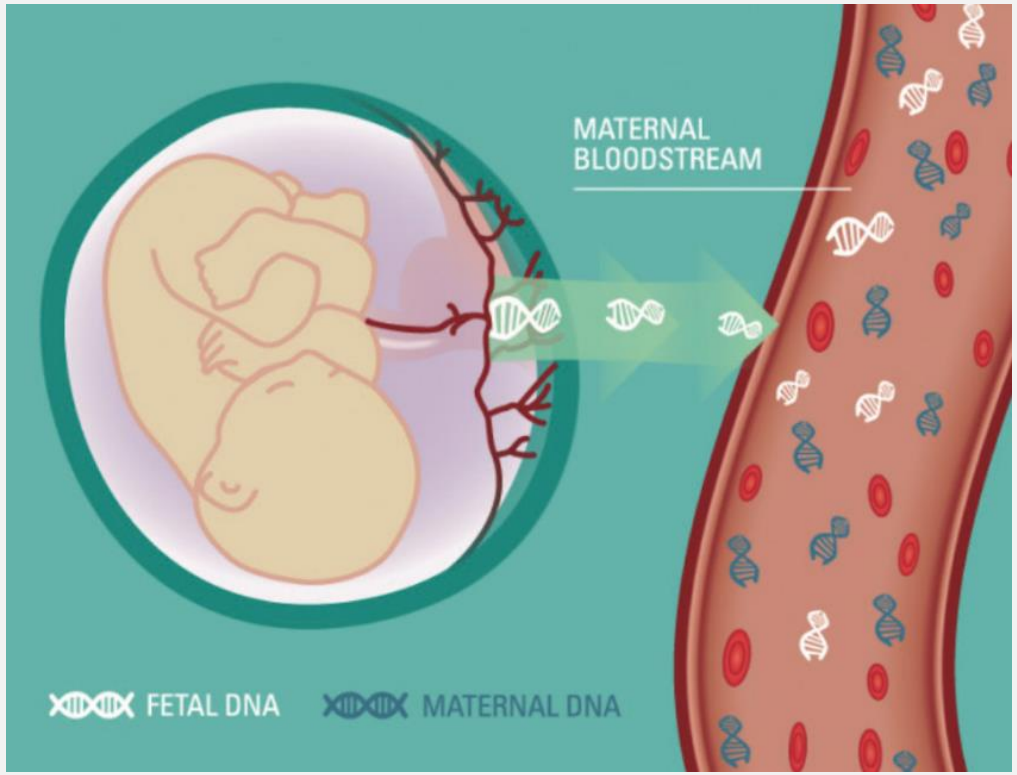
Vigilancia

System/Concern	Evaluation	Frequency
ENT	Eval for nasal speech quality	After language emergence to screen for VPI
Immunology	Antibody studies to assess for seroconversion	Between ages 9 & 12 mos; consideration of repeat immunologic eval prior to any live virus vaccine
	CBC w/differential	Annually
Endocrine	Serum ionized calcium	• Every 3-6 mos in infancy, every 5 yrs through childhood, then every 1-2 yrs • Preoperatively & postoperatively • Regularly during pregnancy
	TSH & free T4	Annually
Ophthalmology	Ophthalmologic eval	Between ages 1 & 3 yrs or as needed based on symptoms
Audiology	Audiology eval	In infants, preschool age, & school age children
Development	Developmental assessments	Annually
Musculoskeletal	Clinical surveillance for scoliosis	
Dental	Dental exam	Every 6 mos

Diagnóstico

Cribado

- Colegio Americano de Genética y genómica
- recomienda ofrecer TPNI a todos los pacientes para detección de deleción 22q11.2



Dungan, J. S., Klugman, S., Darilek, S., Malinowski, J., Akkari, Y. M. N., Monaghan, K. G., Erwin, A., Best, R. G., & ACMG Board of Directors. (2023). Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genetics in medicine : official journal of the American College of Medical Genetics*, *25*(2), 100336

Cribado

TABLE 3
cfDNA test performance for detection of ≥ 500 kb 22q11.2 deletions in the LCR22 A–D region with the algorithm applied at enrollment and with the updated algorithm

Test parameter	Original algorithm used at enrollment (n=18,014)	Updated algorithm implemented after study completion (n=18,043)
Sensitivity	75.0% (9/12; 95% CI, 42.8–94.5)	83.3% (10/12; 95% CI, 51.6–97.9)
Specificity	99.84% (17,973/18,002; 95% CI, 99.77–99.89)	99.95% (18,022/18,031; 95% CI, 99.91–99.98)
PPV	23.7% (9/38; 95% CI, 11.4–40.2)	52.6% (10/19; 95% CI, 28.9–75.6)
NPV	99.98% (17,973/17,976; 95% CI, 99.95–100)	99.99% (18,022/18,024; 95% CI, 99.96–100)
Positive likelihood ratio[a]	468.75	1666.00
Negative likelihood ratio[a]	0.25	0.17

LCR, low-copy repeats; *NPV*, negative predictive value; *PPV*, positive predictive value.

[a] Positive likelihood ratio is calculated as sensitivity/100–specificity and the negative likelihood ratio is calculated as 100–sensitivity/specificity.

Dar et al. Performance of cell-free DNA prenatal screening for 22q11.2 deletion syndrome. Am J Obstet Gynecol 2022.

Dar P, Jacobsson B, Clifton R, et al. Cell-free DNA screening for prenatal detection of 22q11.2 deletion syndrome. *Am J Obstet Gynecol*. 2022;227(1):79.e1-79.e11

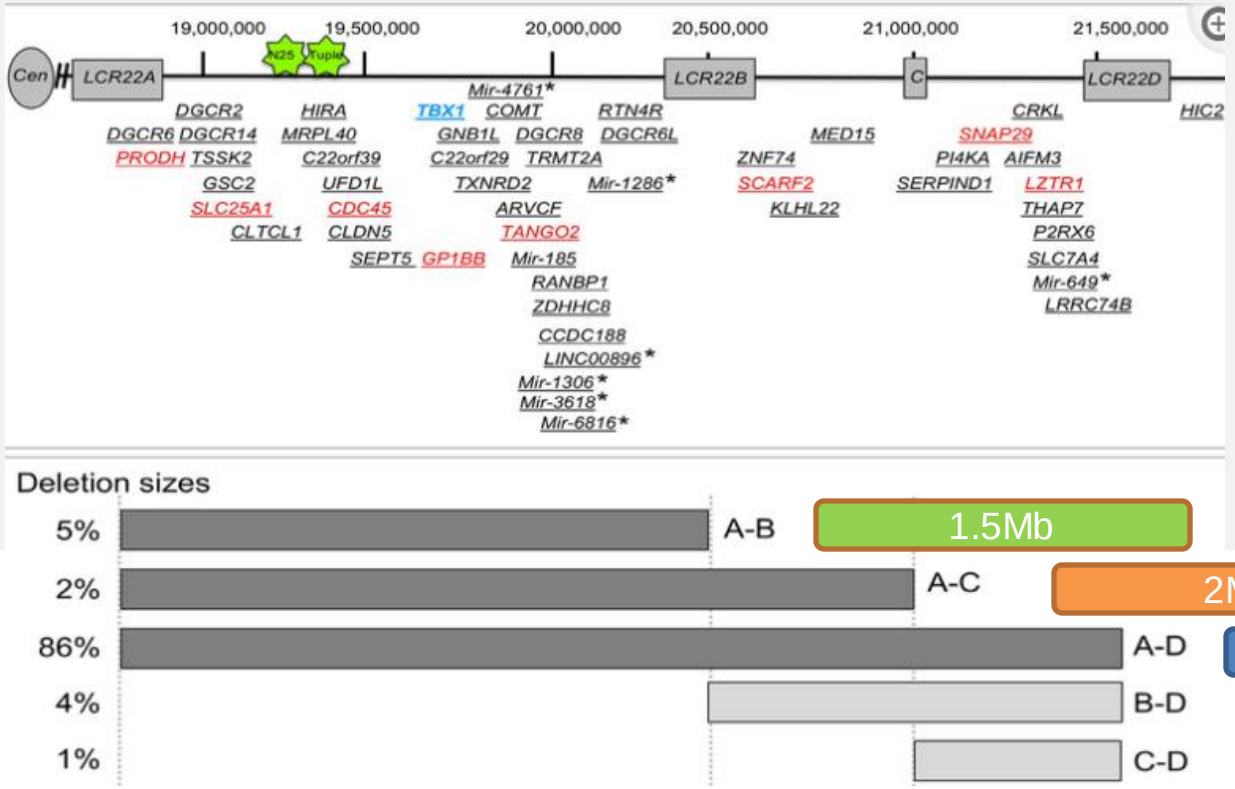
Cribado

	TOTAL			CV			AFC			Product of conception			Newborn			
High-risk cfDNA result	HR cases (*n*)	TP (*n*)	PPV (%)	HR cases (*n*)	TP (*n*)	PPV (%)	HR cases (*n*)	TP (*n*)	PPV (%)	HR cases (*n*)	TP (*n*)	PPV (%)	HR cases (*n*)	TP (*n*)	PPV (%)	*p* Value CV versus AFC
22q11.2DS	30	6	20.0	6	2	33.3	25	4	16.0	0	0	0.0	0	0	0.0	≥0.05
dup22q11.2	2	0	0.0	0	0	0.0	2	0	0.0	0	0	0.0	0	0	0.0	NA
del1p36	8	0	0.0	0	0	0.0	8	0	0.0	0	0	0.0	0	0	0.0	NA
del15q11.2	12	1	8.3	2	0	0.0	10	1	10.0	0	0	0.0	0	0	0.0	≥0.05
del5p	4	1	25.0	1	0	0.0	3	1	33.3	0	0	0.0	0	0	0.0	≥0.05
del17p11.2	1	0	0.0	0	0	0.0	1	0	0.0	0	0	0.0	0	0	0.0	NA

Grati, FR, Bestetti, I, De Siero, D, et al. Positive predictive values and outcomes for uninformative cell-free DNA tests: an Italian multicentric Cytogenetic and cytogenomic Audit of diagnOstic testing (ICARO study). *Prenat Diagn*. 2022; 42(13): 1575- 1586

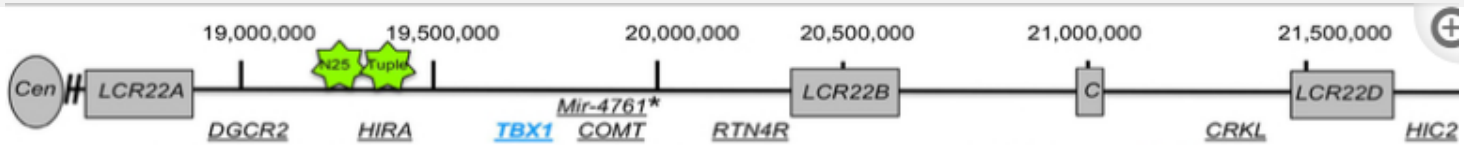
Diagnóstico

- Identificación de una deleción Heterocigota en el cromosoma 22q11.2



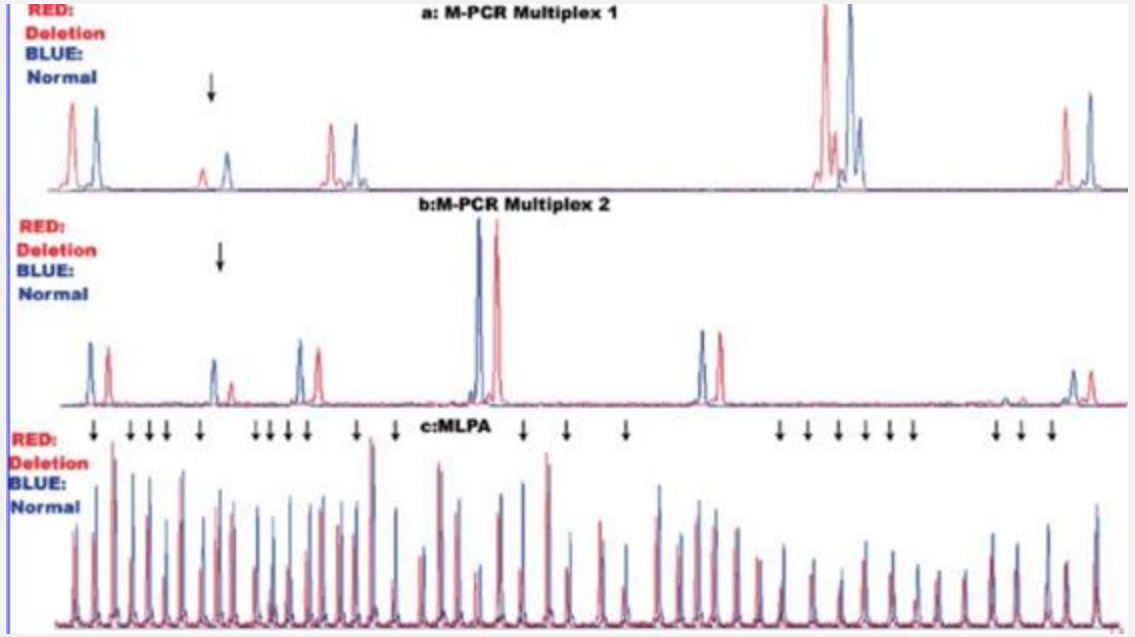
Fish

- 2 sondas disponibles
  - N25 y Tuple
- No detecta deleciones anidadas fuera de la región A-B



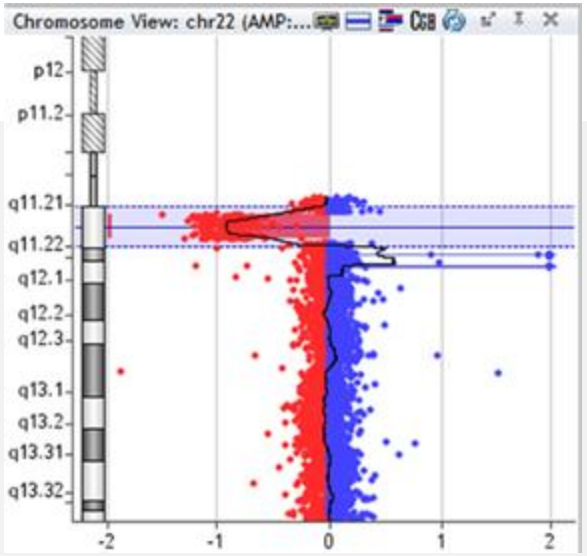
MLPA

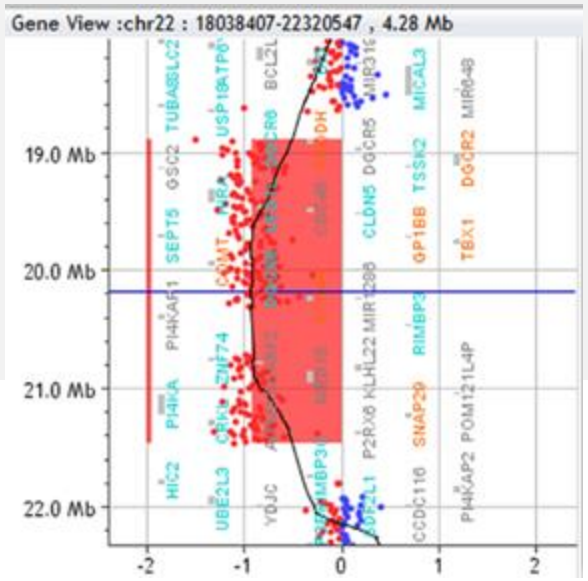
- Se han diseñado sondas que mapean la mayoría del segmento
- Puede identificar deleciones atípicas



Array

- Permite un análisis exhaustivo de múltiples ganancias y pérdidas de ADN en genomas enteros.
- Sólo requiere ADN
- Análisis hasta en menos de 5 días
- Mayor resolución (hasta 0.5Kb o 500 pb)
- Mayor grado de automatización
- Son altamente limitados y apuntan a un gen específico o una región cromosómica a la vez.
- Permite identificar deleciones pequeñas/atípicas que el FISH no detecta.





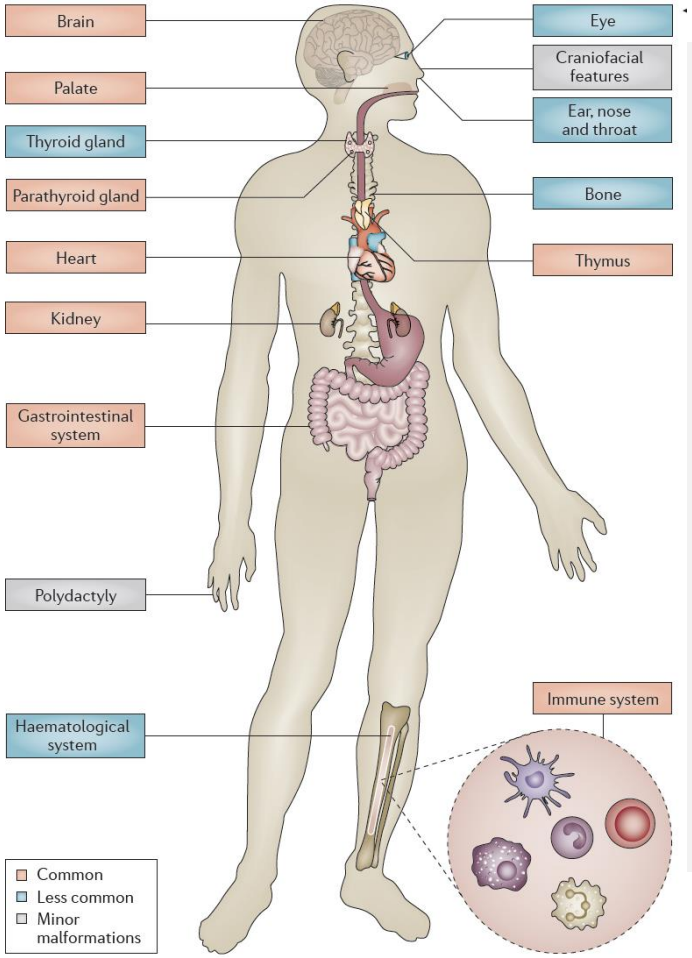
Asesoramiento Genético

Asesoramiento genético

- 90% de *novo*
- Herencia autosómica dominante
- Búsqueda de variante en padres
- Riesgo de descendencia
  - Padre afectado 50%
  - Si padres no afectados, recurrencia 1%

Embarazo de portadora deleción 22q11.2

- Riesgo de recurrencia
  - Vigilancia prenatal
- Riesgo de la madre
  - Vía aérea
  - Trastornos hormonales
  - Trastornos renales
  - Alteraciones hematológicas
  - Sistema inmune



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Deleción 22q11.2
Defectos cardiacos y extracardiacos

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Mayo 2023

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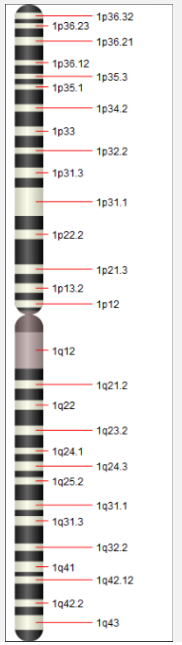
Facultad de Medicina, Universidad de Chile

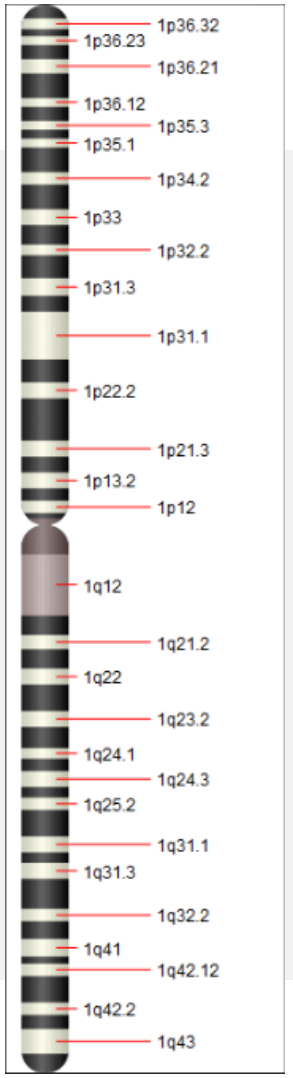
Deleción 1p36



Deleción 1p36

- 1981
- Reporte de caso

- Mujer de 4 años
- Retardo mental
- Fontanelas amplias
- Hipotonía generalizada
- Soplo sistólico
- Cariotipo 45,XX,ter rea(1;21)
- Autor sugere que deleción microscópica de 1p podría causar fenotipo



Gajecka M, Mackay KL, Shaffer LG. 2007. Monosomy 1p36 deletion syndrome. Am J Med Genet Part C Semin Med Genet 145C:346–356

Epidemiología

- 1:5000 RNV
- Deleción terminal más común
- Afecta a hombres y mujeres por igual
- 95% de *novo*
- 60% en el cromosoma derivado de la madre

Jordan, V. K., Zaveri, H. P., & Scott, D. A. (2015). 1p36 deletion syndrome: an update. *The application of clinical genetics*, *8*, 189–200.

Características clínicas

- HETEROGENEO
- 1p36 compuesto por 30Mb

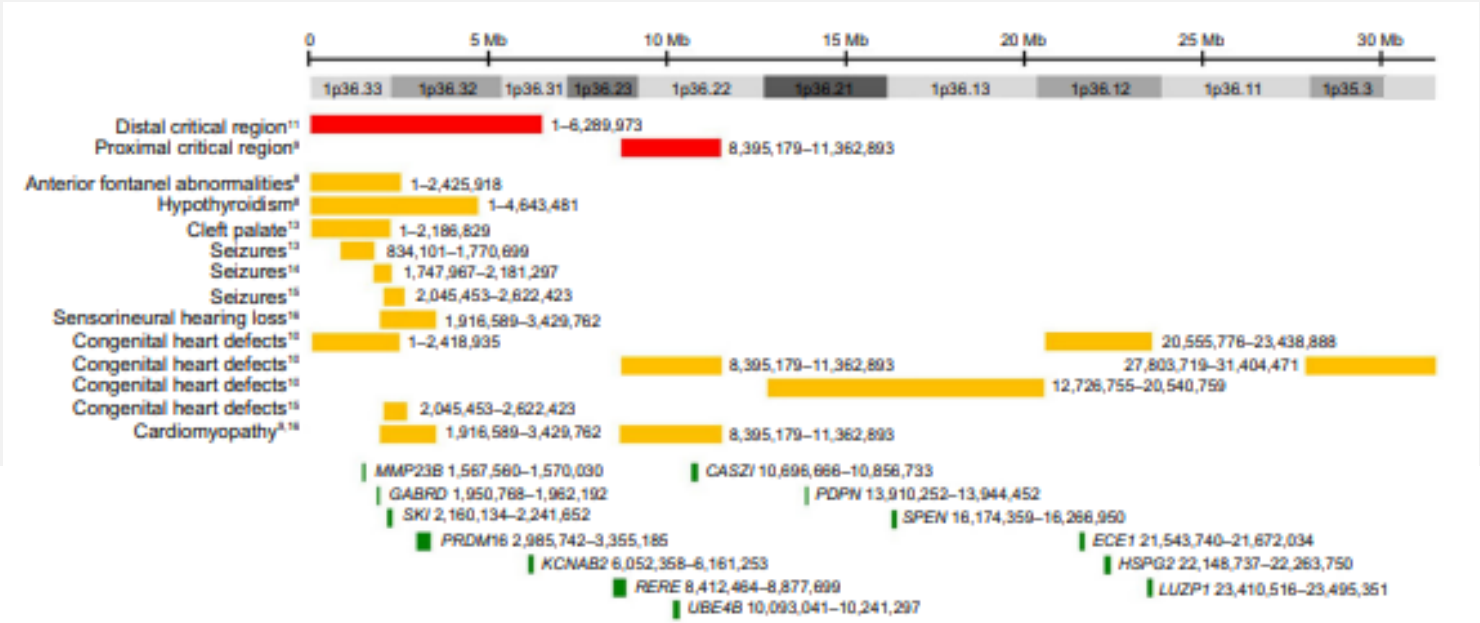


TABLE I. Clinical Features Found in Subjects With 1p36 Terminal or Interstitial Deletions

Feature	Affected (total subjects examined)	Percentage
Dysmorphic features		
Large anterior fontanelle	34 (46)	74
Microcephaly	28 (46)	61
Brachycephaly	25 (46)	54
Low hairline	20 (42)	48
Small ears	21 (44)	48
Low-set ears	23 (47)	49
Ear asymmetry	18 (45)	40
Thickened ear helices	26 (45)	58
Synophrys	6 (28)	21
Deep-set eyes	36 (49)	73
Hypertelorism	15 (40)	38
Small palpebral fissures	10 (37)	27
Upslanting palpebral fissures	12 (44)	27
Downslanting palpebral fissures	11 (43)	26
Midface hypoplasia	21 (41)	51
Flat nasal bridge	40 (54)	74
Pointed chin	29 (46)	63
Clinodactyly	27 (45)	60
Neurological		
Mental retardation	39 (41)	95
Developmental delay	67 (67)	100
Speech delay	56 (57)	98
Seizures	44 (56)	79
Epileptic encephalopathy	10 (32)	31
Hypotonia	59 (64)	92
Feeding difficulties	36 (47)	77
Oropharyngeal dysphasia	17 (35)	49
Self-abusive behavior	21 (38)	55
Opthalmologic and audiologic		
Hypermetropia	13 (32)	41
Myopia	12 (30)	40
Strabismus	28 (42)	67
Visual inattentiveness	12 (27)	44
Hearing problems	40 (52)	77
Conductive hearing loss	16 (35)	46
Sensorineural hearing loss	19 (33)	58
Gastrointestinal		
Constipation	28 (43)	65
Reflux	23 (41)	56
Ulcer	1 (26)	4
Hiatal hernia	2 (26)	8
Discomfort	4 (23)	17

Feature	Affected (total subjects with heart defects)	Percentage of subjects with a particular heart defect
Cardiovascular		
Cardiomyopathy	18 (59)	31
Structural congenital heart defects	44 (59)	75

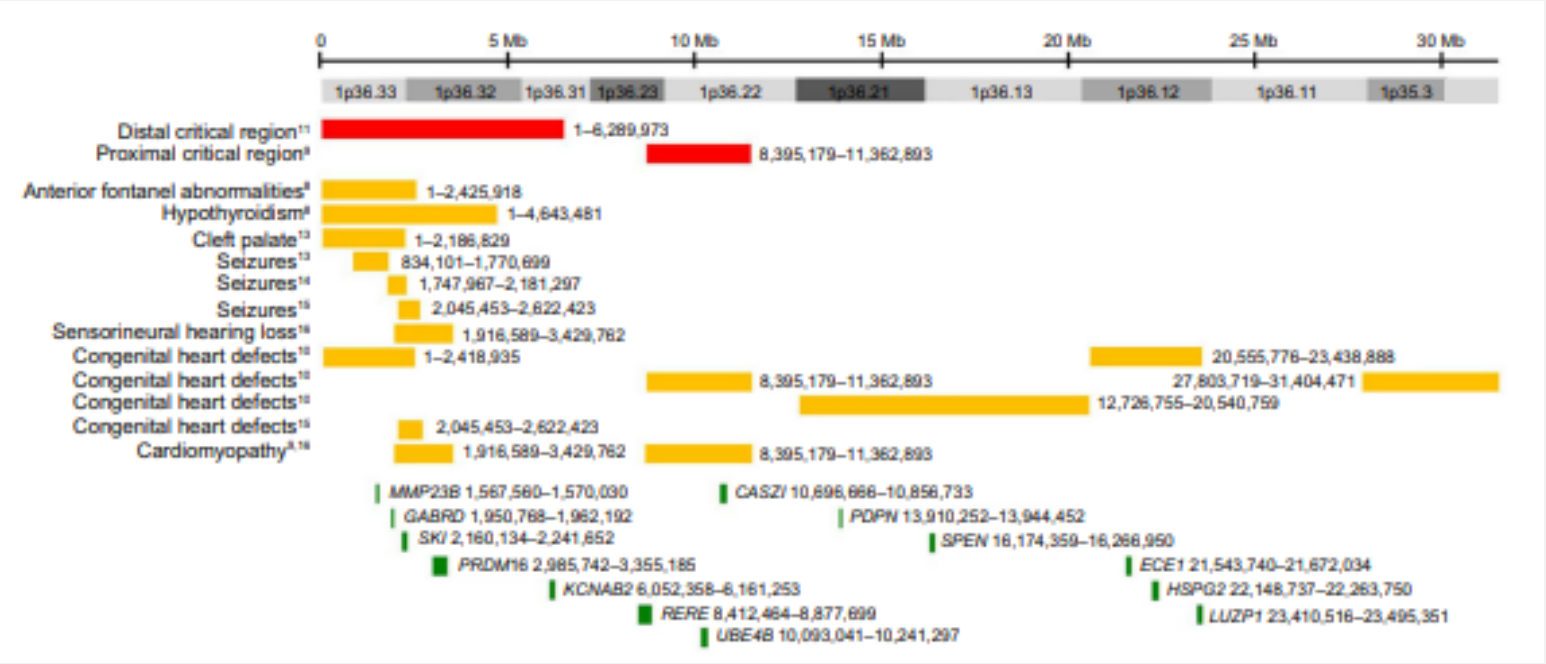
(*Continued*)

Feature	Affected (total subjects with heart defects)	Percentage of subjects with a particular heart defect
Patent foramen ovale	14 (59)	24
Patent ductus arteriosus	16 (59)	27
Ventricular septal defects	17 (59)	29
Atrial septal defect	5 (59)	8
Ebstein anomaly	2 (59)	3
Bicommissural aortic valve	2 (59)	3

Feature	Affected (total subjects who had an MRI)	Percentage of subjects showing a particular feature after MRI
MRI abnormalities		
Polymicrogyria	10 (50)	20
Leukoencephalopathy	14 (50)	28
Generalized atrophy	9 (50)	18
Prominent ventricles	13 (50)	26

- Malformaciones SNC 88%
- CHD 71-75%
- Convulsiones 44-79%
- Anomalías esqueléticas 41%

Deleción 1p36



- 1,5 a 10,5 Mb
- 2 regiones críticas
- Múltiples genes involucrados

DVL1, SKI, RERE, PDPN, SPEN, CLCNKA, ECE1, HSPG2, LUZP1,* and *WASPF2

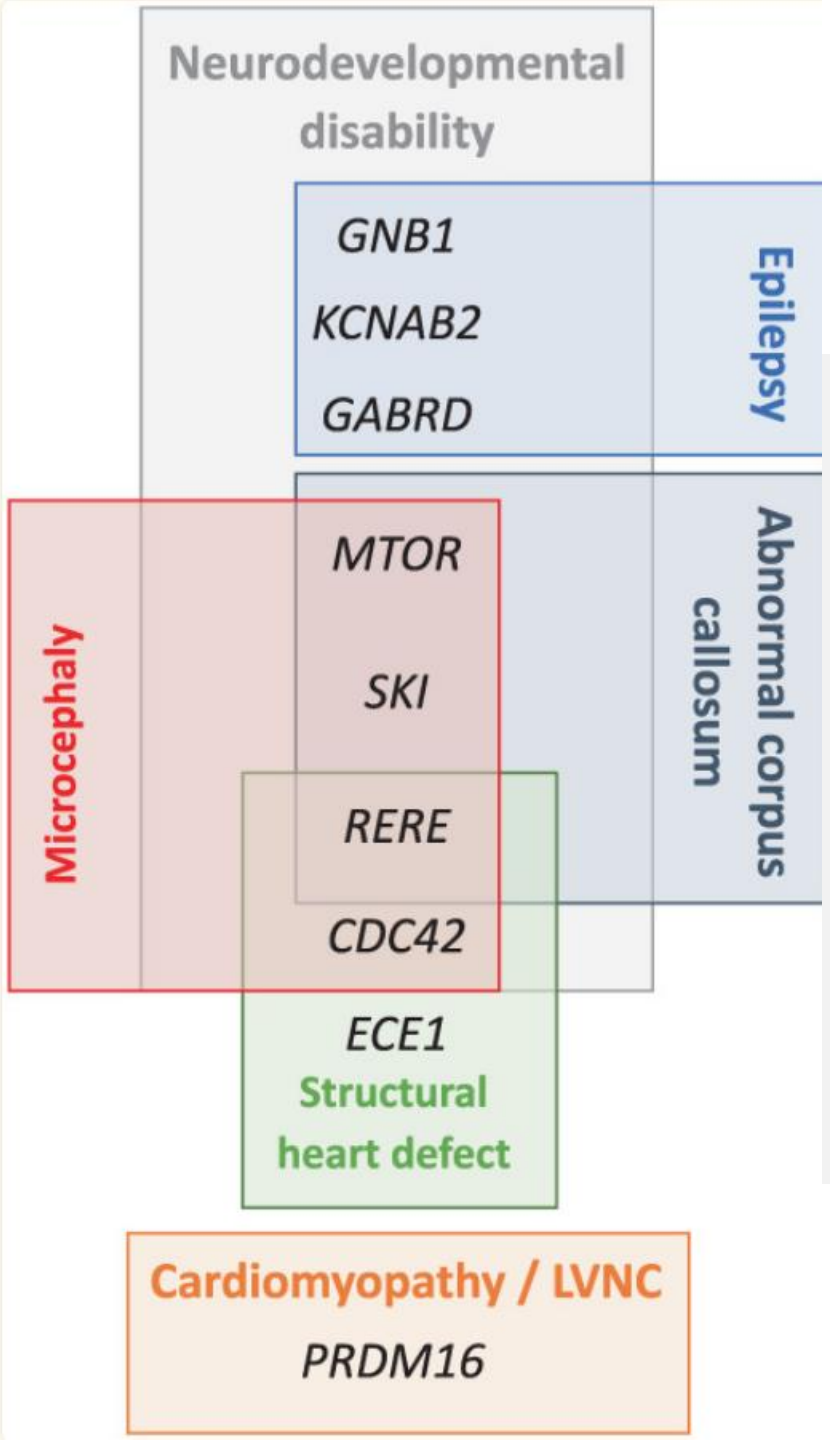
Comúnmente involucradas en CHD

Lodato, V., Orlando, V., Alesi, V., Di Tommaso, S., Bengala, M., Parlapiano, G., Agnolucci, E., Cicenia, M., Calì, F., Digilio, M. C., Drago, F., Novelli, A., & Baban, A. (2021). 1p36 Deletion Syndrome and the Aorta: A Report of Three New Patients and a Literature Review. *Journal of cardiovascular development and disease*, *8*(11), 159

Table 1 Summary of genes that may contribute to 1p36 deletion phenotypes

Gene (OMIM#)	Phenotypes possibly associated with haploinsufficiency	Similar phenotypes seen in animal models	References
MMP23B (OMIM# 603321)	Large, late-closing anterior fontanel	Not reported	Gajecka et al[18]
GABRD (OMIM# 137163)	Neurodevelopmental abnormalities, neuropsychiatric problems, seizures	Mice: depression-like and anxiety-like behaviors during the postpartum period	Mihalek et al,[21] Maguire and Mody,[22] Dibbens et al,[23] Lenzen et al[24]
SKI (OMIM# 64780)	Developmental delay, intellectual disability, seizures, orofacial clefting, congenital heart defects	Mice: neural tube defects, abnormal forebrain morphology, midline facial clefting, reduced skeletal muscle mass Zebrafish: craniofacial cartilage deficits, severe cardiac anomalies	Colmenares et al,[27] Doyle et al,[28] Carmignac et al[29]
PRDM16 (OMIM# 605557)	Left vertricular noncompaction, dilated cardiomyopathy	Mice: ventricular hypoplasia, abnormal ventricular morphology, cleft palate Zebrafish: bradycardia, reduced cardiac output, decreased cardiomyocyte number, partial uncoupling of cardiomyocytes, reduced impulse propagation velocity	Arndt et al,[33] Bjork et al[35]
KCNAB2 (OMIM# 601142)	Developmental delay, intellectual disability, seizures	Mice: impaired associative learning and memory, sporadic seizures, cold swim-induced tremors	Perkowski and Murphy,[37] McCormack et al[38]
RERE (OMIM# 605226)	Short stature, developmental delay, intellectual disability, brain anomalies, vision problems, hearing loss, renal anomalies, congenital heart defects, cardiomyopathy	Mice: postnatal growth retardation, reduced brain size and weight, decreased numbers of NeuN-positive hippocampal neurons, cerebellar foliation defects, delayed Purkinje cell maturation and migration, microphthalmia, hearing loss, renal agenesis, congenital heart defects, cardiac fibrosis Zebrafish: microphthalmia, inconsistent startle response, decreased microphonic potentials	Kim et al,[40,41] Plaster et al,[42] Schilling et al[43]
UBE4B (OMIM# 613565)	Cardiomyopathy and neurodevelopmental phenotypes	Mice: reduced cardiac trabeculation, undeveloped and compact myocardial layer, high levels of cardiac-restricted apoptosis, defective assembly of myosin in cardiomyocytes, axonal dystrophy in the nucleus gracilis, degeneration of Purkinje cells, hindlimb gait abnormalities, impaired rotarod performance	Kaneko-Oshikawa et al[45]
CASZ1 (OMIM# 609895)	Congenital heart defects and cardiomyopathy	Mice: abnormally shaped cardiac ventricular apices, ventricular septal defects, hypoplastic myocardium, abnormalities in ventricular cell alignment and fiber orientation	Liu et al[47]
PDPN (OMIM# 608863)	Congenital heart defects, cardiomyopathy	Mice: congenital heart defects; hypoplasia of the sinoatrial node, primary atrial septum, and dorsal atrial wall; thin, perforated cardinal and pulmonary veins	Mahtab et al[49,50]
SPEN (OMIM# 613484)	Congenital heart defects, cardiomyopathy, short stature, neurodevelopmental phenotypes	Mice: defective formation of the cardiac septum and muscle, postnatal growth retardation, reduced brain weight, hypoplastic cerebral cortex and hippocampus, enlarged lateral ventricles of the brain	Kuroda et al,[52] Yabe et al[53]
ECE1 (OMIM# 600423)	Congenital heart defects	Mice: congenital heart defects	Hofstra et al,[55] Yanagisawa et al[56]
HSPG2 (OMIM# 142461)	Cleft palate, congenital heart defects	Mice: cleft palate, congenital heart defects	Abdel-Aziz and Azab,[60] Costell et al[61,62]
LUZP1 (OMIM# 601422)	Congenital heart defects, cleft palate, brain anomalies	Mice: congenital heart defects, cleft palate, brain anomalies	Hsu et al[63]

Jordan, V. K., Zaveri, H. P., & Scott, D. A. (2015). 1p36 deletion syndrome: an update. *The application of clinical genetics*, *8*, 189–200. https://doi.org/10.2147/TACG.S65698



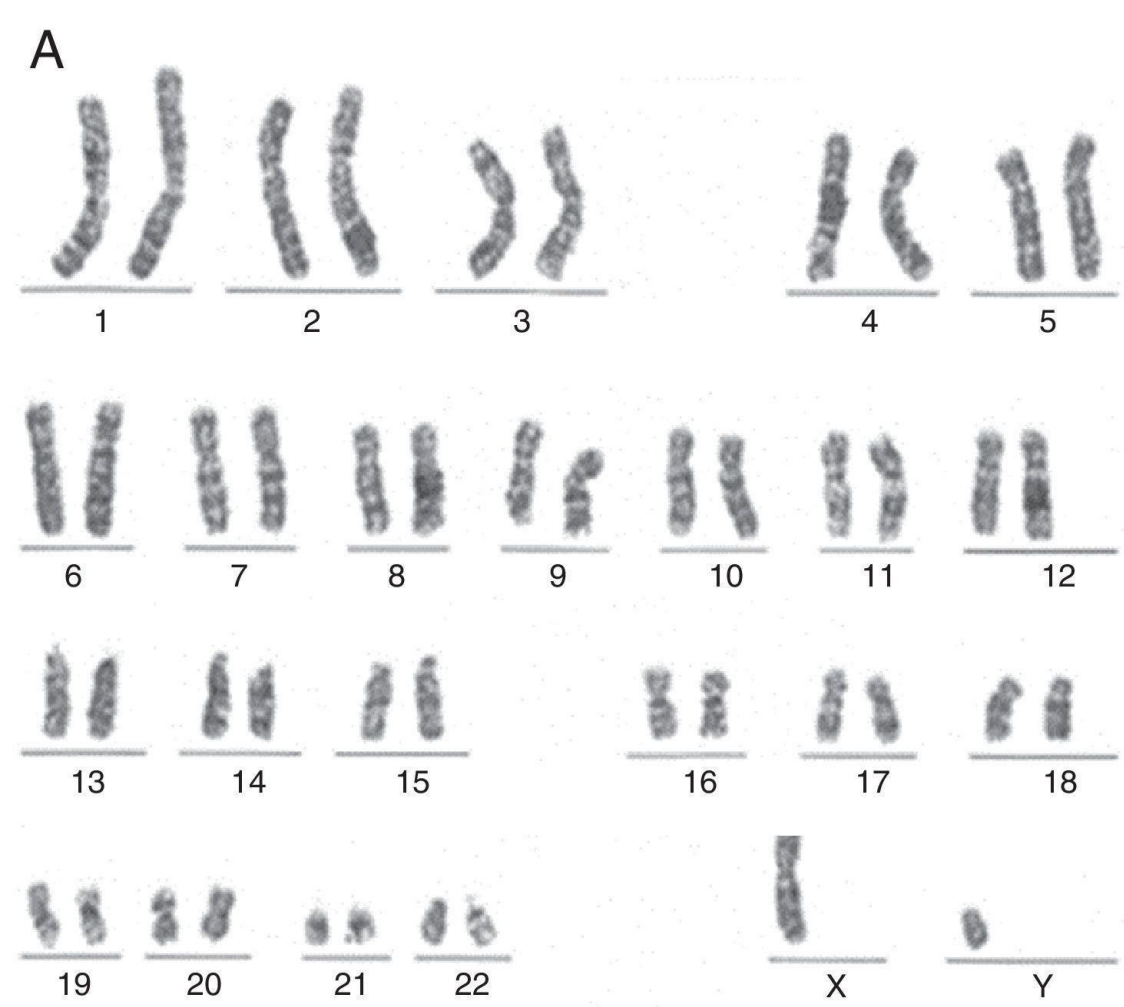
Jacquin, C. et al (2023). 1p36 deletion syndrome: Review and mapping with further characterization of the phenotype, a new cohort of 86 patients. *American journal of medical genetics. Part A*, *191*(2), 445–458

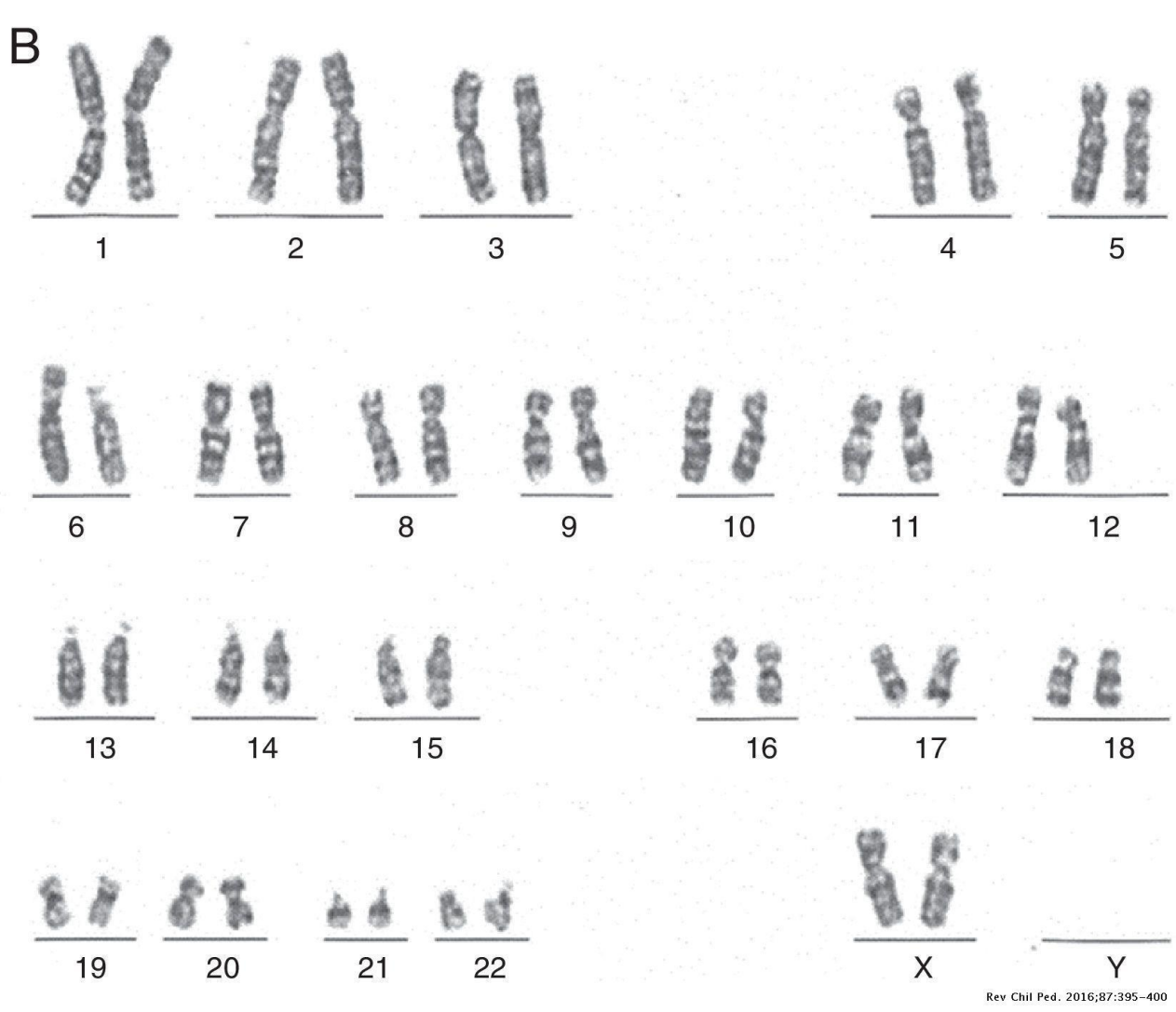
Diagnóstico

Asesoramiento genético

- 95% de *novo*
- En caso de Padre portador de traslocación balanceada
- Herencia autosómica dominante
- Alto riesgo de aborto. 30 a 50% de recurrencia

Fernández Pineda, Monica, Ramírez-Cheyne, Julián, Isaza, Carolina, & Saldarriaga, Wilmar. (2016). Un caso de deleción parcial 1p36.1 y trisomía parcial 6p diagnosticadas por cariotipo. *Revista chilena de pediatría*, *87*(5), 395-400.





- 44,XY,der(1)t(1;6)(p36.1;p21.1)

- 46,XX,t(1;6)(p36.1;p21.1)

Fernández Pineda, Monica, Ramírez-Cheyne, Julián, Isaza, Carolina, & Saldarriaga, Wilmar. (2016). Un caso de deleción parcial 1p36.1 y trisomía parcial 6p diagnosticadas por cariotipo. *Revista chilena de pediatría*, *87*(5), 395-400.

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