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

Estudio Genético en Displasias Esqueléticas

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Introducción

- Prevalencia de 1:4000 RNV.
  - 23% mortinatos, el 32% mueren en periodo neonatal.
- Corresponden al 5% de los trastornos genéticos identificados en el período neonatal.
- Aprox 50% son letales en el período perinatal.
- Letales más comunes: Displasia Tanotofórica (29%), Osteogénesis Imperfecta tipo II (14%) y Acondrogénesis (9%).

The Fetal Medicine Foundation, Fetal-abnormalities: Skeleton, Skeletal-dysplasia © 2021 The Fetal Medicine Foundation.
Mortier G. et al, Nosology and classification of genetic skeletal disorders: 2019 revision. American Journal of Medical Genetics, Sept 2019.

Introducción

- El descubrimiento incidental requiere de un examen sistemático de las extremidades, la cabeza, el tórax y la columna para llegar al diagnóstico correcto.
  - Enfoque orientado a distinción de formas letales de no letales.
- Dg prenatal → asesoramiento y toma de decisiones.

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Dysplasia	Prevalence	Etiology	Prognosis	Features
Thanatophoric dysplasia	1 in 10,000	Sporadic	Lethal	Limbs: very short. Thorax: narrow. Trunk: normal. Head: large with prominent forehead.
Type I				Femurs: curved (telephone receiver).
Type II				Femurs: straight. Skull: cloverleaf-shaped.
Osteogenesis imperfecta	1 in 15,000	Autosomal dominant		Fragile bones. Several types but the most severe cases that present prenatally are types II and III.
Type II			Lethal	Limbs: short with fractures. Thorax small with multiple fractures of ribs. Head: hypomineralization of the skull.
Type III			Variable	Multiple fractures, usually present at birth, resulting in scoliosis and very short stature.
Achondroplasia	1 in 25,000	Autosomal dominant	Normal	Limbs: short, but >22 weeks. Head: large with prominent forehead. Spine: lumbar lordosis.
Achondrogenesis	1 in 40,000		Lethal	Limbs: severe shortening. Thorax: narrow. Trunk: short. Head: large with prominent forehead.
Type I		Autosomal recessive		Skull: hypomineralization. Spine: hypomineralization. Thorax: rib fractures.
Type II		Sporadic		Skull: no hypomineralization. Spine: hypomineralization. Thorax: no rib fractures.

Asphyxiating thoracic dystrophy	1 in 70,000	Autosomal recessive	Variable	Limbs: short, but >22 weeks. Thorax: narrow and short.
Ellis–Van Creveld syndrome	1 in 100,000	Autosomal recessive	Variable	Limbs: acromelic and mesomelic shortening, postaxial polydactyly. Thorax: small. Other: heart defects in >50% of cases.
Hypophasphatasia	1 in 100,000	Autosomal recessive	Lethal	Limbs: very short. Thorax: small. Other: hypomineralization of all bones.
Campomelic dysplasia	1 in 200,000	Autosomal recessive	Lethal	Limbs: short, bowed leg bones. Thorax: narrow, hypoplastic scapulae. Head: large with small face.
Jarcho–Levin syndrome	1 in 200,000	Autosomal recessive	Variable	Limbs: normal length. Thorax: short narrow. Trunk: short. Fused vertebral bodies and ribs.
Diastrophic dysplasia	1 in 500,000	Autosomal recessive	Normal	Limbs: very short and bowed. Joints: flexion contractures, talipes. Spine: scoliosis. Other: 'hitchhiker thumb'.

Group/name of disorder	Inheritance	Gene(s)	OMIM number	ORPHANET code	Notes
1. FGFR3 chondrodysplasia group					
Thanatophoric dysplasia type 1	AD	*FGFR3*	187600	18060	Includes previous San Diego type
Thanatophoric dysplasia type 2	AD	*FGFR3*	187601	93274	
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	AD	*FGFR3*	616482	85165	
Achondroplasia	AD	*FGFR3*	100800	15	
Hypochondroplasia	AD	*FGFR3*	146000	427	
Camptodactyly, tall stature and hearing loss syndrome (CATSHL)	AD, AR	*FGFR3*	610474	85164	Loss-of-function mutations
See also group 33 for craniosynostosis syndromes linked to *FGFR3* mutations, as well as LADD syndrome in group 41 for another *FGFR3*-related phenotype					

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9. Ciliopathies with major skeletal involvement					
Chondroectodermal dysplasia (Ellis-van Creveld)	AR	*EVC1*	225500	289	See also Weyers acrofacial (acrodental) dysostosis in group 34
	AR	*EVC2*			
	AR	*WDR35*			
	AR	*DYNC2LI1*			
Short rib–polydactyly syndrome (SRPS) type 1/3 (Saldino–Noonan/Verma–Naumoff)	AR	*DYNC2H1*	613091	93270	There is significant clinical and radiological overlap between SRP1/3 and ATD. Some forms of both remain unlinked to the known genes.
	AR	*IFT80*		93271	
	AR	*WDR34*			
	AR	*WDR60*			
	AR	*DYNC2LI1*			
Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	*DYNC2H1*	613091	474	Dynein motor
	AR	*DYNC2LI1*			
	AR	*WDR34*			
	AR	*TCTEX1D2*			
	AR	*WDR60*			
	AR	*WDR19*			Retrograde transport (IFT-A)
	AR	*IFT140*			

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ESTUDIO GENÉTICO

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- >90% asociado a mutaciones en genes específicos.
- 40-49% de los casos, US no es suficiente para diferenciar el tipo de displasia esquelética.
- Importancia en el diagnóstico de displasias esqueléticas letales.

Table 1. Selected lethal or life-limiting skeletal dysplasias

Skeletal dysplasia	OMIM*	ORPHA code**	Inheritance	Gene/genes (chromosome location)
Thanatophoric dysplasia type I type II	 187600 187601	2655 1860 93274	AD	*FGFR3* (4p16. 3)
Osteogenesis imperfecta type II	166210	216804	AD	*COL1A1* (17q21.33) *COL1A2* (7q21.3)
Achondrogenesis type Ia type Ib type II	 200600 600972 200610	932 93299 93298 93296	AR – type Ia, Ib AD – type II	*TRIP11* (14q32) – type Ia *SLC26A2* (5q32) – type Ib *COL2A1* (*12q13.11*) – type II
Campomelic dysplasia	114290	140	AD	*SOX9* (17q24)
Asphyxiating thoracic dystrophy	208500	474	AR	*DYNC2H1* (11q22.3), *DYNC2LI1* (2p21), *DYNC2I2* (9q34.11), *DYNLT2B* (3q29), *DYNC2I1* (7q36.3), *WDR19* (4p14), *IFT140* (16p13.3), *TTC21B* (2q24.3), *IFT80* (3q25.33), *IFT172* (2p23.3), *IFT81* (12q24.11), *IFT52* (20q13.12), *TRAF3IP1* (2q37.3), *CFAP410* (21q22.3), *CEP120* (5q23.2), *KIAA0586* (14q23.1), *KIAA0753* (17p13.1)
Fibrochondrogenesis type 1 type 2	 228520 614524	 2021	 AR – type 1 AR or AD – type 2	 *COL11A1* (1p21) – type 1 *COL11A2* (6p21.3) – type 2
Atelosteogenesis type I type II type III	 108720 256050 108721	 1190 56304 56305	 AD – type I, III AR – type II	 *FLNB* (3p14) – type I, III *SLC26A2* (5q32) – type II
Homozygous achondroplasia	100800	15	AD (homozygous mutation)	*FGFR3* (4p16.3)

* OMIM – https://omim.org; ** Orphanet – https://www.orpha.net; AR (autosomal recessive) – homozygous mutation or compound heterozygous mutations; AD (autosomal dominant) – heterozygous mutation.

Prenatal diagnosis of fetal skeletal dysplasia using targeted next-generation sequencing: an analysis of 30 cases

Yan Liu[1], Li Wang[2], Yi-Ke Yang[1], Ying Liang[3], Tie-Juan Zhang[2], Na Liang[2], Li-Man Yang[2], Si-Jing Li[2], Dan Shan[1] and Qing-Qing Wu[2*]

- 30 casos; 15 malformaciones esqueléticas sistémicas; 15 malformaciones esqueléticas locales.
- Cordocentesis o muestra de tejido muscular en mortinatos.
- Cariograma → WGS → NGS
- Si (+), testeo a padres.

Liu et al. Diagnostic Pathology (2019) 14:76

Resultados

- 2/30 casos → Trisomía 18
- Anomalías focales → 6/13 WGS (+)
- Anomalías sistémicas → 15/15 NGS (+)

Liu et al. Diagnostic Pathology (2019) 14:76

Rapid prenatal diagnosis of skeletal dysplasia using medical trio exome sequencing: Benefit for prenatal counseling and pregnancy management

Jin Han[1] | Yan-Dong Yang[2] | Yi He[3] | Wen-Jie Liu[4] | Li Zhen[1] | Min Pan[1] | Xin Yang[1] | Victor Wei Zhang[4,5] | Can Liao[1] | Dong-Zhi Li[1]

- 27 casos con sospecha de DE por US.
- 88,9% (24/27) → alteración genética
- 1/27 → T18
- COL1A1, COL1A2 y FGFR3 → 66,7% (18/27)

Han et al. Prenatal Diagnosis. 2020;40:577–584.

Whole Exome Sequencing Aids the Diagnosis of Fetal Skeletal Dysplasia

Hui Tang[1,2†], Qin Zhang[1,2†], Jingjing Xiang[1,2†], Linliang Yin[1,2], Jing Wang[3] and Ting Wang[1,2*]*

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- 16 casos.
- 1/16 → deleción en gen DMD, heredado.
- 11/16 → WES (+): DYNC2H1 (1), ALPL (2), FGFR3 (2), COL1A2 (3), COL1A1 (2), HSPG2 (1)

Tang et al. Front. Genet. (2021) 12:599863.

Combined exome sequencing and deep phenotyping in highly selected fetuses with skeletal dysplasia during the first and second trimesters improves diagnostic yield

Xinyue Zhang[1] | Yuan Ren[1] | Rui Song[1] | Longxia Wang[2] | Hong Xu[2] | Xiaoxiao Xie[1] | Honghui Zhou[1] | Pei Sun[3] | Manli Zhang[4] | Qingdong Zhao[1] | Yanqin You[1] | Zhiying Gao[1] | Yuanguang Meng[1] | Yanping Lu[1]

- 27 casos
- 77,8% (21/27) → COL1A1, FGFR3, COL2A1, COL1A2, FLNB, DYNC2LI1 y TRIP11.
- De novo 19/27)

Zhang, et al. Prenatal Diagnosis. 2021;1–13.

Conclusiones

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- Detección de Displasias Esqueléticas letales → ¿Interrupción?
- Consejería para padres:
  - Pronóstico post natal
  - Estudio genético preimplantacional

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