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

Diagnóstico genético en malformaciones del Sistema Nervioso Central

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Hoja de ruta


Introducción
Importancia del Dg prenatal
Métodos de diagnóstico genético
Importancia del Fenotipo
Conclusión y recomendaciones

Introducción

- 2-3% de fetos con alteraciones estructurales
- Las anomalías congénitas se asocian en 25% de los casos a alteraciones genéticas

12% de ingresos pediátricos

30% de muertes neonatales y 50% de muertes neonatales e infantiles

Kagan, Karl Oliver et al. “Antenatal screening for chromosomal abnormalities.” Archives of gynecology and obstetrics vol. 305,4 (2022): 825-835.

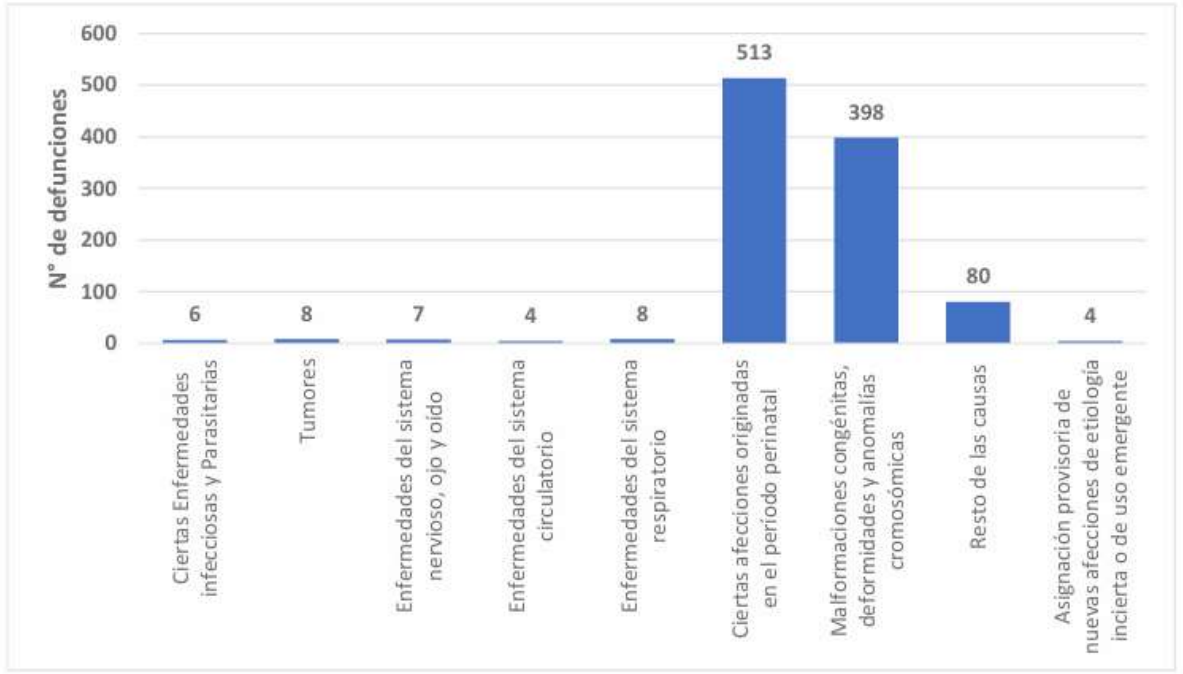
Wapner, Ronald J et al. “Chromosomal microarray versus karyotyping for prenatal diagnosis.” The New England journal of medicine vol. 367,23 (2012)

Wojcik, Monica H et al. “Genetic disorders and mortality in infancy and early childhood: delayed diagnoses and missed opportunities.” Genetics in medicine : official journal of the American College of Medical Genetics vol. 20,11 (2018): 1396-1404

Introducción

38,7% de mortalidad infantil en Chile

Gráfico 20: Principales causas de muerte de las defunciones de menores de un año, 2021



Fuente: INE, en base a estadísticas vitales, 2021.

Anuario de Estadísticas Vitales. Período de información: 2021.
Comité Nacional de Estadísticas Vitales.

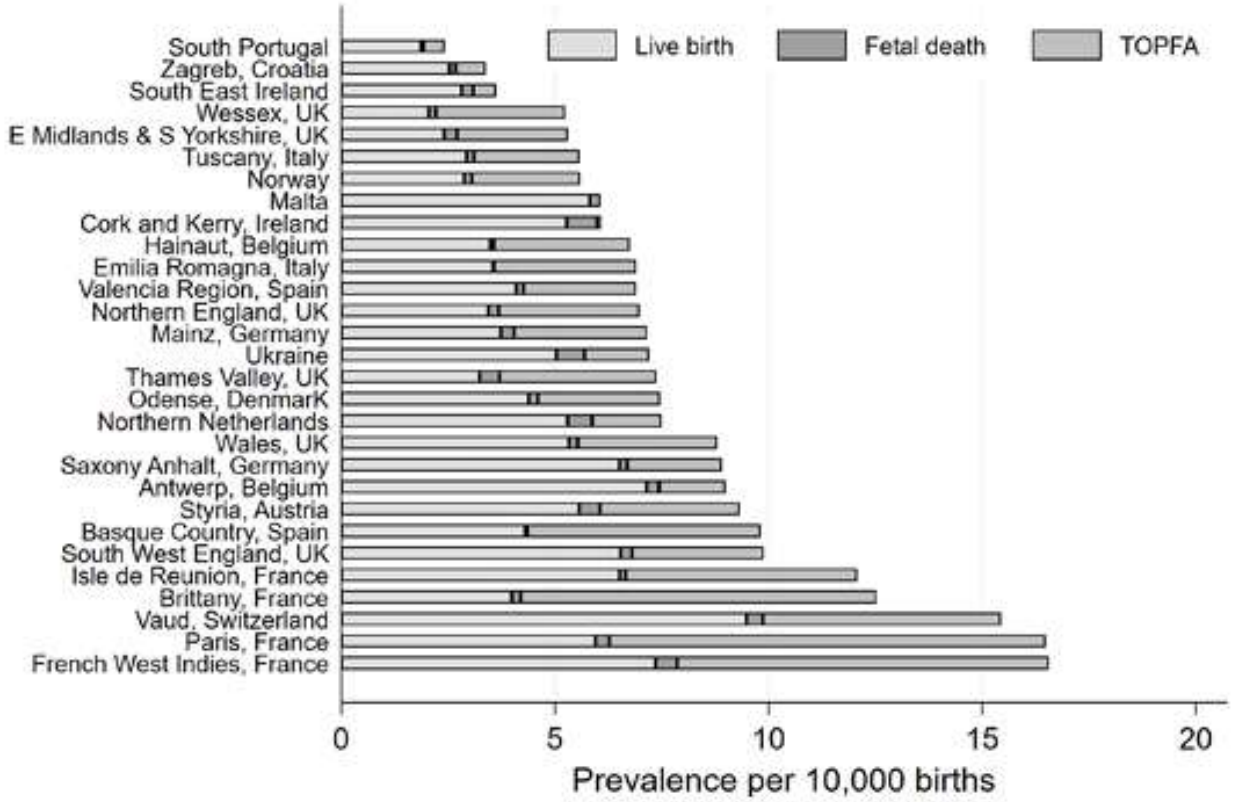
Prevalencia de anomalías del SNC

- En Europa 9,5 (95% IC 8,5-11,2) por 10,000 partos

48% aisladas

25% anomalías no SNC

27% alteraciones genéticas



Morris, J. K., et al. (2019). Epidemiology of congenital cerebral anomalies in Europe: A multicentre, population-based EUROCAT study. *Archives of Disease in Childhood*, *104*(12), 1181–1187.

Prevalencia de anomalías del SNC

Table 3 Classification of congenital cerebral anomaly cases according to associated anomalies and genetic diagnosis; 29 EUROCAT registries, 2005–2014

ICD-10 code	Q04.2	Q04.1	Q04.4	Q04.5	Q04.3	Q04.0	Q04.8	Q04.6	Q04.9	Q04
Associated anomalies and genetic diagnoses, n (%)	Holoprosencephaly	Arhinencephaly	Septo-optic dysplasia	Megalencephaly	Other reduction deformities of brain	Congenital malformations of corpus callosum	Other specified congenital malformations of brain	Congenital cerebral cysts	Congenital malformation of brain, unspecified	All cases
Isolated cerebral anomaly	305 (35)	2 (6)	68 (72)	35 (71)	663 (47)	764 (52)	180 (47)	251 (67)	112 (46)	2380 (48)
Chromosomal	309 (36)	21 (46)	1 (1)	0 (0)	203 (14)	280 (16)	68 (12)	43 (8)	39 (14)	876 (18)
Patau syndrome	206 (24)	11 (33)	0 (0)	0 (0)	31 (2)	24 (2)	2 (1)	0 (0)	11 (5)	285 (6)
Edward's syndrome	31 (4)	1 (3)	0 (0)	0 (0)	50 (4)	55 (4)	10 (3)	24 (6)	7 (3)	178 (4)
Down's syndrome	3 (0)	0 (0)	1 (1)	0 (0)	23 (2)	17 (1)	11 (3)	1 (0)	6 (2)	62 (1)
Genetic syndrome	13 (2)	4 (12)	1 (1)	8 (16)	152 (11)	92 (6)	31 (8)	15 (4)	13 (5)	329 (7)
Teratogenic syndromes including maternal infections*	0 (0)	0 (0)	1 (1)	0 (0)	34 (2)	17 (1)	15 (4)	9 (2)	13 (5)	89 (2)
Multiple congenital anomaly	238 (28)	10 (30)	23 (24)	6 (12)	372 (26)	364 (25)	109 (28)	63 (17)	68 (28)	1253 (25)
With congenital heart defects	68 (8)	3 (9)	8 (9)	1 (2)	133 (9)	143 (10)	40 (10)	22 (6)	30 (12)	448 (9)
With congenital limb anomalies	42 (5)	2 (6)	4 (4)	3 (6)	125 (9)	94 (6)	26 (7)	13 (3)	17 (7)	326 (7)
With congenital eye anomalies	46 (5)	2 (6)	9 (10)	0 (0)	21 (1)	43 (3)	6 (2)	8 (2)	5 (2)	140 (3)

*Under-reporting is likely to have occurred.
ICD-10, International Classification of Diseases, 10th Revision.

Morris, J. K., et al. (2019). Epidemiology of congenital cerebral anomalies in Europe: A multicentre, population-based EUROCAT study. *Archives of Disease in Childhood*, *104*(12), 1181–1187.

Diagnóstico de anomalías del SNC

Fetal abnormality	Total	NT>95th percentile	Diagnosis 11–13 weeks	Diagnosis 20–24 weeks	Diagnosis >24 weeks	Outcome TOP	Outcome Misc/ IUD	Outcome LB	First trimester detection in previous studies
Neural tube									
Acrania/iniencephaly	29	8 (27.6%)*	29 (100%)	—	—	29	—	—	31/32 (96.9%)
Encephalocele	—	—	—	—	—	—	—	—	2/2 (100%)
Open *spina bifida*	21	1 (4.7%)	3 (14.3%)	18	—	21	—	—	7/19 (36.8%)
Hemivertabrae	1	—	—	1	—	—	—	1	2/3 (66.7%)
Sacrococcygeal teratoma	—	—	—	—	—	—	—	—	1/2 (50.0%)
Brain									
Microcephaly	1	—	—	—	1[a]	—	—	1	0/1 (0.0%)
Craniosynostosis	1	—	—	1	—	1	—	—	0/1 (0.0%)
Corpus callosum agenesis	10	1 (10.0%)	—	10	—	7	1	2	0/1 (0.0%)
Ventriculomegaly	11	—	1 (9.1%)	9	1[b]	9	—	2	3/19 (15.8%)
Holoprosencephaly	—	—	—	—	—	—	—	—	7/9 (77.8%)
Alobar	2	—	2 (100%)	—	—	2	—	—	—
Semilobar	1	—	—	1	—	1	—	—	—
Cerebellar hypoplasia	3	—	—	3	—	3	—	—	5/10 (50.0%)
Vermian agenesis	4	—	—	4	—	3	—	1	—

Syngelaki, A., Chelemen, T., Dagklis, T., Allan, L., & Nicolaides, K. H. (2011). Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. Prenatal Diagnosis, 31(1), 90–102.

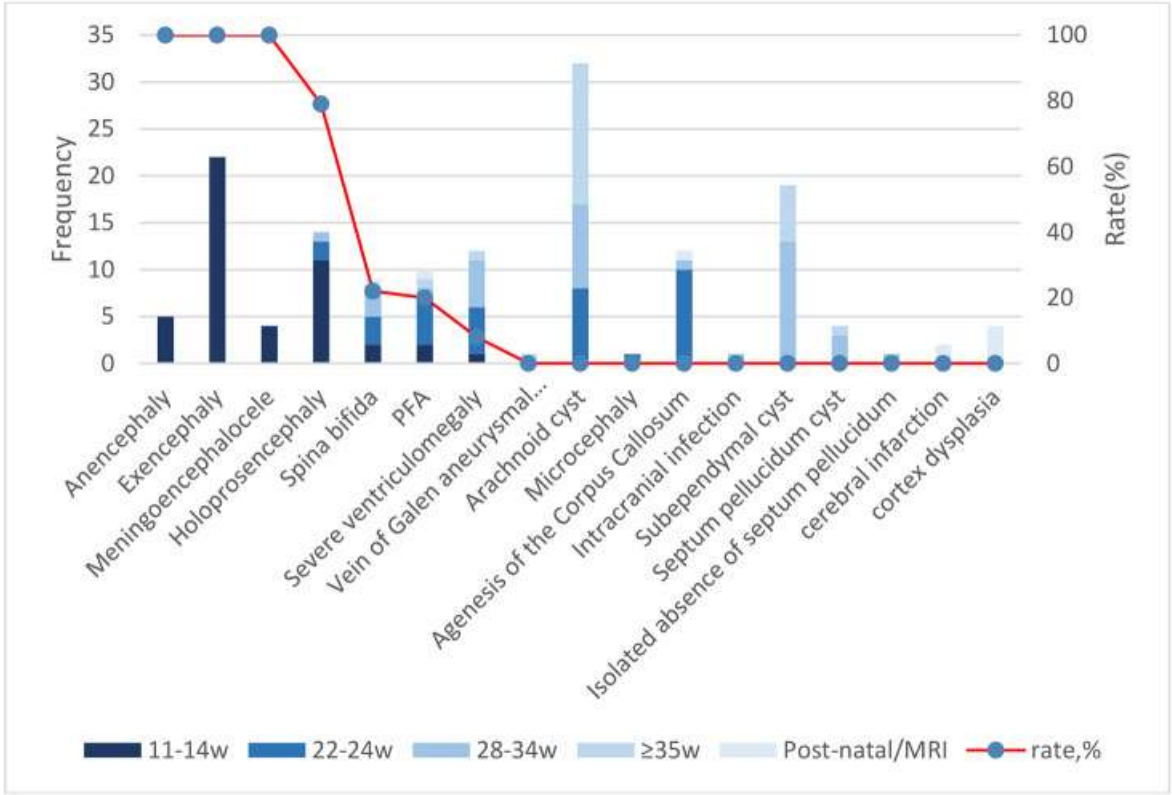
Defect	*Total*	*NT > 95th percentile*	*Detection: First trimester*	*Detection: Second trimester*	*Detection: Third trimester*	*Detection: Postnatal*
Central nervous system						
Acrania	48	0 (0)	48 (100)	0 (0)	0 (0)	0 (0)
Alobar holoprosencephaly	10	2 (20.0)	10 (100)	0 (0)	0 (0)	0 (0)
Encephalocele	15	5 (33.3)*	15 (100)	0 (0)	0 (0)	0 (0)
Open spina bifida	59	6 (10.2)*	35 (59.3)	24 (40.7)	0 (0)	0 (0)
Hypoplastic cerebellum/vermis	15	0 (0)	2 (13.3)	13 (86.7)	0 (0)	0 (0)
Agenesis of corpus callosum	26	2 (7.7)	0 (0)	25 (96.2)	1 (3.8)	0 (0)
Schizencephaly	3	0 (0)	0 (0)	2 (66.7)	1 (33.3)	0 (0)
Septo-optic dysplasia	1	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
Microcephaly	9	0 (0)	0 (0)	1 (11.1)	8 (88.9)	0 (0)
Severe ventriculomegaly	18	0 (0)	0 (0)	14 (77.8)	4 (22.2)	0 (0)
Arachnoid cyst	14	1 (7.1)	0 (0)	5 (35.7)	9 (64.3)	0 (0)
Brain hemorrhage	2	0 (0)	0 (0)	1 (50.0)	1 (50.0)	0 (0)
Dural venous sinus thrombosis	2	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)
Craniosynostosis	2	1 (50.0)	0 (0)	1 (50.0)	1 (50.0)	0 (0)
Occipital dermoid cyst	1	1 (100)*	0 (0)	1 (100)	0 (0)	0 (0)
Blake's pouch cyst	4	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)
Brain tumor	2	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)

Syngelaki, A., Hammami, A., Bower, S., Zidere, V., Akolekar, R., & Nicolaides, K. H. (2019). Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11–13 weeks' gestation. *Ultrasound in Obstetrics & Gynecology*, *54*(4), 468–476.

Diagnóstico de anomalías del SNC

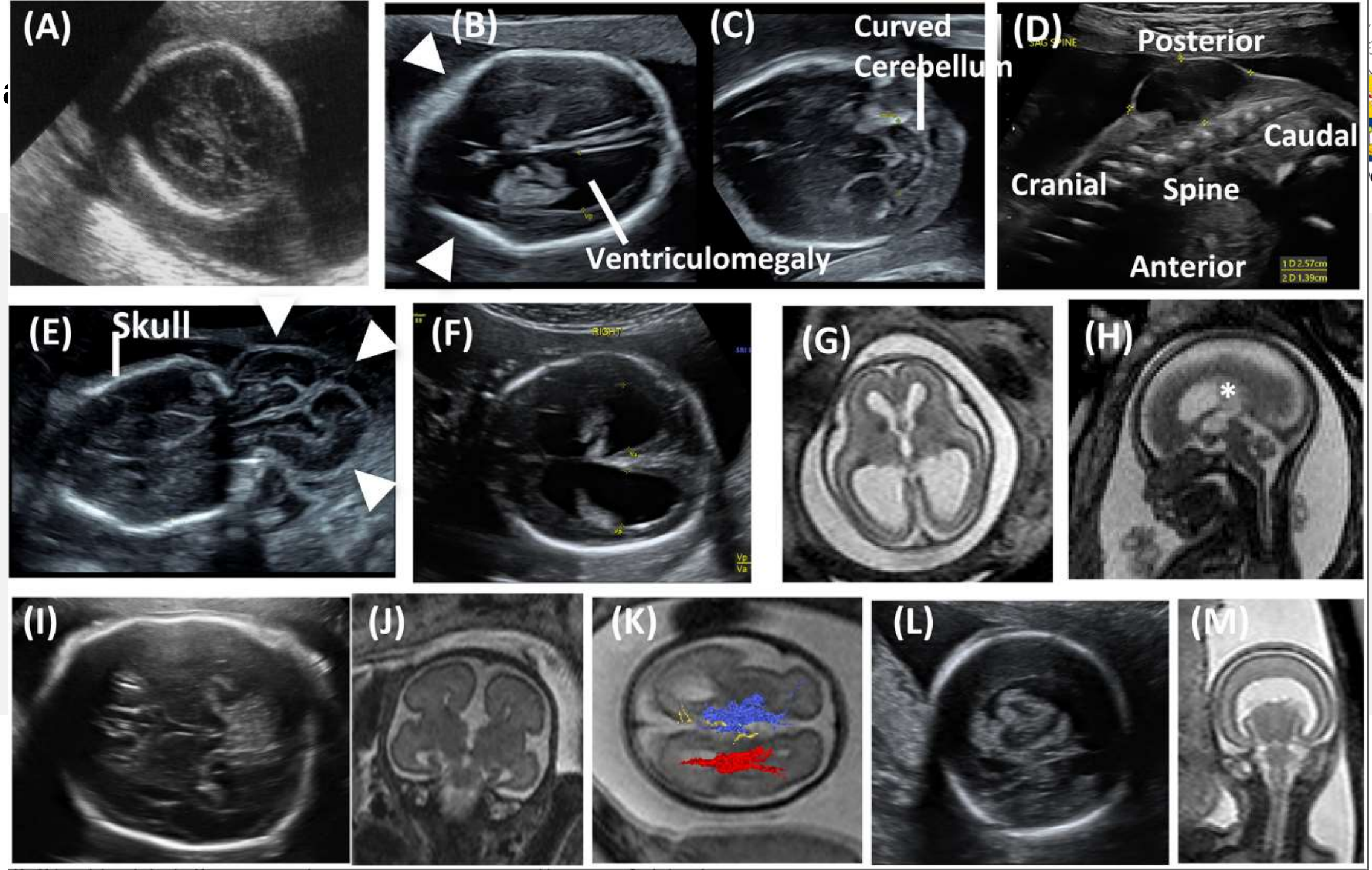
The pregnancy outcomes of the cases with CNS anomalies

Gestational age of diagnosed or suspected abnormality	Number of cases with CNS anomalies (detection rate)	Pregnancy outcome		
		TOP	Misc/IUD	LB
1st trimester scan	45(32%)	43(96%)	2(4%)	0
2nd trimester scan	31(22%)	26(84%)	0	5(16%)
3rd trimester scan	35(25%)	5(14%)	0	30(86%)
Late 3rd trimester scan	23(16%)	0	0	23(100%)



Hu, Y. et al. (2023). The role of routine first-trimester ultrasound screening for central nervous system abnormalities: a longitudinal single-center study using an unselected cohort with 3-year experience. *BMC Pregnancy and Childbirth*, *23*(1). https://doi.org/10.1186/S12884-023-05644-Z

Dia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Cerebellum
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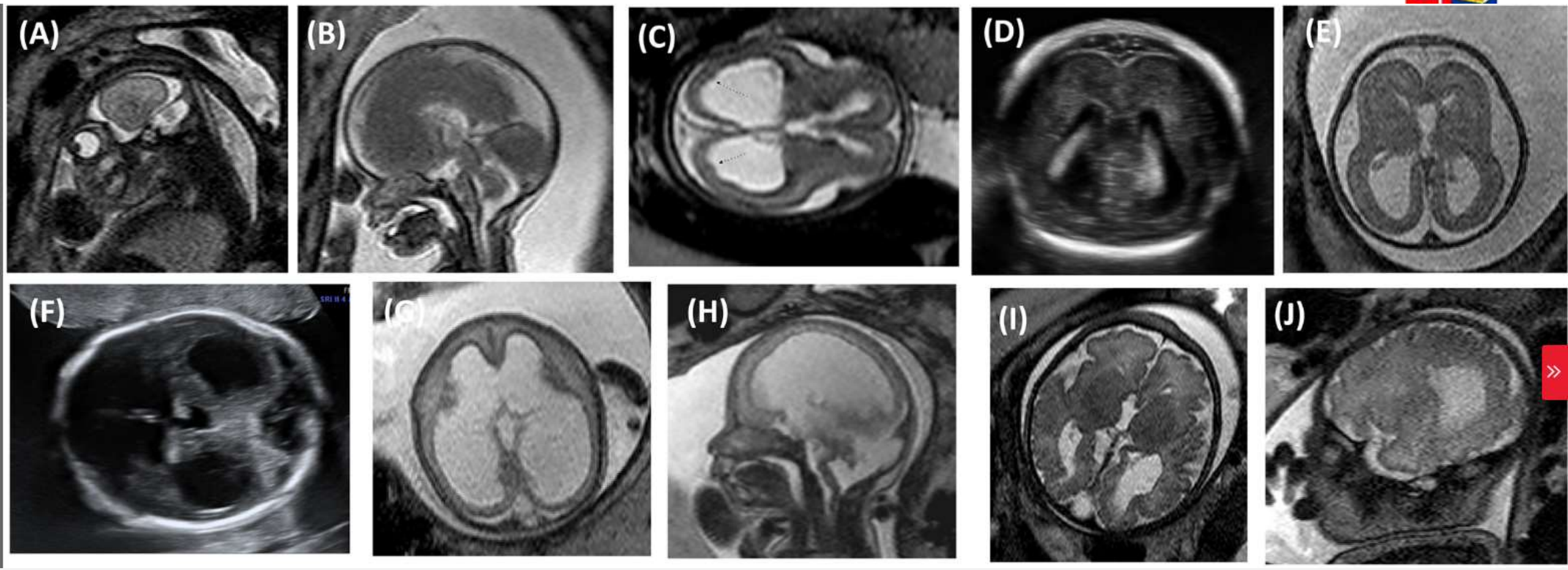
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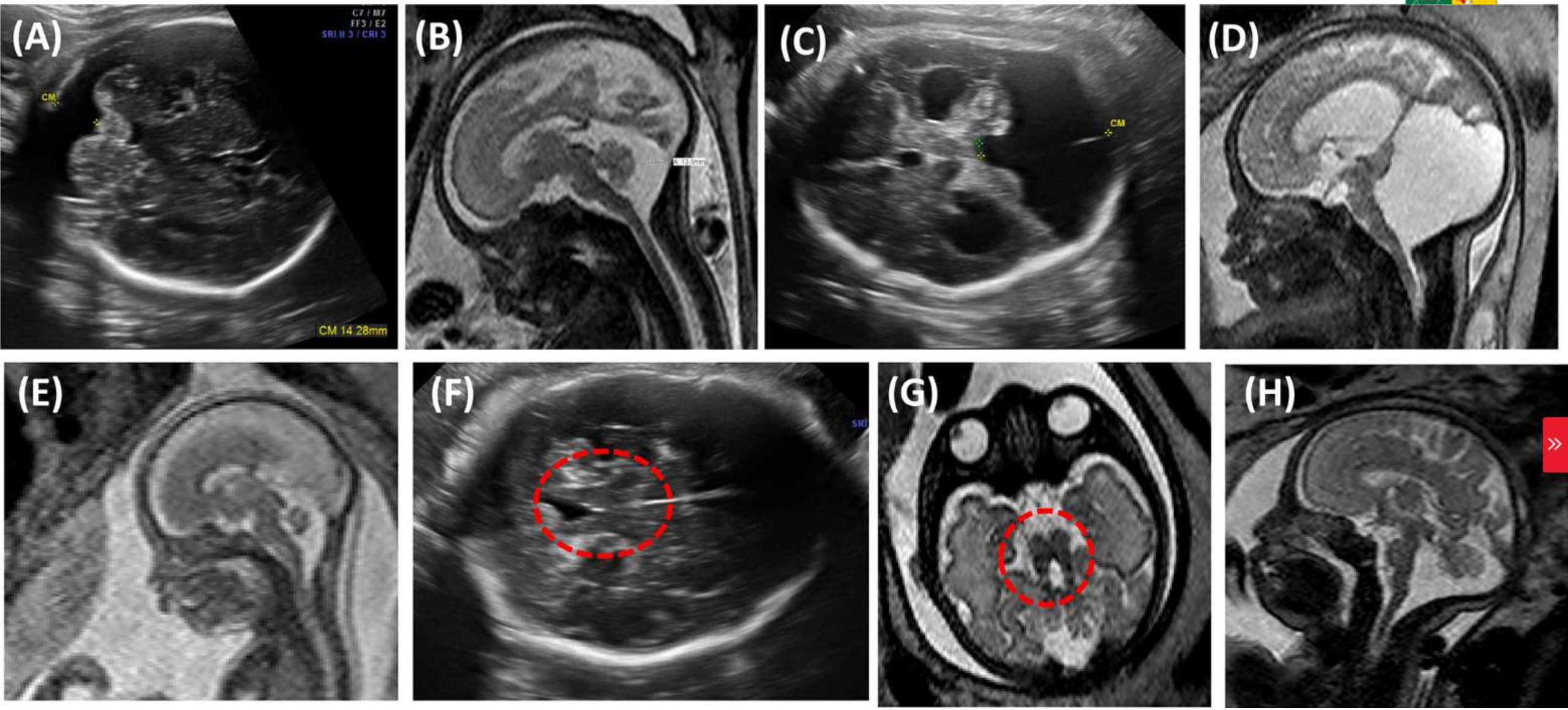
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Ley 21.030

CERPO

Ministerio de Salud

Gobierno de Chile

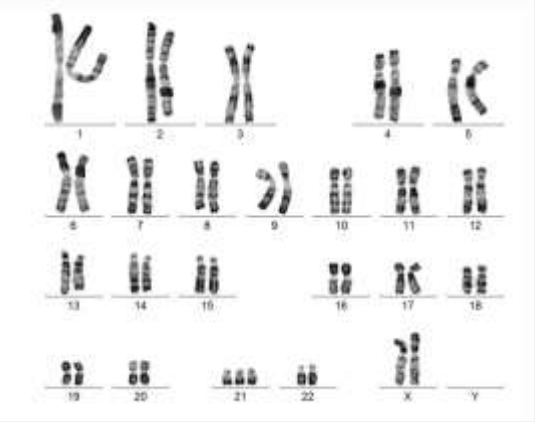
NORMA TÉCNICA NACIONAL

ACOMPAÑAMIENTO Y ATENCIÓN INTEGRAL A LA MUJER QUE SE ENCUENTRA EN ALGUNA DE LAS TRES CAUSALES QUE REGULA LA LEY 21.030

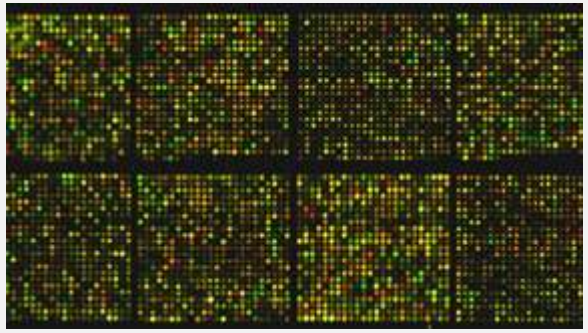
Subsecretaría de Salud Pública

Detección de alteraciones genéticas en fetos con anomalías estructurales

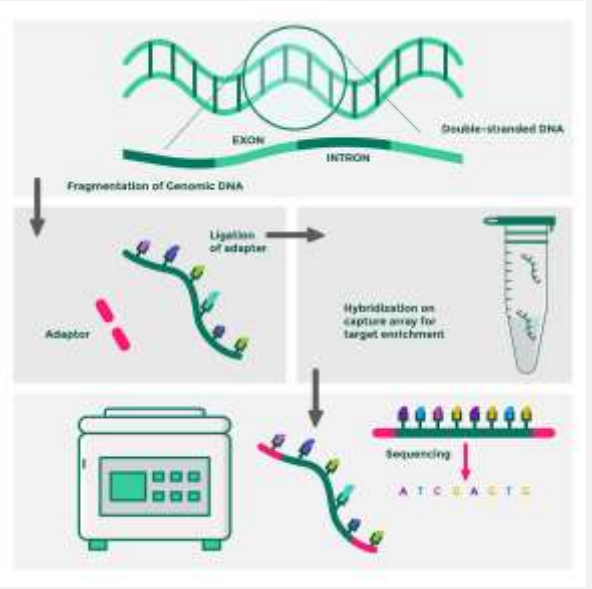
Hasta 30%



6% de rendimiento



8,5% de rendimiento



Wapner, Ronald J et al. “Chromosomal microarray versus karyotyping for prenatal diagnosis.” The New England journal of medicine vol. 367,23 (2012): 2175-84.

Lord, Jenny et al. “Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study.” Lancet (London, England) vol. 393,10173 (2019): 747-757

Cariotipo en anomalías del SNC

Aislada 2.8%

11,3%

Múltiple 16,7%

Otros sistemas 25%

TABLE 2 | The rates of chromosomal abnormalities in isolated CNS abnormalities and CNS abnormalities with other ultrasound abnormalities.

Classification	Number of fetuses	Number of chromosomal abnormalities	Trisomy 18	Trisomy 21	Trisomy 13	Other chromosome number abnormalities	Structural chromosomal abnormalities	p-values
Isolated CNS abnormalities	318	13 (4.1%)	2	5	1	1	4	–
CNS abnormalities with other ultrasound abnormalities	217	23 (10.6%)	9	3	2	1	8	–
Total	535	36 (6.7%)	11	8	3	2	12	0.003

$p < 0.05$ compared with isolated CNS anomalies and CNS abnormalities with other ultrasound abnormalities via χ^2 test.
CNS, central nervous system.

Karyotyping	Total	Isolated CNS anomalies			Non-isolated CNS anomalies
		Single	Multiple	*n*	
Number	124	72	12	84	40
Normal karyotype	110	70	10	80	30
Abnormal karyotype (*n*, %)	14 (11.3)	2 (2.8)	2 (16.7)	4 (4.8)	10 (25.0)
χ^2		4.375		11.081	
P		0.036		0.001	

Cai, Meiying et al. “Clinical Utility and the Yield of Single Nucleotide Polymorphism Array in Prenatal Diagnosis of Fetal Central Nervous System Abnormalities.” Frontiers in molecular biosciences vol. 8 666115. 18 May. 2021

Tao, Huimin et al. “Genetic etiology and pregnancy outcomes of fetuses with central nervous system anomalies.” Archives of gynecology and obstetrics vol. 309,6 (2024): 2567-2574

Rendimiento de CMA por sobre Cariotipo

TABLE 5 | The rates of Pathogenic CNVs in isolated CNS abnormalities and CNS abnormalities with other ultrasound abnormalities.

Classification	Number of fetuses	Number of fetuses with abnormal CNVs	P CNVs	VUS CNVs	p-values
Isolated CNS abnormalities	318	26	8 (2.5%)	18 (5.7%)	–
CNS abnormalities with other ultrasound abnormalities	217	15	10 (4.6%)	5 (2.3%)	–
Total	535	41	18 (3.4%)	23 (4.5%)	0.187

$p > 0.05$ compared with isolated CNS anomalies and CNS abnormalities with other ultrasound abnormalities via χ^2 test.
CNS, Central Nervous System; P, pathogenic; CNVs, copy number variations; VUS, uncertain clinical significance.

SNParray

CNV-seq	Total	Isolated CNS anomalies			Non-isolated CNS anomalies
		Single	Multiple	*n*	
Number	73	43	10	53	20
Normal	60	39	8	47	13
CNVs (*n*, %)	13 (17.8)	4 (9.3)	2 (20.0)	6 (11.3)	7 (35.0)
P/LP CNVs (*n*, %)	8 (11.0)	1 (2.3)	1 (10.0)	2 (3.8)	6 (30.0)
VUS (*n*, %)	5 (6.8)	3 (7.0)	1 (10.0)	4 (7.5)	1 (5.0)
Additional CNVs (*n*, %)	8 (11.0)	4 (9.3)	1 (10.0)	5 (9.4)	3 (15.0)
χ^2		0.925		5.562	
P		0.336		0.018	

CNV-seq

Cai, Meiying et al. “Clinical Utility and the Yield of Single Nucleotide Polymorphism Array in Prenatal Diagnosis of Fetal Central Nervous System Abnormalities.” Frontiers in molecular biosciences vol. 8 666115. 18 May. 2021

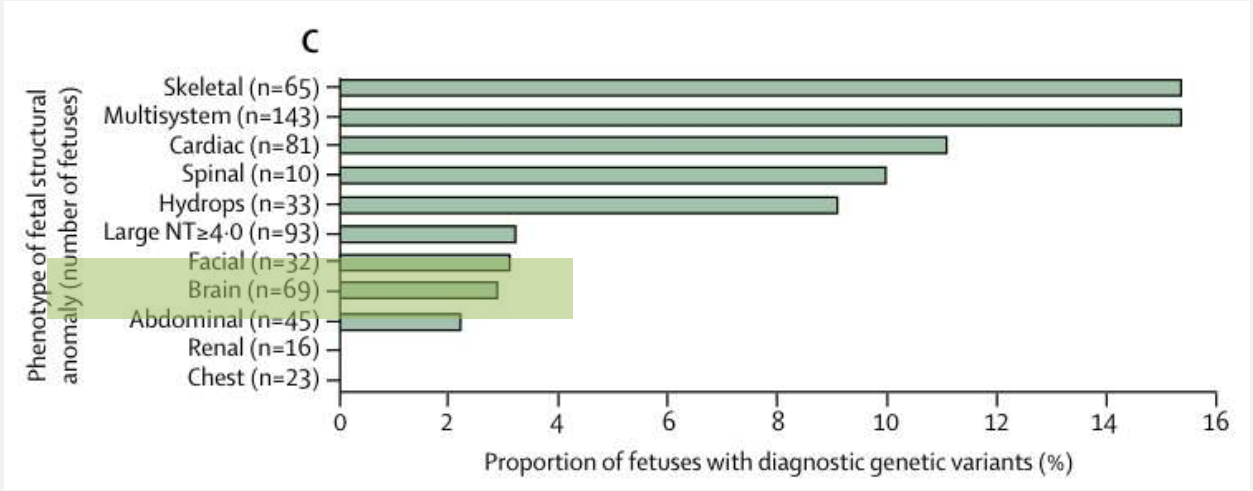
Tao, Huimin et al. “Genetic etiology and pregnancy outcomes of fetuses with central nervous system anomalies.” Archives of gynecology and obstetrics vol. 309,6 (2024): 2567-2574

Rendimiento de exoma por sobre CMA

	Number of fetuses*	Diagnostic genetic variants (% trios)	Bioinformatic signatures (% trios)	Number of bioinformatic signatures that are also a diagnostic variant†
Heart	77 (49)	4 (5%)	17 (22%)	4 (24%)
Nuchal	51 (32)	6 (12%)	10 (20%)	4 (40%)
Central nervous system	49 (29)	11 (22%)	16 (33%)	9 (56%)
Skeletal	34 (12)	8 (24%)	8 (24%)	6 (75%)
Intrauterine growth restriction	29 (5)	3 (10%)	5 (17%)	3 (60%)
Renal	25 (13)	4 (16%)	6 (24%)	1 (17%)
Lymphatic or effusion	21 (5)	5 (24%)	3 (14%)	2 (67%)
Other isolated anomalies‡	15 (15)	0	0	..

Fetuses with several anomalies are counted several times. *Number in brackets is the number of fetuses with a single structural anomaly in this anatomical system. †Frequencies reflect the proportion of diagnostic genetic variants that overlapped with a bioinformatic signature. ‡Abdominal wall (n=3), face (n=3), gastrointestinal tract (n=6), spine (n=1), and thorax (n=2).

***Table 2:* Distribution of diagnostic genetic variants and bioinformatic signatures across the anatomical systems of unselected fetuses with structural anomalies**



Petrovski, Slavé et al. “Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study.” Lancet (London, England) vol. 393,10173 (2019): 758-767.

Lord, Jenny et al. “Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study.” Lancet (London, England) vol. 393,10173 (2019): 747-757

Fetal central nervous system anomalies: When should we offer exome sequencing?

Caitlin Baptiste[1] | Rhiannon Mellis[2] | Vimla Aggarwal[1] | Jenny Lord[3] | Ruth Eberhardt[4] | Mark D. Kilby[5,6] | Eamonn R. Maher[7] | Ronald Wapner[8] | Jessica Giordano[9] | Lyn Chitty[2]

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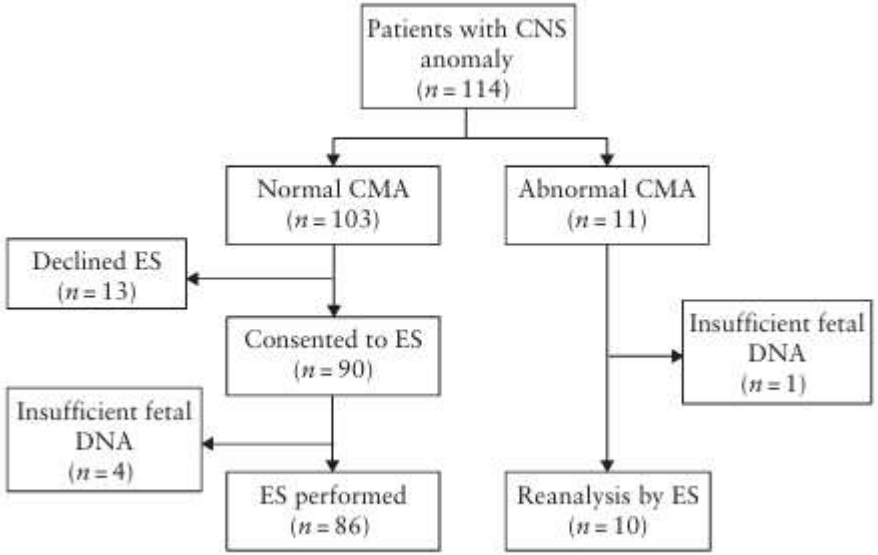
TABLE 1 Rates of likely pathogenic variants on exome sequenicng (ES) in fetuses with central nervous system (CNS) anomalies and the genes involved

	N	LP/p finding on ES (%)	Genes involved
Isolated, single CNS anomaly	97	7 (7.2)	
Mild ventriculomegaly	23	3 (13.0)	CHD7[a], B3GLCT[a], ARID1A
Moderate ventriculomegaly	15		
Severe ventriculomegaly	18	1 (5.6)	KIDINS220
Unknown severity of ventriculomegaly	8		
Agenesis of the corpus callosum	10	3 (30.0)	L1CAM[a], SHH, PTCH1
Cerebellar hypoplasia	2		
Dandy walker	5		
Encephalocele	3		
Holoprosencephaly	6		
Parenchymal defect	1		
Intracranial hemorrhage	1		
Other	5		
Multiple CNS anomalies	63	12 (19.0)	FLNA[a], C5ORF42, CHD7[a], GPSM2, TUBB3, ARMC9, RAC1, OCRL, TUBA1A, ASPM, TUBB[a], PIK3R2
Anomalies in multiple organ systems including CNS	108	18 (16.7)	TSC2[a], TMEM67[a], SCN2A[a], COL4A1[a], CE0, CC2D2A, FLVCR2[a], FGFR2, PORCN, CPT2, TCTN2[a], TMEM67[a], PEX1, ISPD, CHD7, CDKN1C[a], RAB23[a], TCTN3

- 30% de fetos con agenesia del cuerpo calloso presentaron una variante patogénica
- En alteración aislada del SNC el rendimiento fue de 7,2%
- Múltiples malformaciones del SNC 19%
- Otros sistemas comprometidos 16,7%

¿WES en lugar de CMA?



Clinical category	*CMA*	*ES*
Multisystem	5/40 (13)	14/32 (44)
Complex brain	5/32 (16)	14/24 (58)
MCD	0/11 (0)	3/9 (33)
Brain damage	0/14 (0)	3/9 (33)
Subependymal/arachnoid cysts	0/5 (0)	1/4 (25)
Midline anomaly	0/4 (0)	2/3 (67)
MBHB	1/6 (17)	0/3 (0)
Neural tube defect	0/2 (0)	1/2 (50)
Total	11/114 (10)	38/86 (44)

Data are given as *n*/*N* (%). MBHB, midbrain–hindbrain malformation; MCD, malformation of cortical development.

44% DE RENDIMIENTO EN COMPARACIÓN CON CMA

Yaron, Y et al. “Exome sequencing as first-tier test for fetuses with severe central nervous system structural anomalies.” Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology vol. 60,1 (2022): 59-67.

Problemas comunes
Ventriculomegalia

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- Leve
- Moderada
- Severa

1,5 a 5% asociadas a infecciones

18% severas con otras alteraciones estructurales

- VM leve y moderada
- Anomalías detectadas en cariograma 9%
- Leve 9%; Severa 5%
- Aislada 3%, no aislada 13%

- Incremento diagnóstico de CMA 12%

- Exoma en VM severa
- Incremento diagnóstico 45%
- Aislada 35%; No Aislada 54%

Daniele Di Mascio, et al. Role of prenatal magnetic resonance imaging in fetuses with isolated severe ventriculomegaly at neurosonography: A multicenter study,
European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 267, 2021

Pasquini L, Masini G, Gaini C, et al. The utility of infection screening in isolated mild ventriculomegaly: an observational retrospective study on 141 fetuses. *Prenat Diagn*. 2014

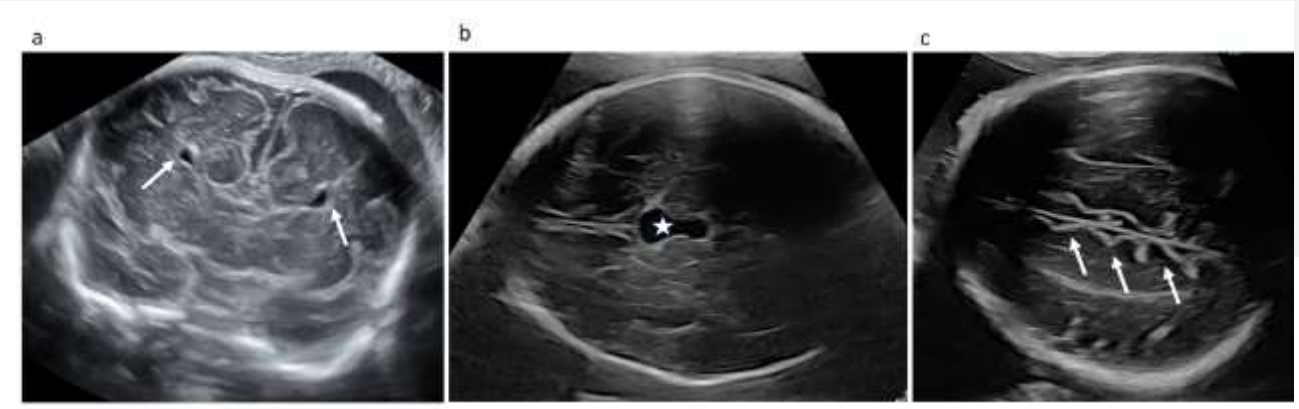
Sun, Yan et al. "Chromosomal microarray analysis vs. karyotyping for fetal ventriculomegaly: a meta-analysis." Chinese medical journal vol. 135,3 268-275. 20 Sep. 2021

Mustafa, Hiba J et al. "Diagnostic yield with exome sequencing in prenatal severe bilateral ventriculomegaly: a systematic review and meta-analysis." American journal of obstetrics & gynecology MFM vol. 5,9 (2023): 101048

Problemas comunes
Agenesia del Cuerpo Calloso

- Anomalía cerebral congénita más común hasta 1,8 por 10.000
- 60% de los casos la ACC total o parcial será concomitante a otras malformaciones del SNC

- En casos con agenesia completa del CC aislada
- Cariograma anormal 4,8%
- Rendimiento del CMA 5,74%



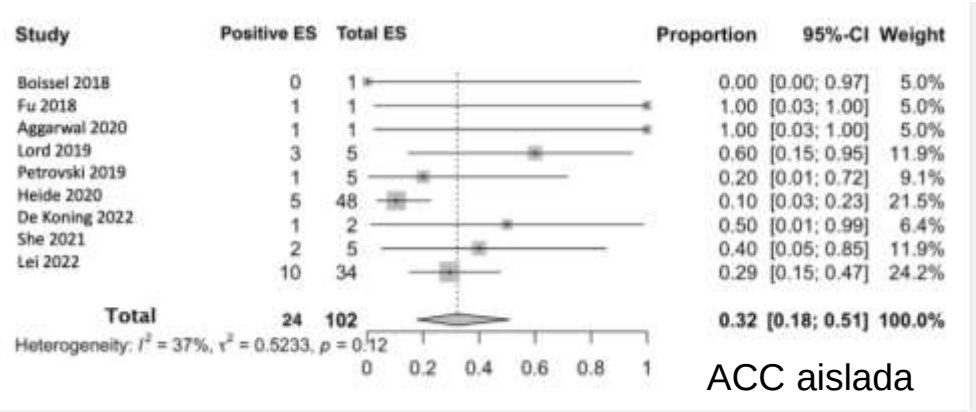
Tsai P, Shinar S. Agenesis of the corpus callosum: what to tell expecting parents? Prenat Diagn. 2023; 43(12): 1527-1535.

Francesco D'Antonio, Giorgio Pagani, Alessandra Familiari, Asma Khalil, Tally-Lerman Sagies, Gustavo Malinger, Zvi Leibovitz, Catherine Garel, Marie Laure Moutard, Gianluigi Pilu, Amar Bhide, Ganesh Acharya, Martina Leombroni, Lamberto Manzoli, Aris Papageorghiou, Federico Prefumo; Outcomes Associated With Isolated Agenesis of the Corpus Callosum: A Meta-analysis. Pediatrics September 2016; 138 (3): e20160445

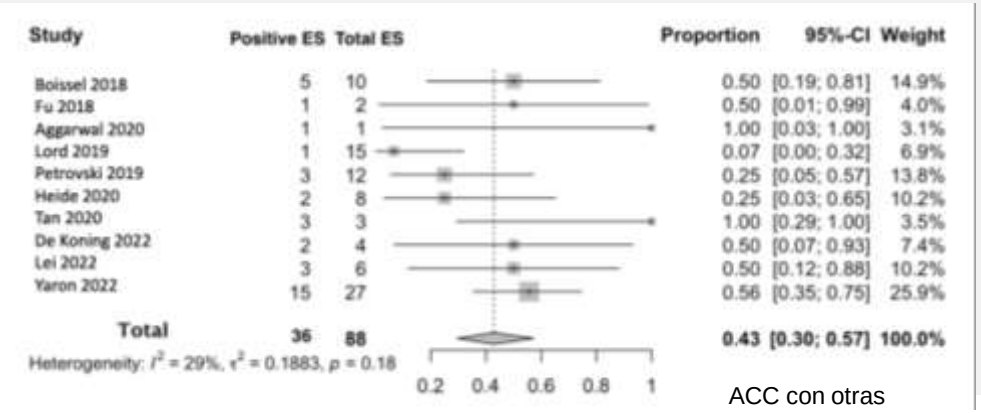
Problemas comunes
Agenesia del Cuerpo Calloso

- El rendimiento diagnóstico de WES tanto en agenesia aislada como asociada a otras malformaciones confiere un rendimiento diagnóstico alto

Group	Studies (*n*)	P/LP (*n*)	ACC cases (*n*)	PP (95% CI) (%)	I^2 (%)
All ACC*	15	100	268	43 (31–56)	64
Isolated ACC†	9	24	102	32 (18–51)	37
ACC with other cranial anomalies	10	36	88	43 (30–57)	29
ACC with extracranial anomalies	12	35	66	55 (35–73)	41



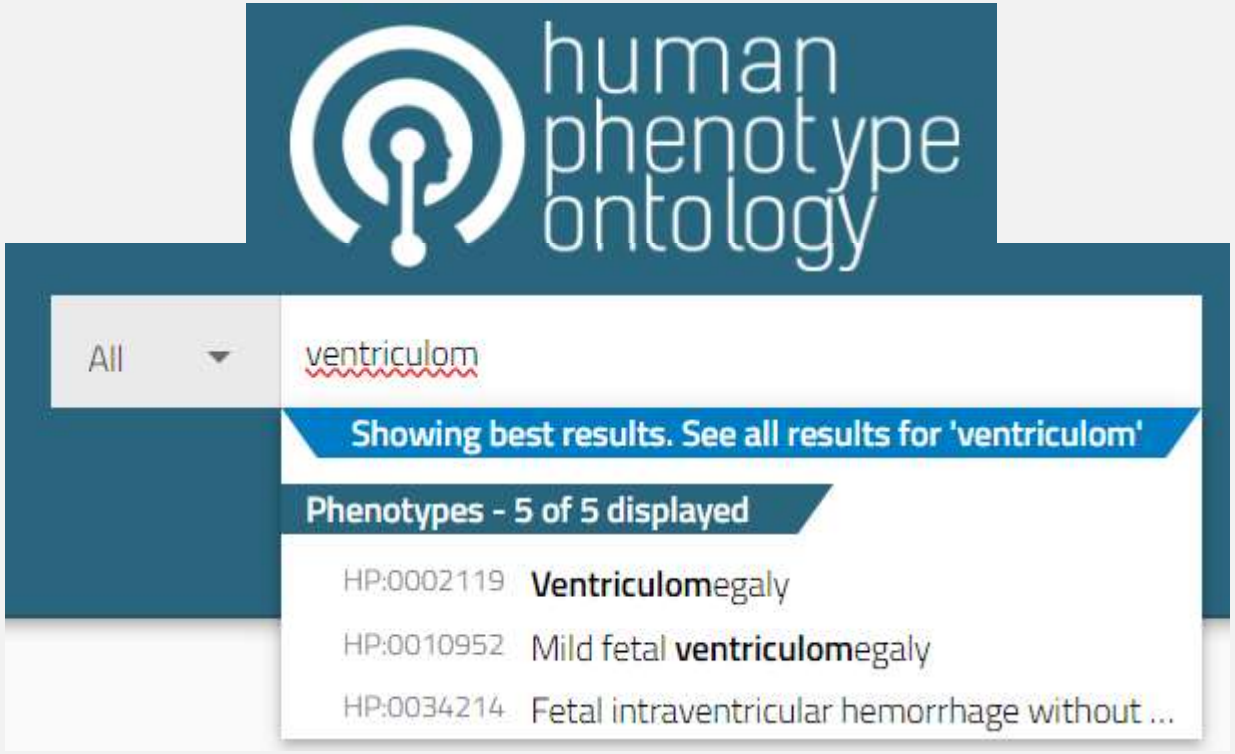
ACC aislada

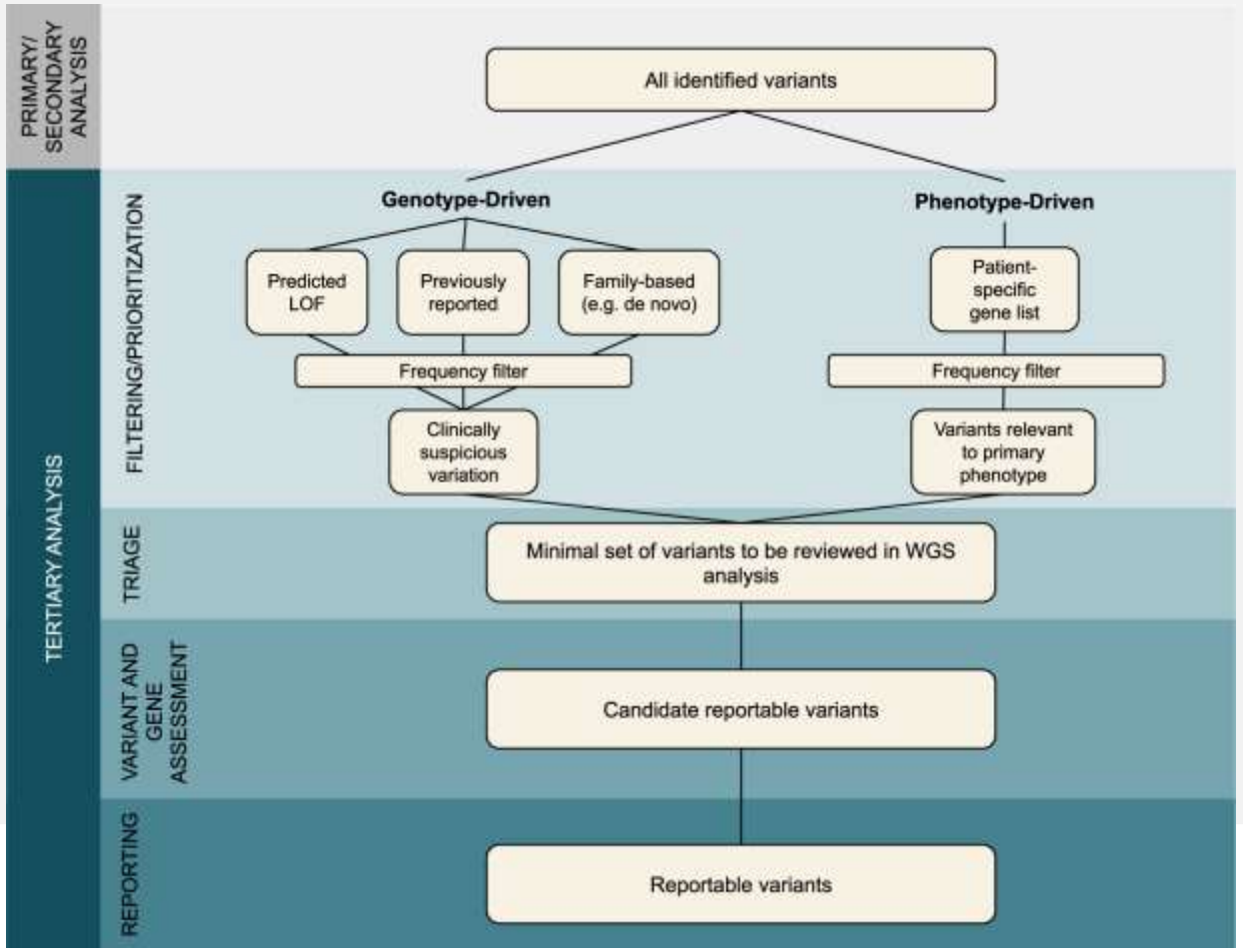


ACC con otras anomalías craneales

Mustafa, H.J., Barbera, J.P., Sambatur, E.V., Pagani, G., Yaron, Y., Baptiste, C.D., Wapner, R.J., Brewer, C.J. and Khalil, A. (2024), Diagnostic yield of exome sequencing in prenatal agenesis of corpus callosum: systematic review and meta-analysis. Ultrasound Obstet Gynecol, 63: 312-320

Importancia del Fenotipo





Austin-Tse, C.A., Jobanputra, V., Perry, D.L. et al. Best practices for the interpretation and reporting of clinical whole genome sequencing. npj Genom. Med. 7, 27 (2022)

Conclusiones y recomendaciones

- 2-3% de fetos presentan anomalías estructurales
- Contribuyen al 12% de los ingresos a unidades pediátricas y al 50% de la mortalidad neonatal e infantil

- Las anomalías del Sistema nervioso central tienen una prevalencia de 9,5 por 10.000 partos
- Un 25% se encuentra asociado a alguna alteración genética

- El diagnóstico precoz es esencial para entregar una adecuada consejería
- Entre un 7 a 11% presentarán alteraciones cromosómicas numéricas o estructurales identificables en el cariograma convencional
- El rendimiento del CMA para detectar CNVs patológicas (o probablemente patológicas) es mayor cuando hay más de una anomalía del SNC o se encuentran otros sistemas comprometidos
- WES puede mejorar el rendimiento diagnóstico en 7,2% por sobre CMA, pero hasta 19% cuando existen múltiples malformaciones del SNC

Conclusiones y recomendaciones

- Si bien el rendimiento del cariograma convenciona es menor que en malformaciones de otros sistemas, este aumenta cuando se trata de malformaciones múltiples, aunque siempre debe ser la primera aproximación para el estudio genético

- Parece razonable, sobretodo en malformaciones múltiples o agenesia de CC aislada continuar con WES por sobre CMA

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Diagnóstico genético en malformaciones del Sistema Nervioso Central

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