NOVEDADES EN EL DIAGNÓSTICO Y TRATAMIENTO DE LA OSTEOGÉNESIS IMPERFECTA



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Reumatología

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Introducción

- Trastorno hereditario del tejido conectivo que afecta a la producción del colágeno

- Caracterizado por:
  - Baja masa ósea
  - Fragilidad ósea



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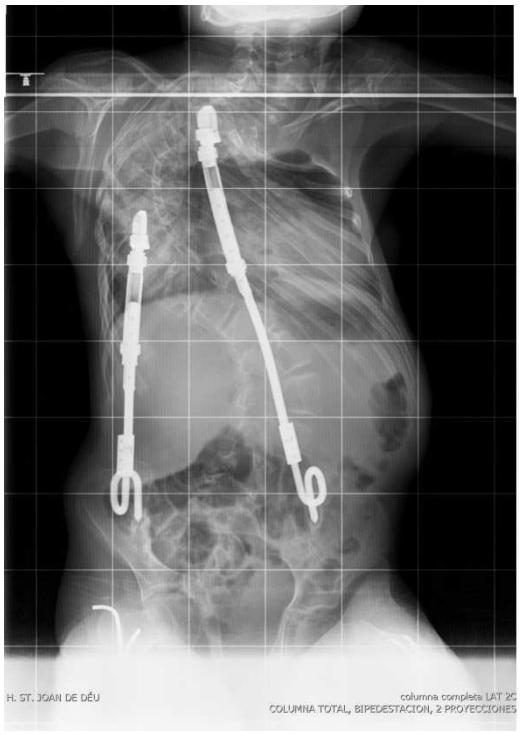
Amplio espectro de manifestaciones:

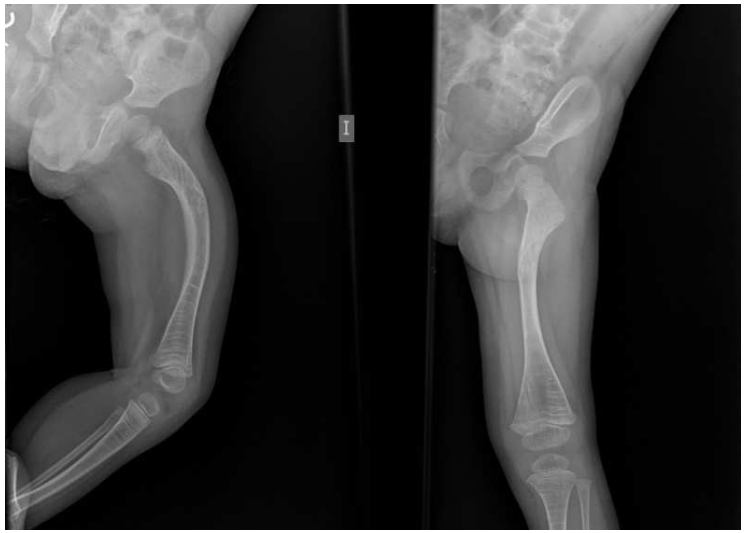






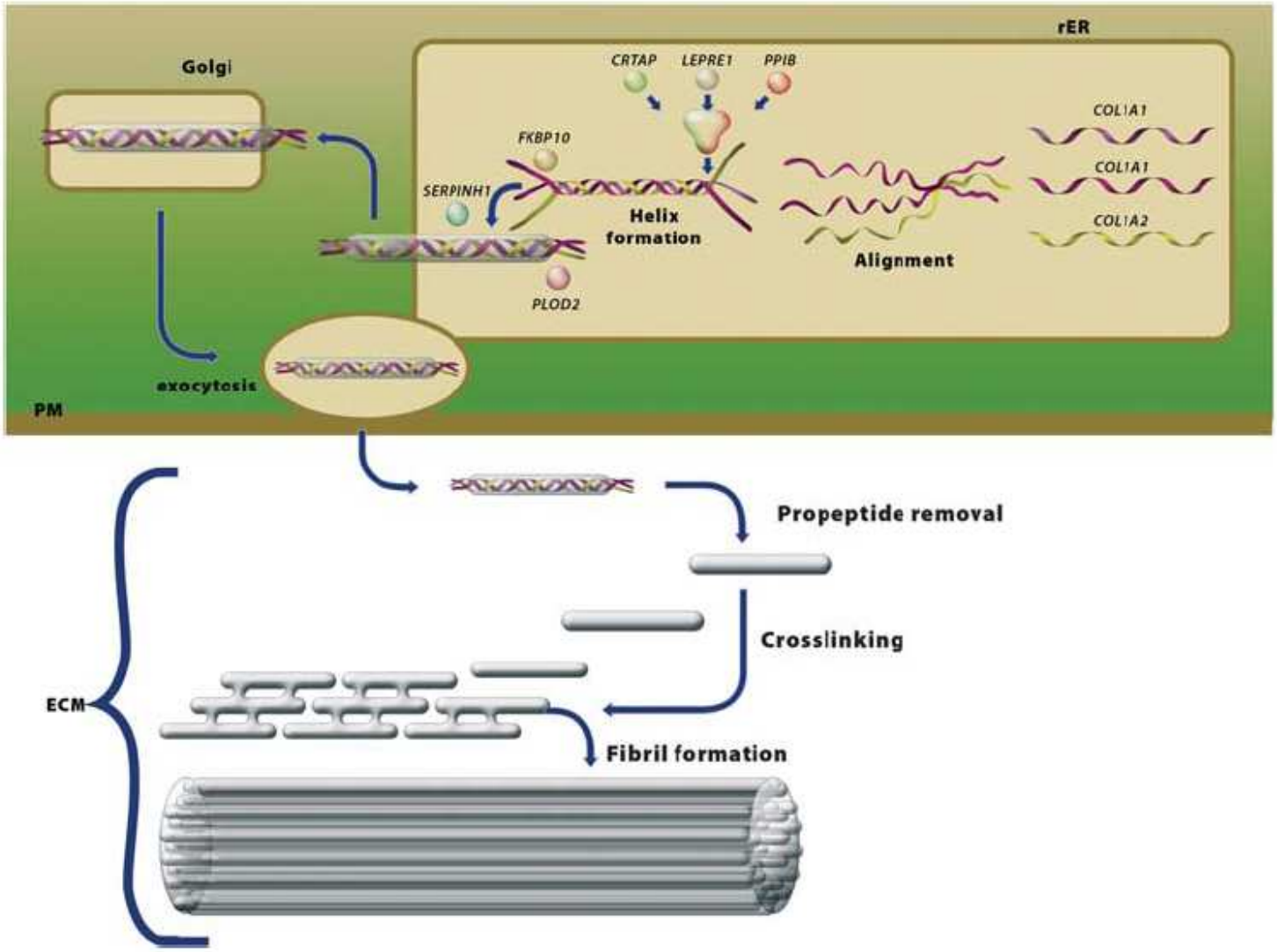






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Etiopatogenia. Formación del colágeno



FS van Dijk. Eur J Hum Genet. 2012

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La clasificación ha ido cambiando con los años

- Clasificación de Sillence (1979)

Table 7 *A nomenclature for OI syndromes*

Suggested numerical type	*Qualifying suffixes*	*Mode of inheritance*	*Reported synonyms and eponyms*
I	Congenita tarda	Autosomal dominant	Dominantly inherited OI with distinctly blue sclerae, Van der Hoeve's syndrome, Trias fragilitas ossium, OI tarda levis, OI tarda type II, OI (mild long bone deformity), Eddowe's syndrome
II	Congenita (always)	Autosomal recessive	Lethal perinatal OI, OI letalis Vrolik, Lethal OI congenita
III	Congenita (tarda)	Autosomal recessive	Progressively deforming OI with normal sclerae, OI congenita, OI tarda gravis, OI (severe long bone deformity), OI congenita type Vrolik, Periosteal dysplasia of Porak and Durante, Osteopsathyrosis idiopathica of Lobstein
IV	Congenita tarda	Autosomal dominant	Dominantly inherited OI with normal sclerae, Osteopsathyrosis idiopathica of Lobstein, Ekman–Lobstein disease

Sillence. J Med Genet 1979



OI tipo I

- Clasificación de Sillence (1979)

Table 7 *A nomenclature for OI syndromes*

Suggested numerical type	*Qualifying suffixes*	*Mode of inheritance*	*Reported synonyms and eponyms*
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III	Congenita (tarda)	Autosomal recessive	Progressively deforming OI with normal sclerae, OI congenita, OI tarda gravis, OI (severe long bone deformity), OI congenita type Vrolik, Periosteal dysplasia of Porak and Durante, Osteopsathyrosis idiopathica of Lobstein
IV	Congenita tarda	Autosomal dominant	Dominantly inherited OI with normal sclerae, Osteopsathyrosis idiopathica of Lobstein, Ekman–Lobstein disease

- La más leve
- Fracturas + escleróticas azules + hipoacusia
- Fx: deambulación-pubertad
- Deformidad mínima
- Talla prácticamente normal
- Dentinogénesis imperfecta variable



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Sillence. J Med Genet 1979

OI tipo II

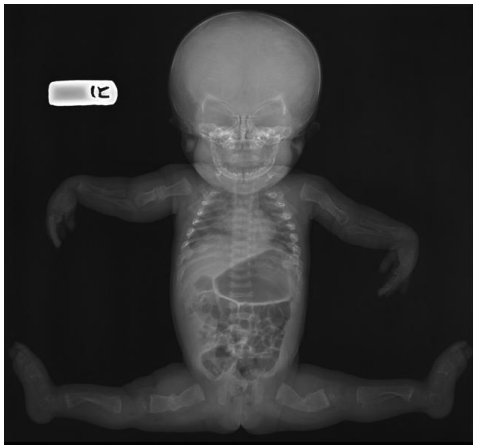
- Clasificación de Sillence (1979)

Table 7 *A nomenclature for OI syndromes*

Suggested numerical type	*Qualifying suffixes*	*Mode of inheritance*	*Reported synonyms and eponyms*
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IV	Congenita tarda	Autosomal dominant	Dominantly inherited OI with normal sclerae, Osteopsathyrosis idiopathica of Lobstein, Ekman–Lobstein disease

- Letal perinatal
- Huesos largos: arqueados y cortos
- Escleras azules o grises
- Cráneo grande y blando
- Muerte por fallo respiratorio (tórax pequeño, fx costales, neumonía..)







Sillence. J Med Genet 1979

OI tipo III

- Clasificación de Sillence (1979)

Table 7 *A nomenclature for OI syndromes*

Suggested numerical type	*Qualifying suffixes*	*Mode of inheritance*	*Reported synonyms and eponyms*
I	Congenita tarda	Autosomal dominant	Dominantly inherited OI with distinctly blue sclerae, Van der Hoeve's syndrome, Trias fragilitas ossium, OI tarda levis, OI tarda type II, OI (mild long bone deformity), Eddowe's syndrome
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IV	Congenita tarda	Autosomal dominant	Dominantly inherited OI with normal sclerae, Osteopsathyrosis idiopathica of Lobstein, Ekman–Lobstein disease

- Progresiva deformante
- La más grave NO letal
- Cientos de fracturas
- Facies triangular, frente abombada
- Escleras azules o grises
- Dentinogénesis imperfecta
- Compresiones vertebrales/ escoliosis
- Platibasia o impresión basilar
- Estatura baja
- Pop corns, coxa vara

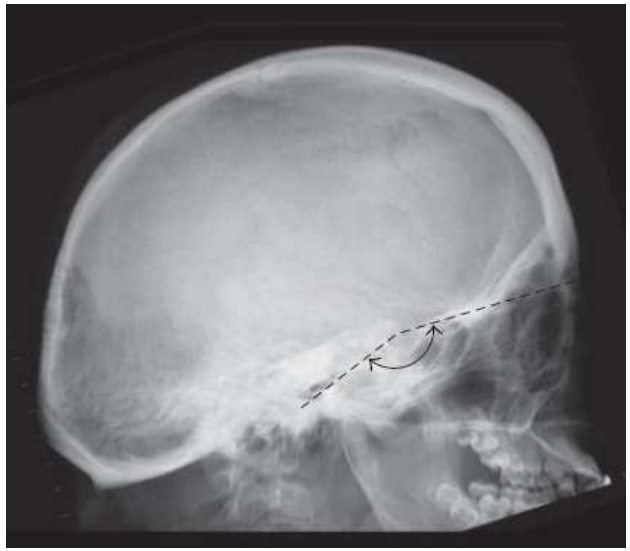


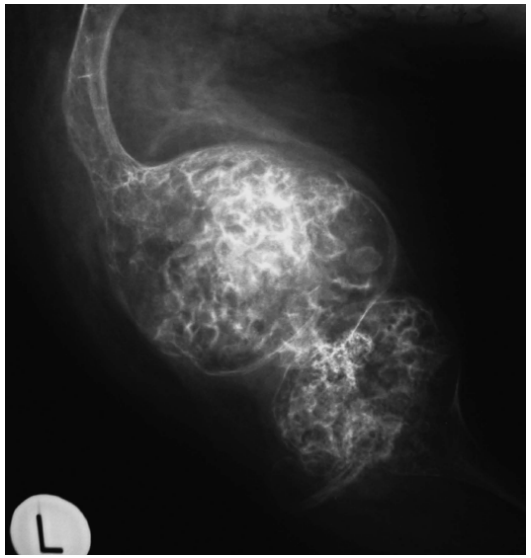
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Sillence. J Med Genet 1979

OI tipo III









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OI tipo IV

- Clasificación de Sillence (1979)

Table 7 *A nomenclature for OI syndromes*

Suggested numerical type	*Qualifying suffixes*	*Mode of inheritance*	*Reported synonyms and eponyms*
I	Congenita tarda	Autosomal dominant	Dominantly inherited OI with distinctly blue sclerae, Van der Hoeve's syndrome, Trias fragilitas ossium, OI tarda levis, OI tarda type II, OI (mild long bone deformity), Eddowe's syndrome
II	Congenita (always)	Autosomal recessive	Lethal perinatal OI, OI letalis Vrolik, Lethal OI congenita
III	Congenita (tarda)	Autosomal recessive	Progressively deforming OI with normal sclerae, OI congenita, OI tarda gravis, OI (severe long bone deformity), OI congenita type Vrolik, Periosteal dysplasia of Porak and Durante, Osteopsathyrosis idiopathica of Lobstein
IV	Congenita tarda	Autosomal dominant	Dominantly inherited OI with normal sclerae, Osteopsathyrosis idiopathica of Lobstein, Ekman–Lobstein disease

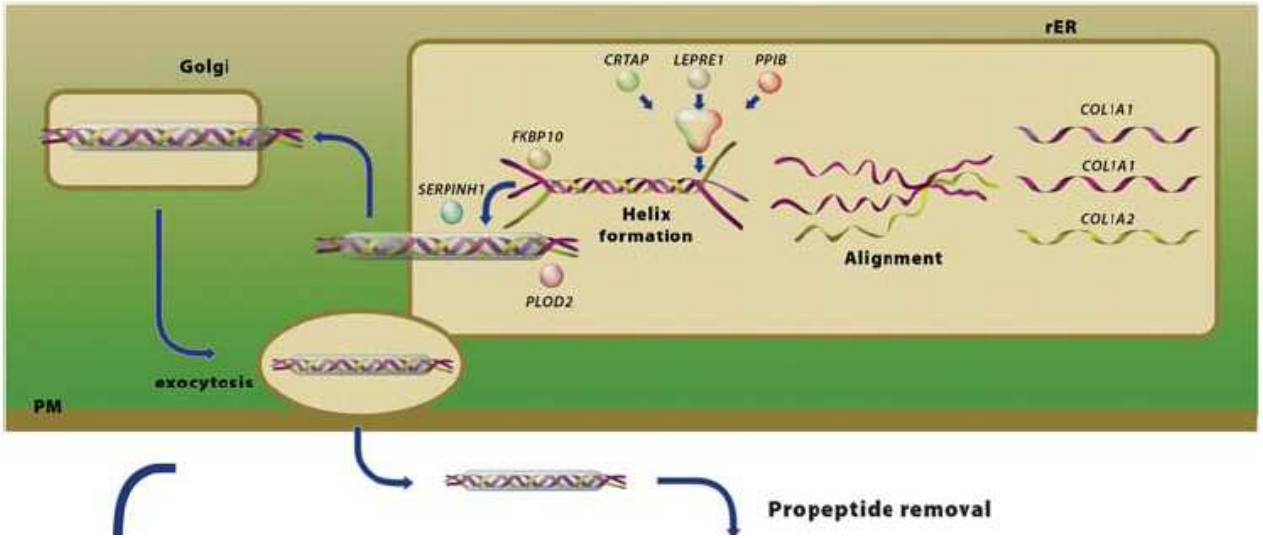
- Amplio rango fenotípico I-----III
- Docenas de fracturas huesos largos
- Pueden alcanzar deambulación
- Variable:
  - Escleras azules
  - Dentinogénesis imperfecta
  - Impresión basilar
  - Hipoacusia
  - Talla



Sillence. J Med Genet 1979

Clasificación de Sillence- correlación genética

	TIPO I	TIPO II	TIPO III	TIPO IV
Severidad	Leve	Letal	Grave	Moderada
Mutaciones	Codón STOP prematuro COL1A1/A2	Sustitución glicina COL1A1/A2	Sustitución glicina COL1A1/A2	Sustitución glicina COL1A1/A2
Correlación	Déficit ***CUANTITATIVO*** colágeno	Déficit ***CUALITATIVO*** de colágeno		



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La clasificación ha ido cambiando con los años

- Tipo IV → reclasificación V, VI, VII **"Expanded Sillence classification"**

Type	Clinical severity	Typical features	Typically associated mutations*
I	Mild non-deforming osteogenesis imperfecta	Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta	Premature stop codon in *COL1A1*
II	Perinatal lethal	Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera	Glycine substitutions in *COL1A1* or *COL1A2*
III	Severely deforming	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
IV	Moderately deforming	Moderately short; mild to moderate scoliosis; greyish or white sclera; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
V	Moderately deforming	Mild to moderate short stature; dislocation of radial head; mineralised interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta	Unknown
VI	Moderately to severely deforming	Moderately short; scoliosis; accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation; white sclera; no dentinogenesis imperfecta	Unknown
VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta	Unknown

*May or may not be detectable in a given patient.

Table 1: **Expanded Sillence classification of osteogenesis imperfecta**



Rauch, Glorieux. Lancet 2004

OI tipo V

Type	Clinical severity	Typical features	Typically associated mutations*
I	Mild non-deforming osteogenesis imperfecta	Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta	Premature stop codon in *COL1A1*
II	Perinatal lethal	Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera	Glycine substitutions in *COL1A1* or *COL1A2*
III	Severely deforming	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
IV	Moderately deforming	Moderately short; mild to moderate scoliosis; greyish or white sclera; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
V	Moderately deforming	Mild to moderate short stature; dislocation of radial head; mineralised interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta	Unknown
VI	Moderately to severely deforming	Moderately short; scoliosis; accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation; white sclera; no dentinogenesis imperfecta	Unknown
VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta	Unknown

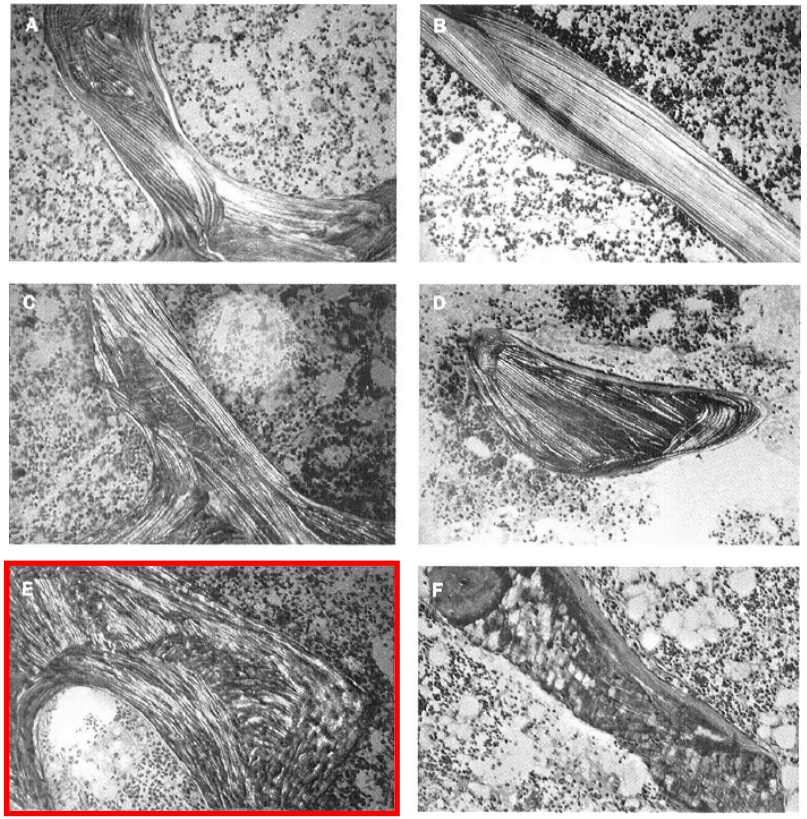
*May or may not be detectable in a given patient.

Table 1: **Expanded Sillence classification of osteogenesis imperfecta**



OI tipo V

- Biopsia ósea característica: disposición de lamelas irregular, muy desorganizada



Rauch, Glorieux. Lancet 2004

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OI tipo V

- Biopsia ósea característica: disposición de lamelas irregular, muy desorganizada
- Características clínicas:
  - Calcificación membrana interosea cúbito-radio – no pueden realizar prono-supinación
  - Callo óseo hiperplásico
  - Banda metafisaria radiopaca







Rauch, Glorieux. Lancet 2004

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OI tipo V

REPORT

A Mutation in the 5′-UTR of *IFITM5* Creates an In-Frame Start Codon and Causes Autosomal-Dominant Osteogenesis Imperfecta Type V with Hyperplastic Callus

Oliver Semler,[2,11] Lutz Garbes,[1,4,7,11] Katharina Keupp,[1,4,8,11] Daniel Swan,[3] Katharina Zimmermann,[1] Jutta Becker,[1] Sandra Iden,[8] Brunhilde Wirth,[1,4,7] Peer Eysel,[5] Friederike Koerber,[6] Eckhard Schoenau,[2] Stefan K. Bohlander,[9,10] Bernd Wollnik,[1,4,8] and Christian Netzer[1,*]

The American Journal of Human Genetics *91*, 349–357, August 10, 2012 349



OI tipo VI

Type	Clinical severity	Typical features	Typically associated mutations*
I	Mild non-deforming osteogenesis imperfecta	Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta	Premature stop codon in *COL1A1*
II	Perinatal lethal	Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera	Glycine substitutions in *COL1A1* or *COL1A2*
III	Severely deforming	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
IV	Moderately deforming	Moderately short; mild to moderate scoliosis; greyish or white sclera; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
V	Moderately deforming	Mild to moderate short stature; dislocation of radial head; mineralised interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta	Unknown
VI	Moderately to severely deforming	Moderately short; scoliosis; accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation; white sclera; no dentinogenesis imperfecta	Unknown
VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta	Unknown

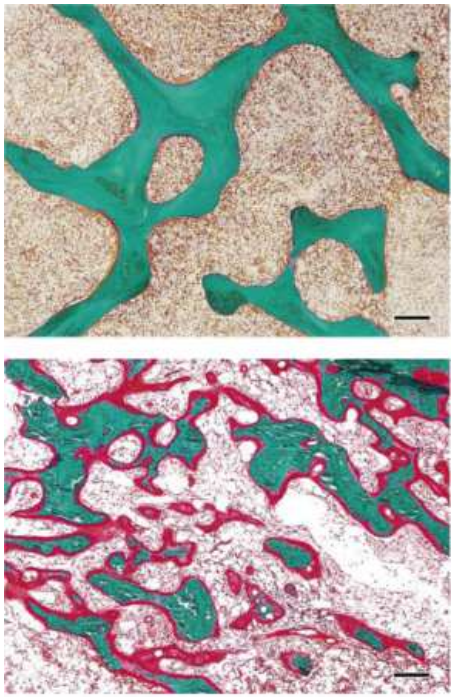
*May or may not be detectable in a given patient.

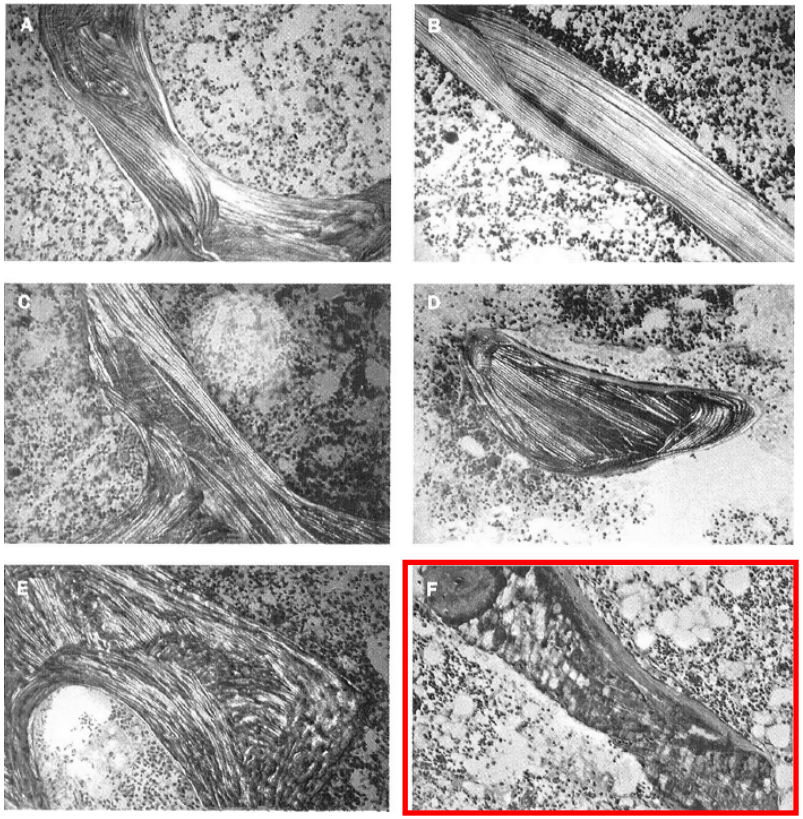
Table 1: **Expanded Sillence classification of osteogenesis imperfecta**



OI tipo VI

- Biopsia ósea: osteoide grueso y patrón de lamelación en escamas de pez
  - Déficit mineralización





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OI tipo VI

- Biopsia ósea: osteoide grueso y patrón de lamelación en escamas de pez
  - Déficit mineralización

- Moderada-grave



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OI tipo VI

Published in final edited form as:
J Bone Miner Res. 2011 December ; 26(12): 2798–2803. doi:10.1002/jbmr.487.

Mutations in *SERPINF1* Cause Osteogenesis Imperfecta Type VI

Erica P. Homan, BA[1,*], Frank Rauch, MD[2,*], Ingo Grafe, MD[1], Caressa Lietman, BS[1], Jennifer A. Doll, PhD[3], Brian Dawson, BS[1], Terry Bertin, BA[1], Dobrawa Napierala, PhD[1], Roy Morello, PhD[4], Richard Gibbs, PhD[1], Lisa White, PhD[1], Rika Miki, PhD[5,6], Daniel H. Cohn, PhD[5,6], Susan Crawford, MD[3], Rose Travers, RT[2], Francis H. Glorieux, MD PhD[2], and Brendan Lee, MD PhD[1,7]

[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA

[2]Genetics Unit, Shriners Hospital for Children and McGill University, 1529 Cedar Avenue, Montréal, Québec, Canada H3G 1A6

- PEDF: Pigment Epithelium Derived Factor
- Niveles indetectables

- PEDF:
  - Potente inhibición de la angiogénesis
  - Inhibición de osteoclastos i osteoclastogénesis a través de la osteoprotegerina y RANKL

- Pobre respuesta a tratamiento con bifosfonatos



OI tipo VII

Type	Clinical severity	Typical features	Typically associated mutations*
I	Mild non-deforming osteogenesis imperfecta	Normal height or mild short stature; blue sclera; no dentinogenesis imperfecta	Premature stop codon in *COL1A1*
II	Perinatal lethal	Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera	Glycine substitutions in *COL1A1* or *COL1A2*
III	Severely deforming	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfecta	Glycine substitutions in *COL1A1* or *COL1A2*
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VII	Moderately deforming	Mild short stature; short humeri and femora; coxa vara; white sclera; no dentinogenesis imperfecta	Unknown

*May or may not be detectable in a given patient.

Table 1: **Expanded Sillence classification of osteogenesis imperfecta**

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OI tipo VII - CRTAP

CRTAP Is Required for Prolyl 3-Hydroxylation and Mutations Cause Recessive Osteogenesis Imperfecta

Roy Morello,[1] Terry K. Bertin,[1] Yuqing Chen,[1,11] John Hicks,[2] Laura Tonachini,[3] Massimiliano Monticone,[3] Patrizio Castagnola,[3] Frank Rauch,[4,5] Francis H. Glorieux,[4,5] Janice Vranka,[6,7] Hans Peter Bächinger,[6,7] James M. Pace,[8] Ulrike Schwarze,[8] Peter H. Byers,[8] MaryAnn Weis,[9] Russell J. Fernandes,[9] David R. Eyre,[9] Zhenqiang Yao,[10] Brendan F. Boyce,[10] and Brendan Lee[1,11,12,*]
[1] Department of Molecular and Human Genetics
[2] Department of Pathology, Texas Children's Hospital
Baylor College of Medicine, Houston, TX 77030, USA
[3] Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy
[4] Genetics Unit, Shriners Hospital for Children, Montreal, Canada
[5] McGill University, Montreal, Canada
[6] Shriners Hospital for Children, Portland, OR 97201, USA
[7] Department of Biochemistry and Molecular Biology, Oregon Health & Science University, OR 97239, USA
[8] Department of Pathology
[9] Department of Orthopaedics and Sports Medicine
University of Washington, Seattle, WA 98195, USA
[10] Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY 14627, USA
[11] Howard Hughes Medical Institute, Houston, TX 77030, USA
[12] One Baylor Plaza, Room 635E, Houston, TX 77030, USA
*Contact: blee@bcm.tmc.edu
DOI 10.1016/j.cell.2006.08.039

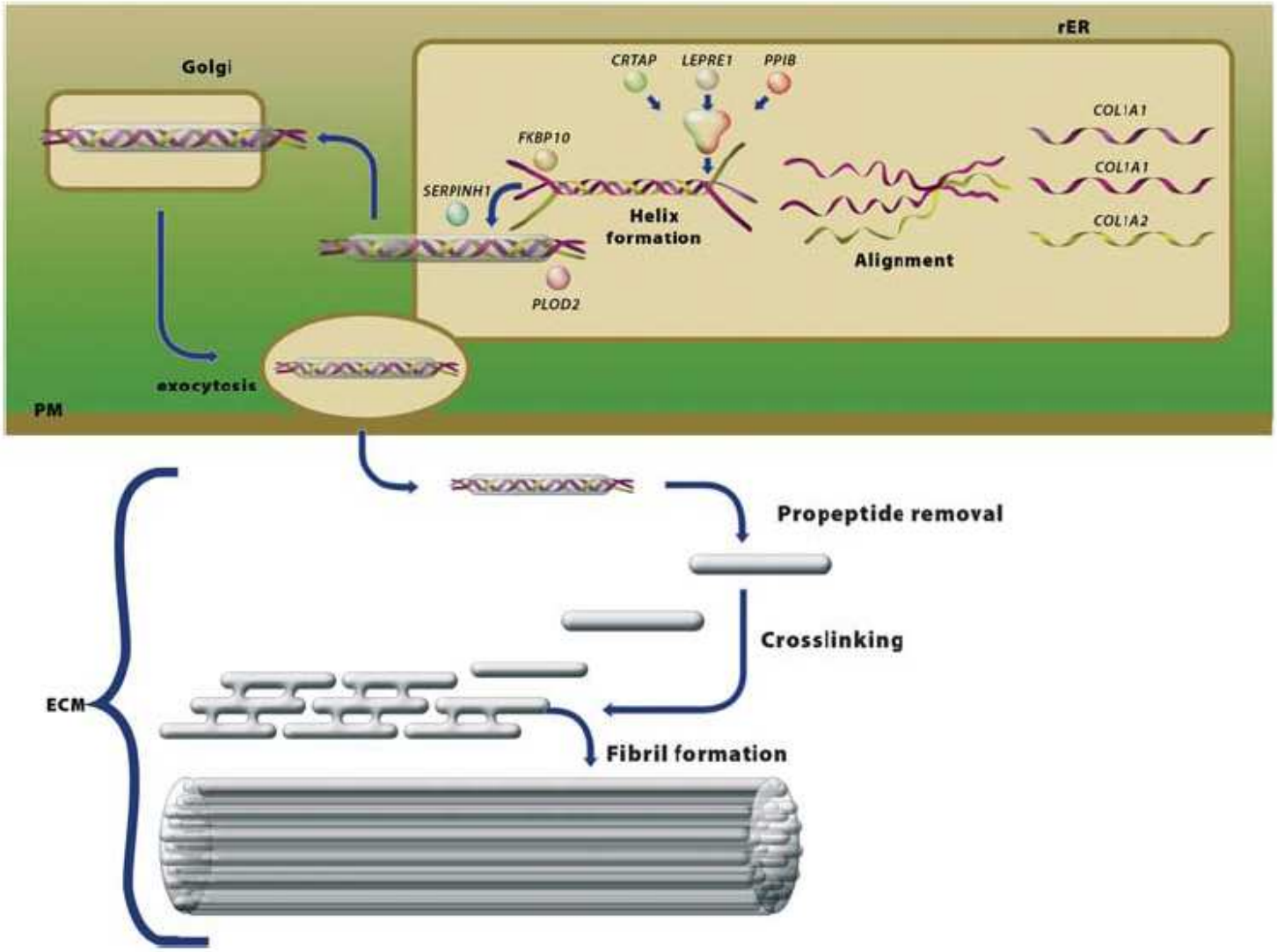




- Fenotipo moderado-grave (letal)
  - Déf. de crecimiento
  - Rizomelia
  - Coxa vara
  - Huesos wormianos
  - Calcificaciones Pop-corn en epífisis

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Complejo 3-hidroxilación (CRTAP/LEPRE/PPIB)



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Nuevas mutaciones

Nature Genetics **39**, 359 - 365 (2007)
Published online: 4 February 2007 | Corrected online: 26 June 2008 | d

There is a Corrigendum (July 2008) associated with this Letter.

Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta

Wayne A Cabral[1,8], Weizhong Chang[1,8], Aileen M Barnes[1], MaryAnn Weis[2], Melissa A Scott[2], Sergey Leikin[3], Elena Makareeva[3], Natalia V Kuznetsova[3], Kenneth N Rosenbaum[4], Cynthia J Tifft[4], Dorothy I Bulas[5], Chahira Kozma[6], Peter A Smith[7], David R Eyre[2] & Joan C Marini[1]

A recessive form of severe osteogenesis imperfecta that is not caused by mutations in type I collagen has long been suspected. Mutations in human *CRTAP* (cartilage-associated protein) causing recessive bone disease have been reported. CRTAP forms a complex with cyclophilin B and prolyl 3-hydroxylase 1, which is encoded by *LEPRE1* and hydroxylates one residue in type I collagen, α1(I)Pro986. We present the first five cases of a new recessive bone disorder resulting from null *LEPRE1* alleles; its



Nuevas mutaciones

PPIB Mutations Cause Severe Osteogenesis Imperfecta

Fleur S. van Dijk,[1] Isabel M. Nesbitt,[6] Eline H. Zwikstra,[1] Peter G.J. Nikkels,[7] Sander R. Piersma,[2] Silvina A. Fratantoni,[2] Connie R. Jimenez,[2] Margriet Huizer,[1] Alice C. Morsman,[6] Jan M. Cobben,[8] Mirjam H.H. van Roij,[1] Mariet W. Elting,[1] Jonathan I.M.L. Verbeke,[3] Liliane C.D. Wijnaendts,[4] Nick J. Shaw,[9] Wolfgang Högler,[9] Carole McKeown,[10] Erik A. Sistermans,[1] Ann Dalton,[6] Hanne Meijers-Heijboer,[1] and Gerard Pals[5,*]

The American Journal of Human Genetics *85*, 521–527, October 9, 2009 **521**



Nuevas mutaciones → Nuevos subtipos

OI Type	Gene Defect	Phenotype
Dominant inheritance		
Classical Sillence types		
I	*COL1A1* null allele	Mild, nondeforming
II	*COL1A1* or *COL1A2*	Lethal perinatal
III	*COL1A1* or *COL1A2*	Progressively deforming
IV	*COL1A1* or *COL1A2*	Moderately deforming
COL1-mutation negative		
V	*IFITM5*	Distinct histology
Recessive inheritance		
Mineralization defect		
VI	*SERPINF1*	Distinct histology
3-Hydroxylation defects		
VII	*CRTAP*	Severe to lethal
VIII	*LEPRE1*	Severe to lethal
IX	*PPIB*	Moderate to lethal



OI tipo VIII – LEPRE1

- Fenotipo Moderado - Grave (letal)
  - Fracturas se inician en útero
  - Deformidades: Huesos largos cortos, curvados y deformados, escoliosis
  - Coxa vara
  - Rizomielia



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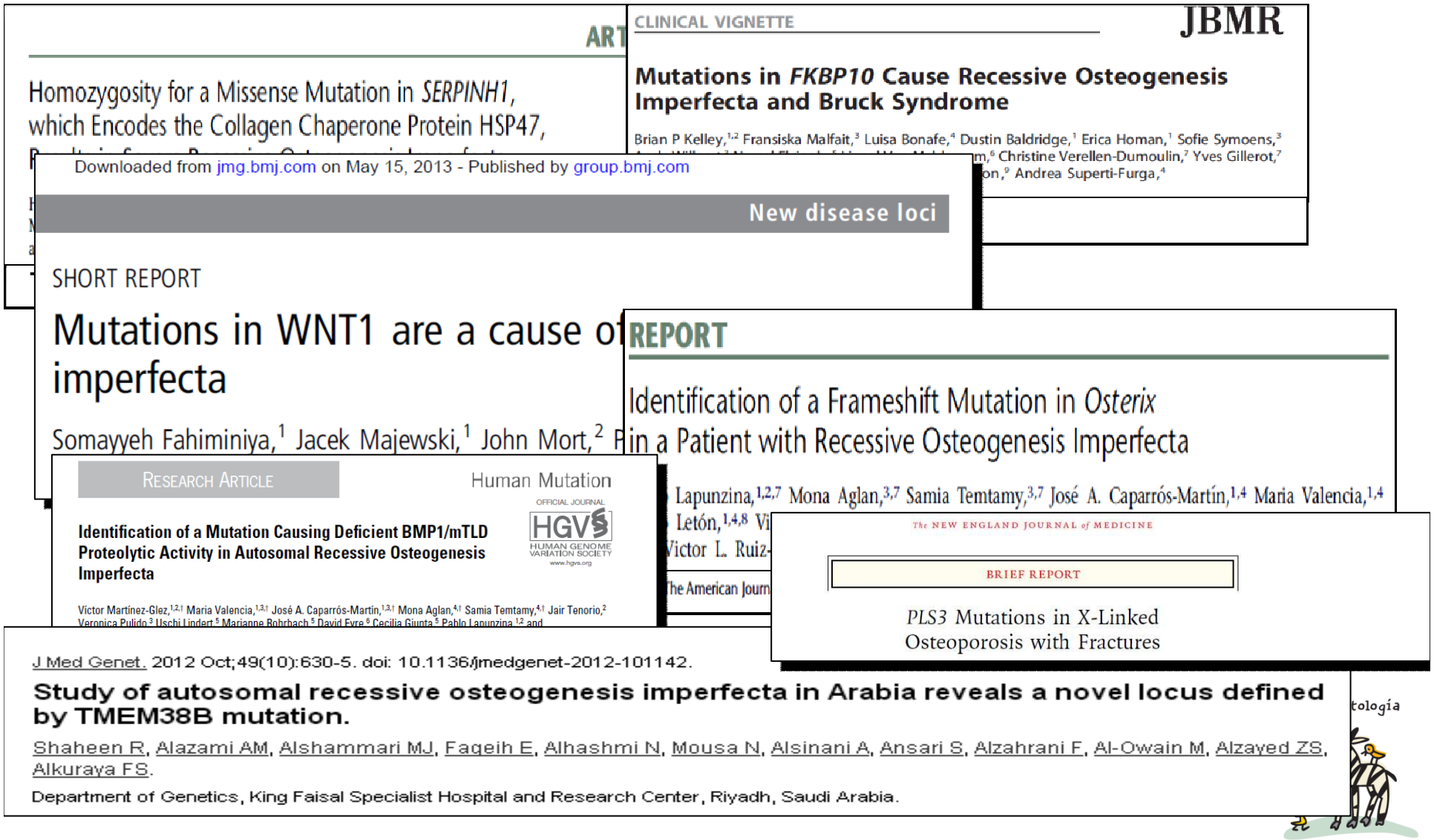
OI tipo IX - PPIB

- Fenotipo moderado – grave
- Similar a VII y VIII, sin rizomielia



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En los últimos años nuevos genes...



Homozygosity for a Missense Mutation in *SERPINH1*, which Encodes the Collagen Chaperone Protein HSP47,

CLINICAL VIGNETTE

JBMR

Mutations in *FKBP10* Cause Recessive Osteogenesis Imperfecta and Bruck Syndrome

Brian P Kelley,[1,2] Fransiska Malfait,[3] Luisa Bonafe,[4] Dustin Baldridge,[1] Erica Homan,[1] Sofie Symoens,[3] Christine Verellen-Dumoulin,[7] Yves Gillerot,[7] Andrea Superti-Furga,[4]

Downloaded from jmg.bmj.com on May 15, 2013 - Published by group.bmj.com

New disease loci

SHORT REPORT

Mutations in WNT1 are a cause of imperfecta

Somayyeh Fahiminiya,[1] Jacek Majewski,[1] John Mort,[2]

REPORT

Identification of a Frameshift Mutation in *Osterix* in a Patient with Recessive Osteogenesis Imperfecta

Lapunzina,[1,2,7] Mona Aglan,[3,7] Samia Temtamy,[3,7] José A. Caparrós-Martín,[1,4] Maria Valencia,[1,4] Letón,[1,4,8] Vi

Victor L. Ruiz-

The American Journ

RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL

HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Identification of a Mutation Causing Deficient BMP1/mTLD Proteolytic Activity in Autosomal Recessive Osteogenesis Imperfecta

Víctor Martínez-Glez,[1,2,†] Maria Valencia,[1,3,†] José A. Caparrós-Martín,[1,3,†] Mona Aglan,[4,†] Samia Temtamy,[4,†] Jair Tenorio,[2] Verónica Pulido,[3] Uschi Lindert,[5] Marianne Rohrbach,[5] David Eyre,[6] Cecilia Giunta,[5] Pablo Lapunzina,[1,2] and

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

PLS3 Mutations in X-Linked Osteoporosis with Fractures

J Med Genet. 2012 Oct;49(10):630-5. doi: 10.1136/jmedgenet-2012-101142.

Study of autosomal recessive osteogenesis imperfecta in Arabia reveals a novel locus defined by TMEM38B mutation.

Shaheen R, Alazami AM, Alshammari MJ, Faqeih E, Alhashmi N, Mousa N, Alsinani A, Ansari S, Alzahrani F, Al-Owain M, Alzayed ZS, Alkuraya FS.

Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

tología

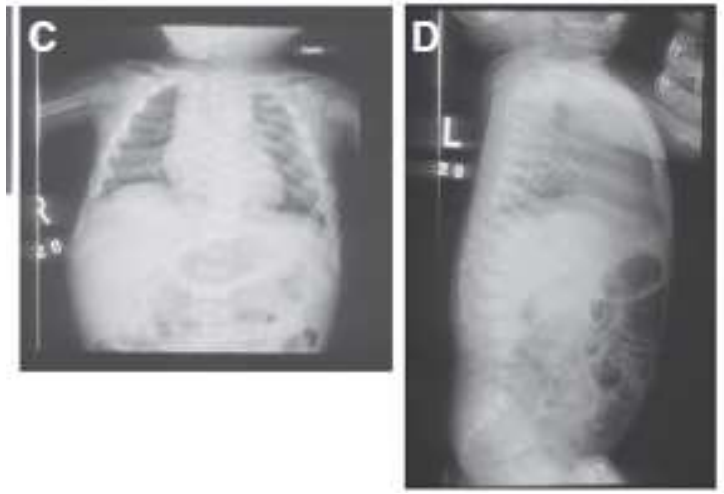
En los últimos años nuevos genes... *SERPINH1*

ARTICLE

Homozygosity for a Missense Mutation in *SERPINH1*, which Encodes the Collagen Chaperone Protein HSP47, Results in Severe Recessive Osteogenesis Imperfecta

Helena E. Christiansen,[1,7] Ulrike Schwarze,[2,7] Shawna M. Pyott,[2] Abdulrahman AlSwaid,[3] Mohammed Al Balwi,[4] Shatha Alrasheed,[3] Melanie G. Pepin,[2] Mary Ann Weis,[5] David R. Eyre,[5] and Peter H. Byers[2,6,*]

The American Journal of Human Genetics *86*, 389–398, March 12, 2010 389





Reumatología

En los últimos años nuevos genes... *FKBP10*

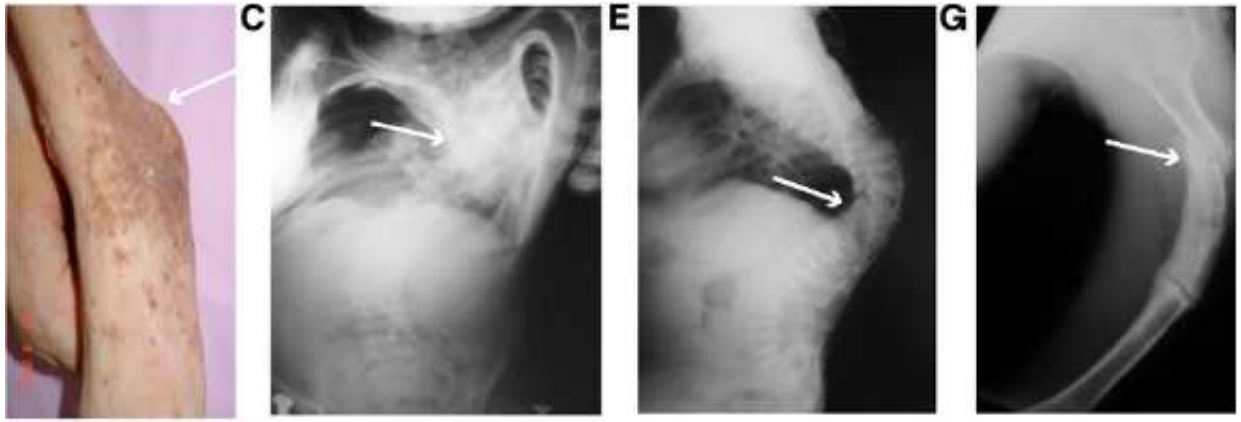
ARTICLE

Mutations in the Gene Encoding the RER Protein FKBP65 Cause Autosomal-Recessive Osteogenesis Imperfecta

Yasemin Alanay,[1] Hrispima Avaygan,[5] Natalia Camacho,[5] G. Eda Utine,[1] Koray Boduroglu,[1] Dilek Aktas,[1] Mehmet Alikasifoglu,[1] Ergul Tuncbilek,[1] Diclehan Orhan,[3] Filiz Tiker Bakar,[4] Bernard Zabel,[9] Andrea Superti-Furga,[9] Leena Bruckner-Tuderman,[10] Cindy J.R. Curry,[11] Shawna Pyott,[12] Peter H. Byers,[12] David R. Eyre,[13] Dustin Baldridge,[14] Brendan Lee,[14] Amy E. Merrill,[5] Elaine C. Davis,[15] Daniel H. Cohn,[6,7,16] Nurten Akarsu,[2] and Deborah Krakow[5,6,8,16,*]

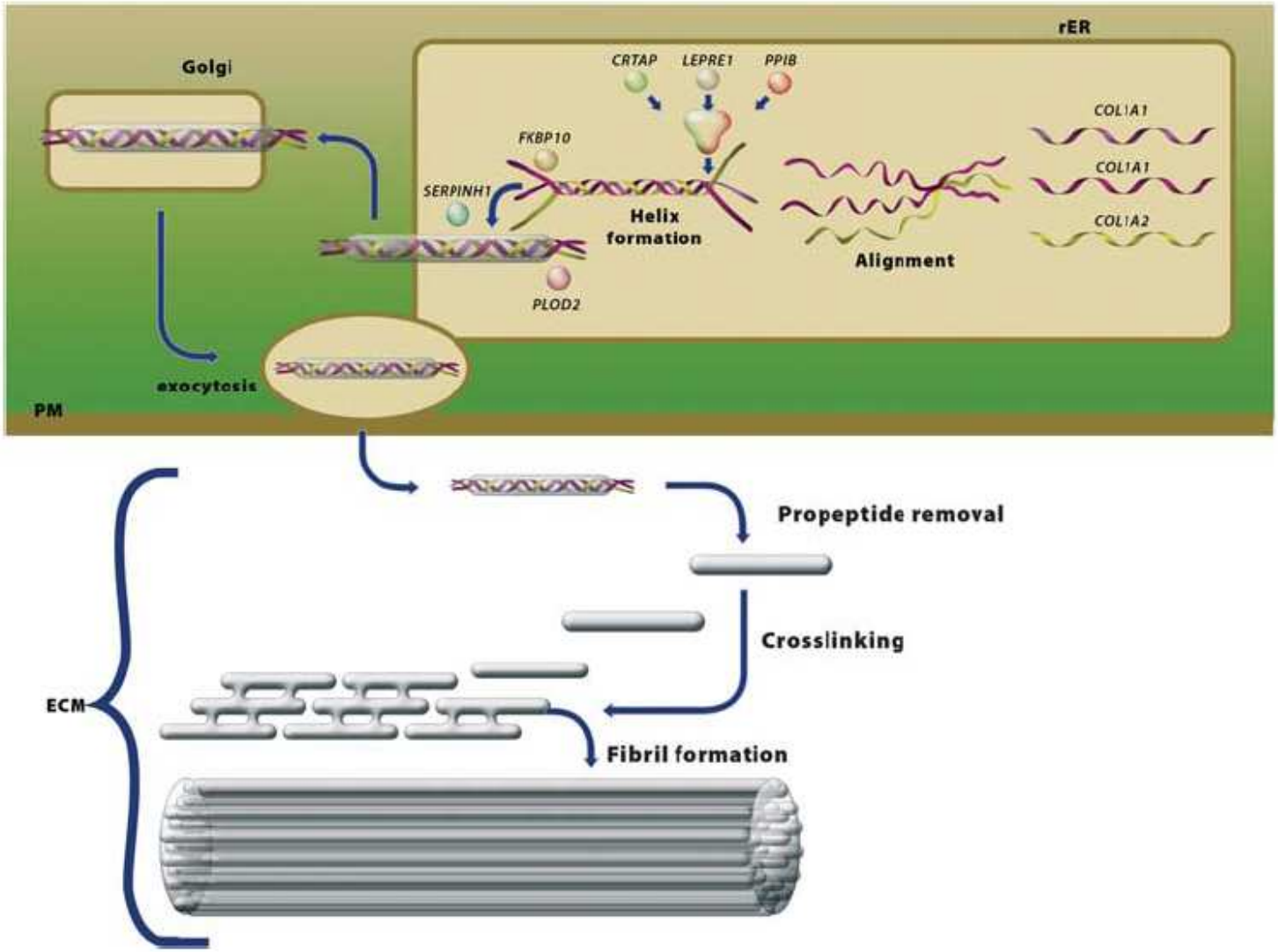
Osteogenesis imperfecta is a clinically and genetically heterogeneous brittle bone disorder that results from defects in the synthesis, structure, or posttranslational modification of type I procollagen. Dominant forms of OI result from mutations in *COL1A1* or *COL1A2*, which encode the chains of the type I procollagen heterotrimer. The mildest form of OI typically results from diminished synthesis of structurally normal type I procollagen, whereas moderately severe to lethal forms of OI usually result from structural defects in one of the type I procollagen chains. Recessively inherited OI, usually phenotypically severe, has recently been shown to result from defects in the prolyl-3-hydroxylase complex that lead to the absence of a single 3-hydroxyproline at residue 986 of the α1(I) triple helical domain. We studied a cohort of five consanguineous Turkish families, originating from the Black Sea region of Turkey, with moderately severe recessively inherited OI and identified a novel locus for OI on chromosome 17. In these families, and in a Mexican-American family, homozygosity for mutations in *FKBP10*, which encodes FKBP65, a chaperone that participates in type I procollagen folding, was identified. Further, we determined that *FKBP10* mutations affect type I procollagen secretion. These findings identify a previously unrecognized mechanism in the pathogenesis of OI.

The American Journal of Human Genetics *86*, 551–559, April 9, 2010 551



Reumatología

Defecto de chaperonas (*SERPINH1/FKBP10*)



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	OI Type	Inheritance	Phenotype	Gene Defect
Classical Sillence Types	I	AD	Mild	Null *COL1A1* allele
	II	AD	Lethal	*COL71A1/COL1A2*
	III	AD	Progressive Deforming	*COL1A1/COL1A2*
	IV	AD	Moderate	*COL1A1/COL1A2*
Unknown Etiology	V	AD	Distinctive Histology	Unknown
	VI	AR?	Mineralization Defect	Unknown
3-Hydroxylation Defects	VII	AR	Severe (Hypomorphic) Lethal (Null)	*CRTAP*
	VIII	AR	Severe to Lethal	*LEPRE1* (P3H1)
	IX	AR	Moderate to Severe	*PPIB* (CyPB)
Chaperone Defects	X	AR	Severe to Lethal	*SERPINH1* (HSP47)
	XI	AR	Progressive Deforming Bruck Syndrome?	*FKBP10* (FKBP65)



En los últimos años nuevos genes... *SP7/OSTERIX*

REPORT

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Pablo Lapunzina,[1,2,7] Mona Aglan,[3,7] Samia Temtamy,[3,7] José A. Caparrós-Martín,[1,4] Maria Valencia,[1,4] Rocío Letón,[1,4,8] Victor Martínez-Glez,[1,2] Rasha Elhossini,[3] Khalda Amr,[3] Nuria Vilaboa,[5,6] and Victor L. Ruiz-Perez[1,4,*]

110 The American Journal of Human Genetics *87*, 110–114, July 9, 2010











Reumatología

En los últimos años nuevos genes... *BMP1/mTLD*

RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL

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www.hgvs.org

Identification of a Mutation Causing Deficient BMP1/mTLD Proteolytic Activity in Autosomal Recessive Osteogenesis Imperfecta

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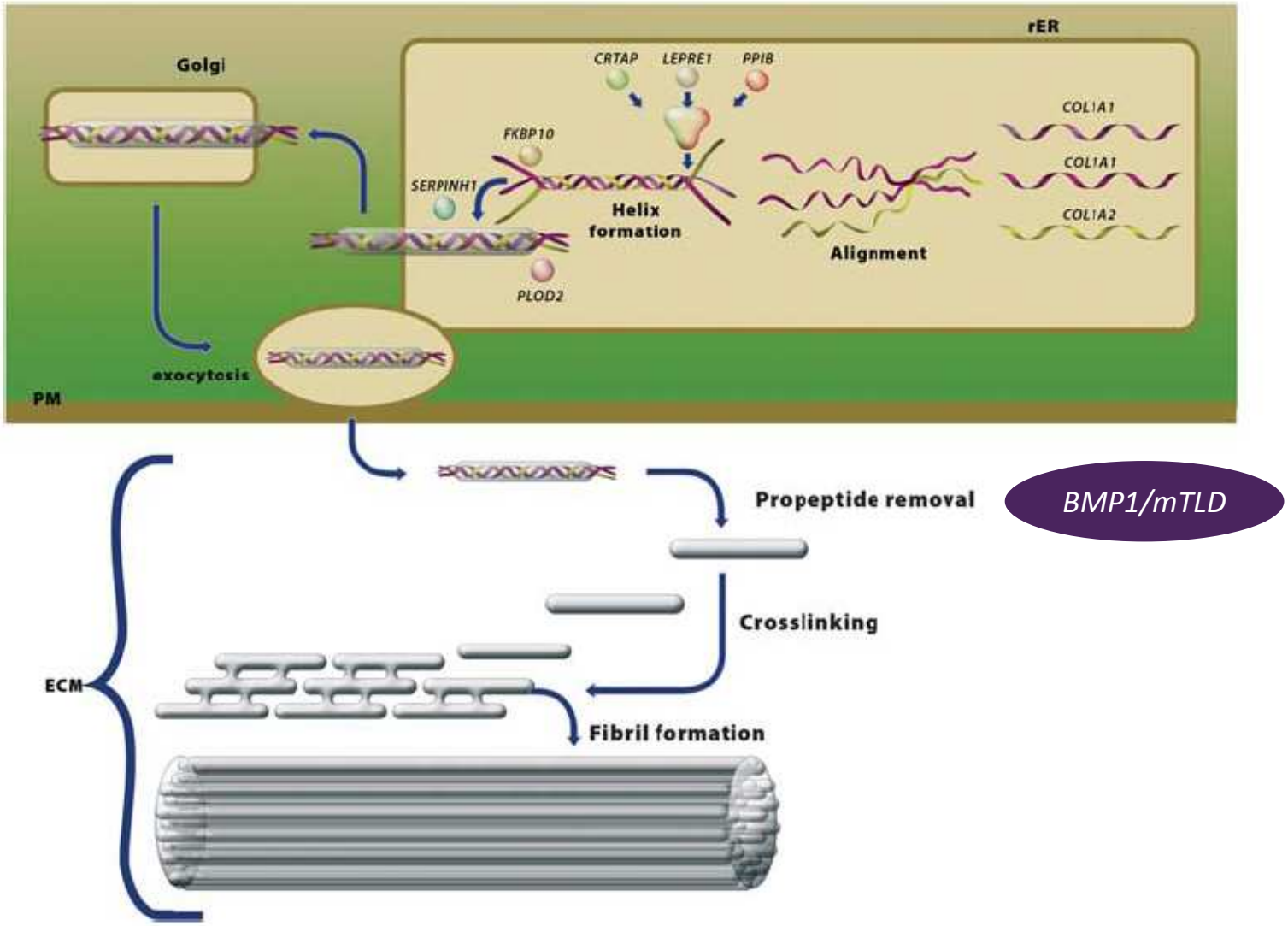
[1]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [2]Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz-IdiPaz, Universidad Autónoma de Madrid, Madrid, Spain; [3]Instituto de Investigaciones Biomédicas, Consejo Superior de Investigaciones Científicas-Universidad Autónoma de Madrid, Madrid, Spain; [4]Human Genetics and Genome Research Division, National Research Centre, Cairo, Egypt; [5]Division of Metabolism, Connective Tissue Unit, University Children's Hospital and Children's Research Center, Zurich, Switzerland; [6]Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, Washington

Communicated by Raymond Dalgleish

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En los últimos años nuevos genes... *BMP1/mTLD*



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En los últimos años nuevos genes... *BMP1/mTLD*

RESEARCH ARTICLE

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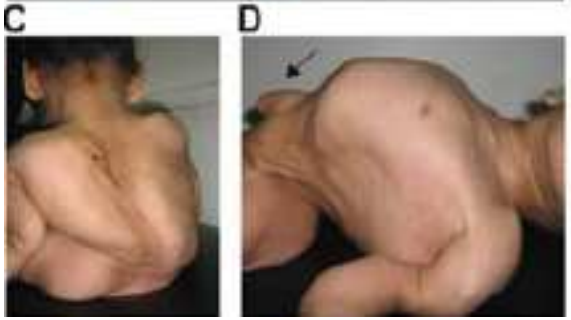
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Reumatología

En los últimos años nuevos genes... *TMEM38B*

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Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

- Codifica un canal de cationes involucrado en liberar calcio de los reservorios intracelulares



Reumatología

En los últimos años nuevos genes... *WNT1*

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SHORT REPORT

Mutations in WNT1 are a cause of osteogenesis imperfecta

Somayyeh Fahiminiya,[1] Jacek Majewski,[1] John Mort,[2] Pierre Moffatt,[2] Francis H Glorieux,[2] Frank Rauch[2]



- Talla baja
- Baja DMO
- Compresiones vertebrales
- Múltiples fx huesos largos



En los últimos años nuevos genes... *PLS3*

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

PLS3 Mutations in X-Linked Osteoporosis with Fractures

Fleur S. van Dijk, M.D., Ph.D., M. Carola Zillikens, M.D., Ph.D., Dimitra Micha, Ph.D., Markus Riessland, Ph.D., Carlo L.M. Marcelis, Ph.D., Christine E. de Die-Smulders, M.D., Ph.D., Janine Milbradt, B.S., Anton A. Franken, M.D., Ph.D., Arjan J. Harsevoort, M.S., Klaske D. Lichtenbelt, M.D., Hans E. Pruijs, M.D., Ph.D., M. Estela Rubio-Gozalbo, M.D., Ph.D., Rolf Zwertbroek, M.D., Youssef Moutaouakil, M.S., Jaqueline Egthuijsen, M.S., Matthias Hammerschmidt, Ph.D., Renate Bijman, B.S., Cor M. Semeins, M.S., Astrid D. Bakker, Ph.D., Vincent Everts, Ph.D., Jenneke Klein-Nulend, Ph.D., Natalia Campos-Obando, M.D., Albert Hofman M.D., Ph.D., Gerard J. te Meerman, Ph.D., Annemieke J.M.H. Verkerk, Ph.D., André G. Uitterlinden, Ph.D., Alessandra Maugeri, Ph.D., Erik A. Sistermans, Ph.D., Quinten Waisfisz, Ph.D., Hanne Meijers-Heijboer, M.D., Ph.D., Brunhilde Wirth, Ph.D., Marleen E.H. Simon, M.D., and Gerard Pals, Ph.D.

SUMMARY

Plastin 3 (PLS3), a protein involved in the formation of filamentous actin (F-actin) bundles, appears to be important in human bone health, on the basis of pathogenic variants in PLS3 in five families with X-linked osteoporosis and osteoporotic fractures that we report here. The bone-regulatory properties of PLS3 were supported by in vivo analyses in zebrafish. Furthermore, in an additional five families (described in less detail) referred for diagnosis or ruling out of osteogenesis imperfecta type I, a rare variant (rs140121121) in PLS3 was found. This variant was also associated with a risk of fracture among elderly heterozygous women that was two times as high as that among noncarriers, which indicates that genetic variation in PLS3 is a novel etiologic factor involved in common, multifactorial osteoporosis.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Pals at the Center for Connective Tissue Research, Department of Clinical Genetics, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, the Netherlands, or at g.pals@vumc.nl.

Drs. van Dijk, Zillikens, Micha, and Riessland contributed equally to this article.

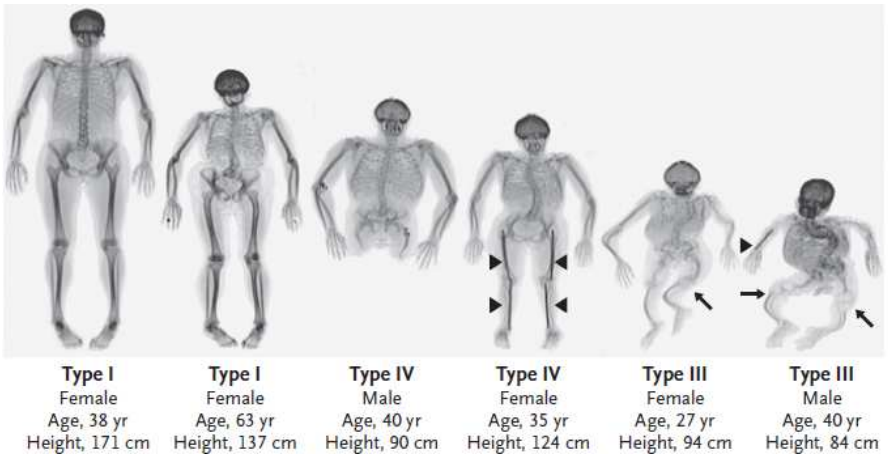
This article was published on October 2, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1308223



Controversias en la clasificación

- Severidad:
  - Leve
  - Moderada
  - Grave – letal



- Defecto molecular

Reumatología

Diagnóstico de OI

- Clínico





- Densitometría ósea

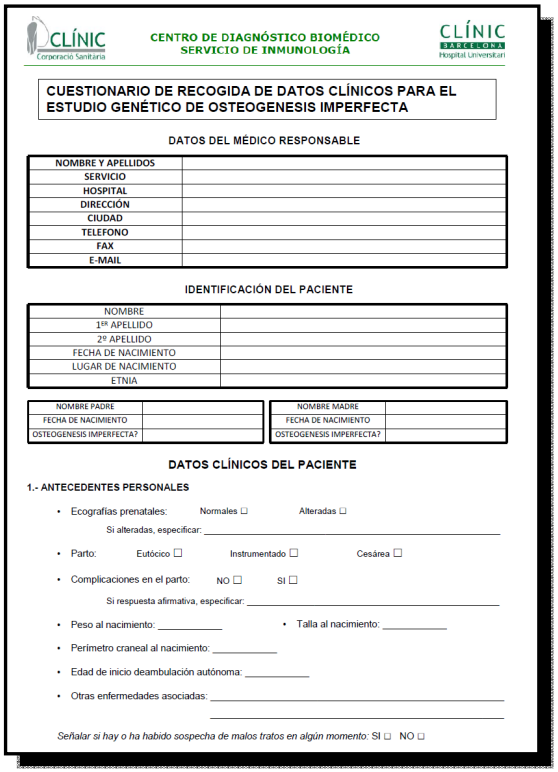
- Estudio genético
  - Relación fenotipo-genotipo
  - Confirmación
  - Consejo genético

Reumatología

Experiencia HSJD – H.Clínic

- Estudio genético Servicio Inmunología H. Clínic

- Genes/Mutaciones:
  - COL1A1
  - COL1A2
  - LEPRE
  - CRTAP
  - PPIB
  - SERPINF1
  - FKBP10
  - SP7



CLÍNIC Corporació Sanitària — CENTRO DE DIAGNÓSTICO BIOMÉDICO SERVICIO DE INMUNOLOGÍA — CLÍNIC BARCELONA Hospital Universitari

CUESTIONARIO DE RECOGIDA DE DATOS CLÍNICOS PARA EL ESTUDIO GENÉTICO DE OSTEOGENESIS IMPERFECTA

DATOS DEL MÉDICO RESPONSABLE

NOMBRE Y APELLIDOS	
SERVICIO	
HOSPITAL	
DIRECCIÓN	
CIUDAD	
TELEFONO	
FAX	
E-MAIL	

IDENTIFICACIÓN DEL PACIENTE

NOMBRE	
1ER APELLIDO	
2º APELLIDO	
FECHA DE NACIMIENTO	
LUGAR DE NACIMIENTO	
ETNIA	

NOMBRE PADRE		NOMBRE MADRE	
FECHA DE NACIMIENTO		FECHA DE NACIMIENTO	
OSTEOGENESIS IMPERFECTA?		OSTEOGENESIS IMPERFECTA?	

DATOS CLÍNICOS DEL PACIENTE

1.- ANTECEDENTES PERSONALES

- Ecografías prenatales: Normales ☐ Alteradas ☐
  Si alteradas, especificar: _____
- Parto: Eutócico ☐ Instrumentado ☐ Cesárea ☐
- Complicaciones en el parto: NO ☐ SI ☐
  Si respuesta afirmativa, especificar: _____
- Peso al nacimiento: _____ • Talla al nacimiento: _____
- Perímetro craneal al nacimiento: _____
- Edad de inicio deambulación autónoma: _____
- Otras enfermedades asociadas: _____

Señalar si hay o ha habido sospecha de malos tratos en algún momento: SI ☐ NO ☐



Experiencia HSJD – H.Clínic

- HSJD – 80 pacientes con OI

30 pacientes Estudio Genético OI (CI) + 6 estudio familiar
- 1 COL1A1
- 2 FKBP10
- 3 NINGUNO

− 6 muestra reciente

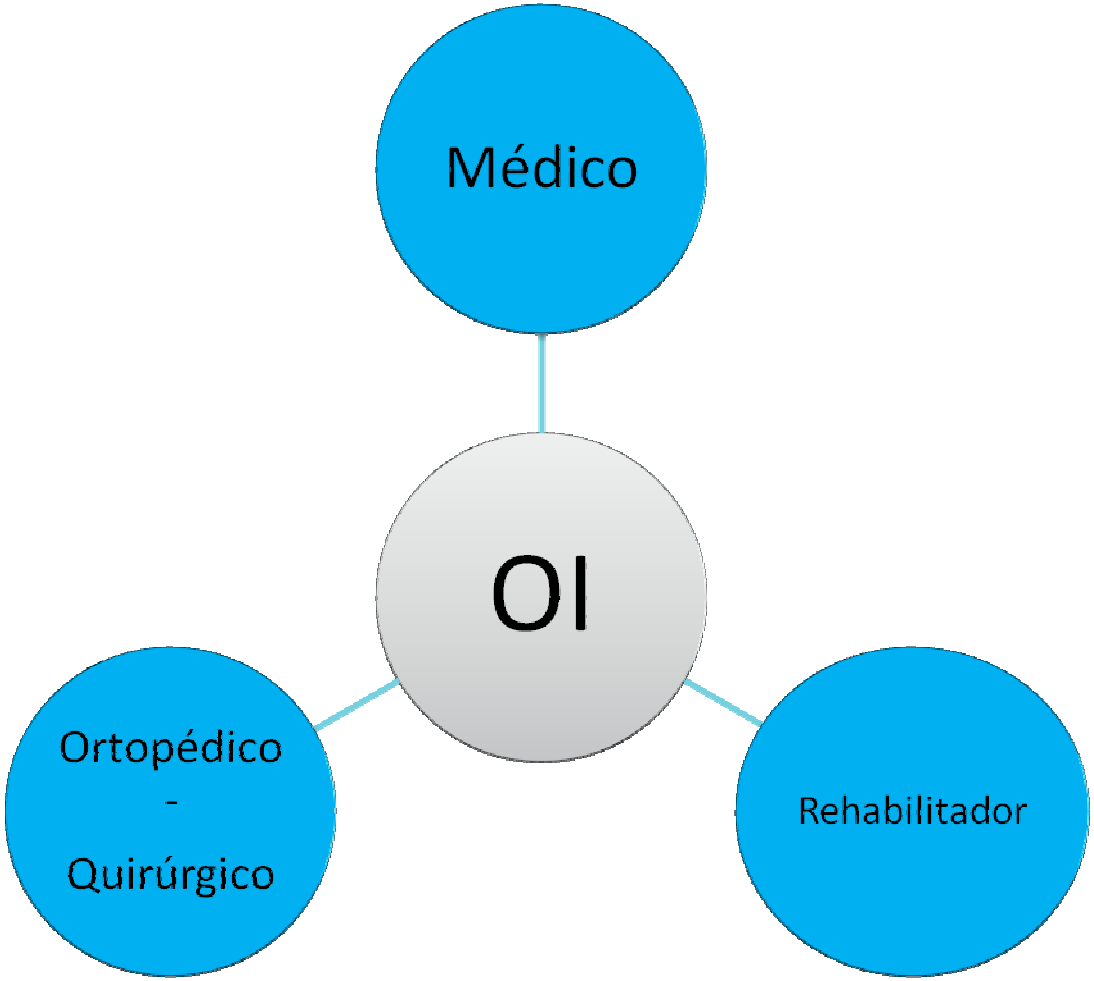
24 resultados
- 10 COL1A1
- 4 COL1A2
- 1 FKBP10
- 9 NINGUNO
  - 7 baja sospecha
  - 2 alta → ampliación



		OI type I	OI type II	OI type III	OI type IV	OI type V	OI type VI	CRTAP	LEPRE1	PPIB	SP7	FKBP10	SERPINH1	BMP1/mTLD	TMEM38B
Sclerae color		blue	dark	blue to grey	normal to grey		normal	normal to	normal to grey		normal	normal to grey	blue	blue	normal
Severity	normal	mild (no deforming)	perinatal lethal	severe incompatible with adulthood	norma, moderately deforming to severe	severe to moderately deforming	normal, moderately deforming to severe	normal to perinatal lethal	severe to perinatal lethal	severe and moderately deforming	severe	severe	mild to severe	severe	different degrees
Stature	normal			short or extremely short	short			short in mild phenotypes			short				
Fractures	rate	few to several/year	many								several/year			10-15/year	improbe in puberty
	starting at	dispers/walk	in utero	at birth					in utero	in utero	3 months after birth	infancy	in utero	utero/ delivery	prenatal to infancy
Long bones appearence	short	bowed femur	short, bowed and deformed				deformed	short, bowed and deformed	short, bowed and deformed		bowed upper and lower limbs, also deformed	short, bowed and deformed	short, bowed and deformed	deformed	
	other							undertubulated	undertubulation (femur)	broad, not well modelated				serpentine in tibiae and fibulae	
Mineralization						low density, irregular bone lamellation	hyperosteiodosis, abnormal lamellation					Distorsioned lamellar structure and fish scale-like pattern		decreased	
Osteoporosis								yes			yes			yes	
Osteopenia												yes	yes	yes	yes
Kyphoscoliosis				yes			yes		scoliosis		scoliosis	yes		yes	
Coxa vara			yes	in 55%				yes	yes			in some			
Ribs			deformities	fractures				gracile					thin		
Rhizomelia								yes	yes						
skull		wormian bones				radial head dislocation, vert compression		wormian bones	wormian bones, large circumference in teen, large frontanelles		micrognathia	wormian bones	triangular face, macrocephaly, micrognatia	wormian bones	
Basilar impression				yes	yes										
Other bone characteristics						calcification interosseous membrane (cubit-radi)		"pop-corn" epiphyses (50%)	"pop-corn" epiphyses						
Hearing loss		progressive in 50% cases		start at teens	adult onset		No				no			no	no
Hypermobility		yes									hyperextensibility of the interphalangeal joints	hyperlaxitude		hypotonia, hyperlaxitude	
DI		rare		sometimes	common		no	indistinguishable from OI type II and III	indistinguishable from OI type II and III		delayed eruption, NO DI		yes	yes	no
Other				weel chair		subluxation, hyperplastic callus formation,						skin blisters, weel chair		umbilical hernia	
Inheritance		AD	AD	AD	AD	AD	AR	AR	AR	AR	AR	AR	AR	AR	
Gene		COL1A1/2	COL1A1/2	COL1A1/2	COL1A1/2	IFITM5	SERPINF1								
			de novo, mosaic amb AR			5% of OI patients	PEDF, Poor biphosphonates response	africans, afro-americans, Irish travelers	africans, afro-americans, Irish travelers						

TRATAMIENTO

Tratamiento



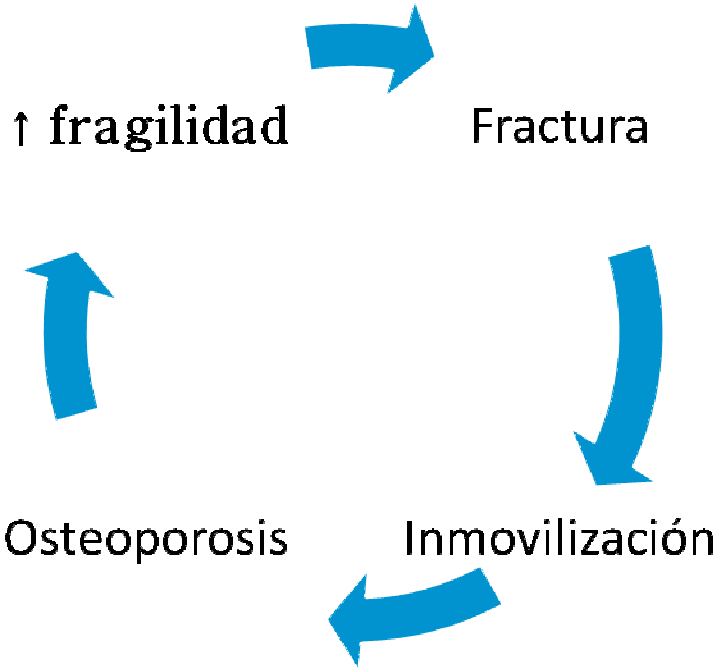
Reumatología

Fisioterapia, rehabilitación

- Maximizar movilidad y otras capacidades funcionales

- Programas de actividad física
  - Prevenir contracturas
  - Pérdida de hueso inducida por inmovilidad

- Ortesis para proteger los MMII durante las fases precoces de movilización





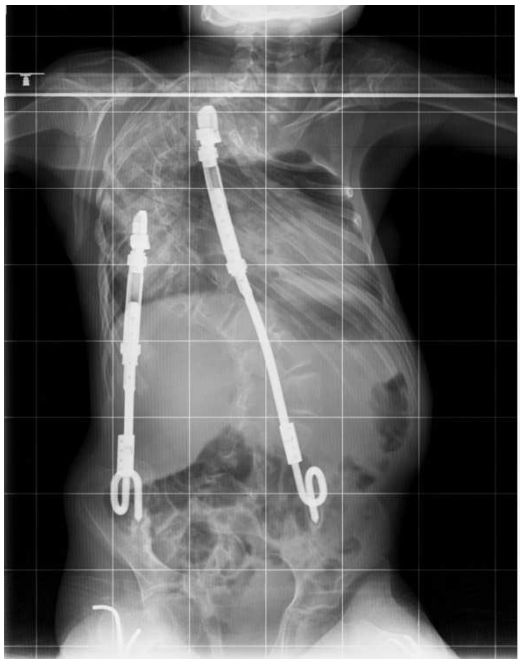
Quirúrgico

- Corrección de la deformidad e incurvación con osteotomías y enclavado
  - A menudo bipedestación y marcha sólo alcanzables con fortalecimiento fémur y tibia con enclavados medulares.
  - Enclavado telescópico expandible
  - Corrección coxa vara

- Cirugía escoliosis



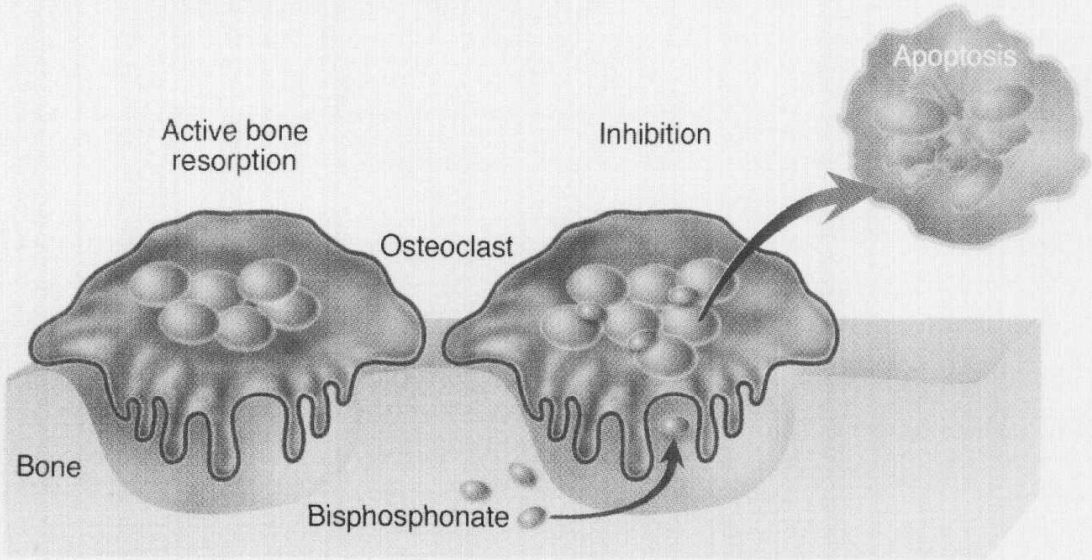




Reumatología

Tratamiento médico

- Bifosfonatos: antirresortivos potentes
  - Inhibición de los osteoclastos



by Ken Beauchamp *J. Clin. Invest.*

Figure 2
Active osteoclasts mediate bone resorption. Osteoclast absorption of bisphosphonates results in the inhibition of osteoclast function and osteoclast apoptosis.

Reumatología

Bifosfonatos

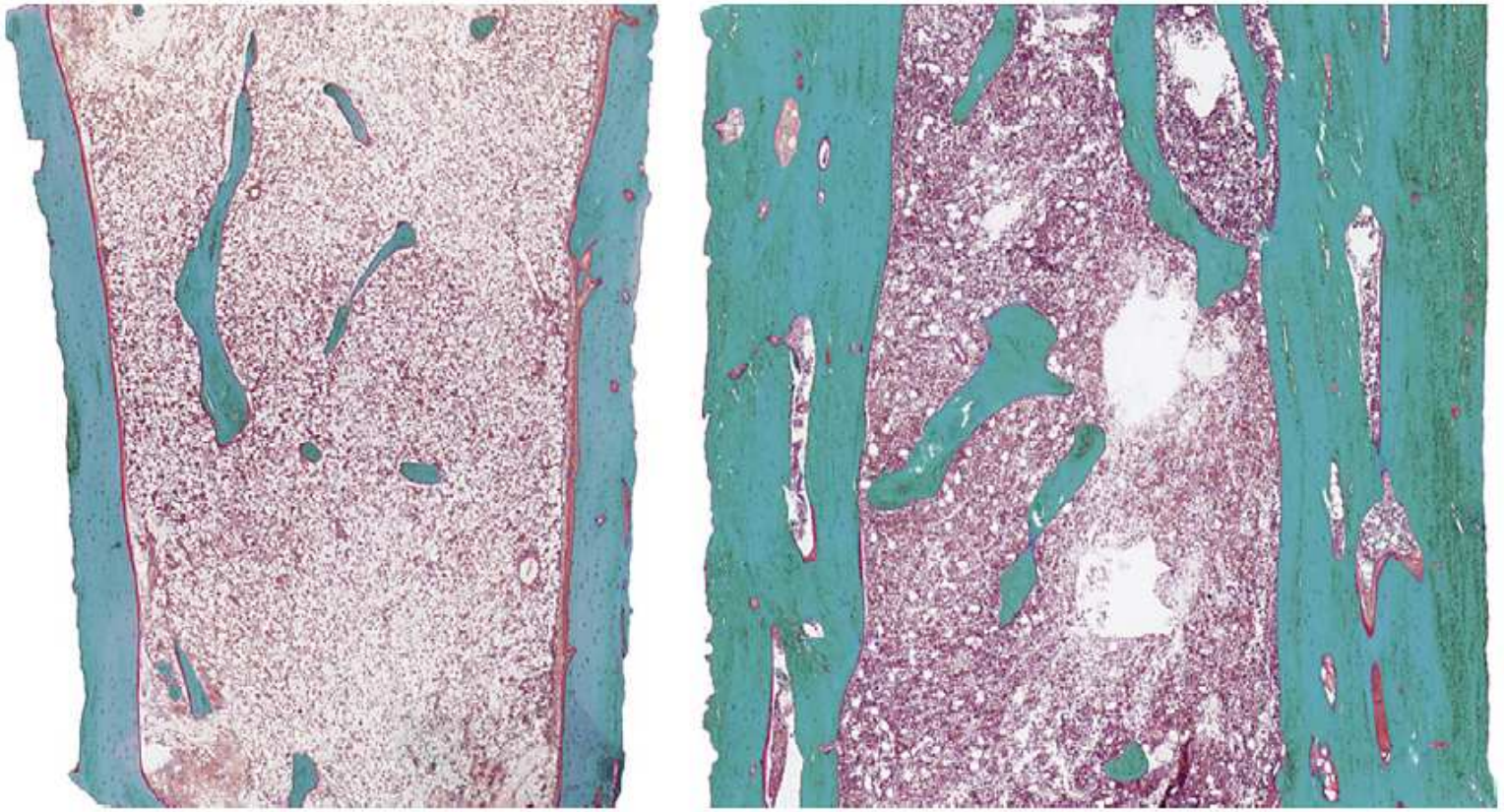
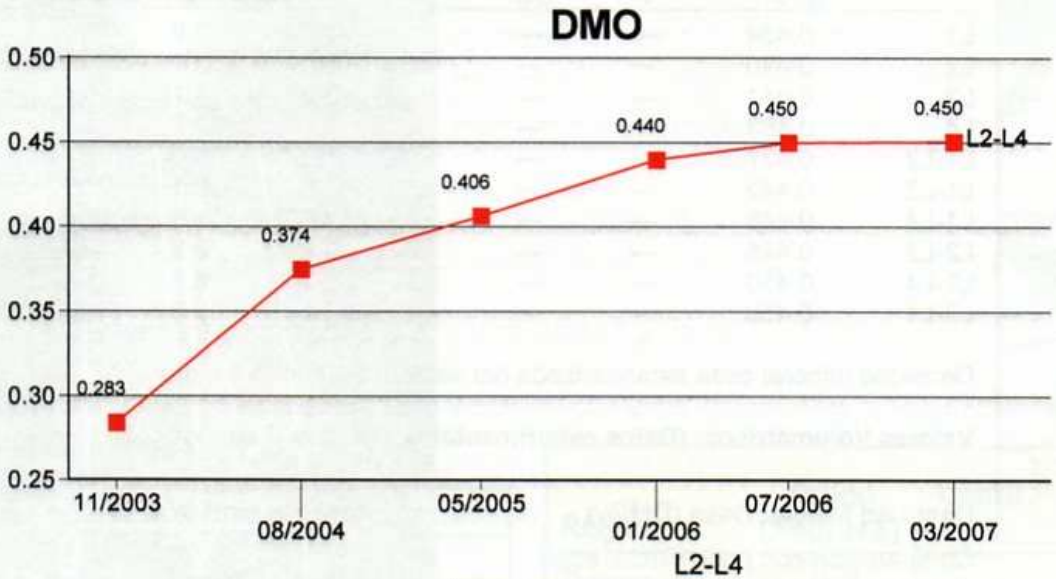


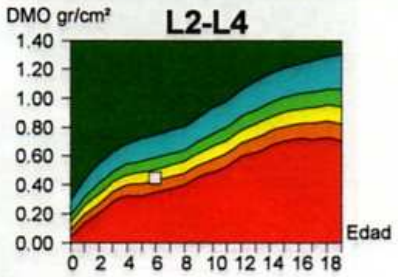
Figure 1. Iliac bone samples in a boy with Type I osteogenesis imperfecta. Left panel, sample obtained at the age of 2 years, at the time of the first pamidronate infusion. Right panel, after 3 years of pamidronate treatment. Cortical thickness more than tripled during the treatment interval.

Reumatología

Bifosfonatos

RESULTADOS:





L2-L4	
Densidad Mineral Osea (DMO)	0.450 g/cm²
Comparación con pobl. similar edad	66 %
Escala Z	-2.23 DE
Cambios respecto última exploración	**0.00 (+0.11%)**
Cambio fisiológico pobl. referencia	0.03 (+4.69%)



Bifosfonatos: duración del tratamiento

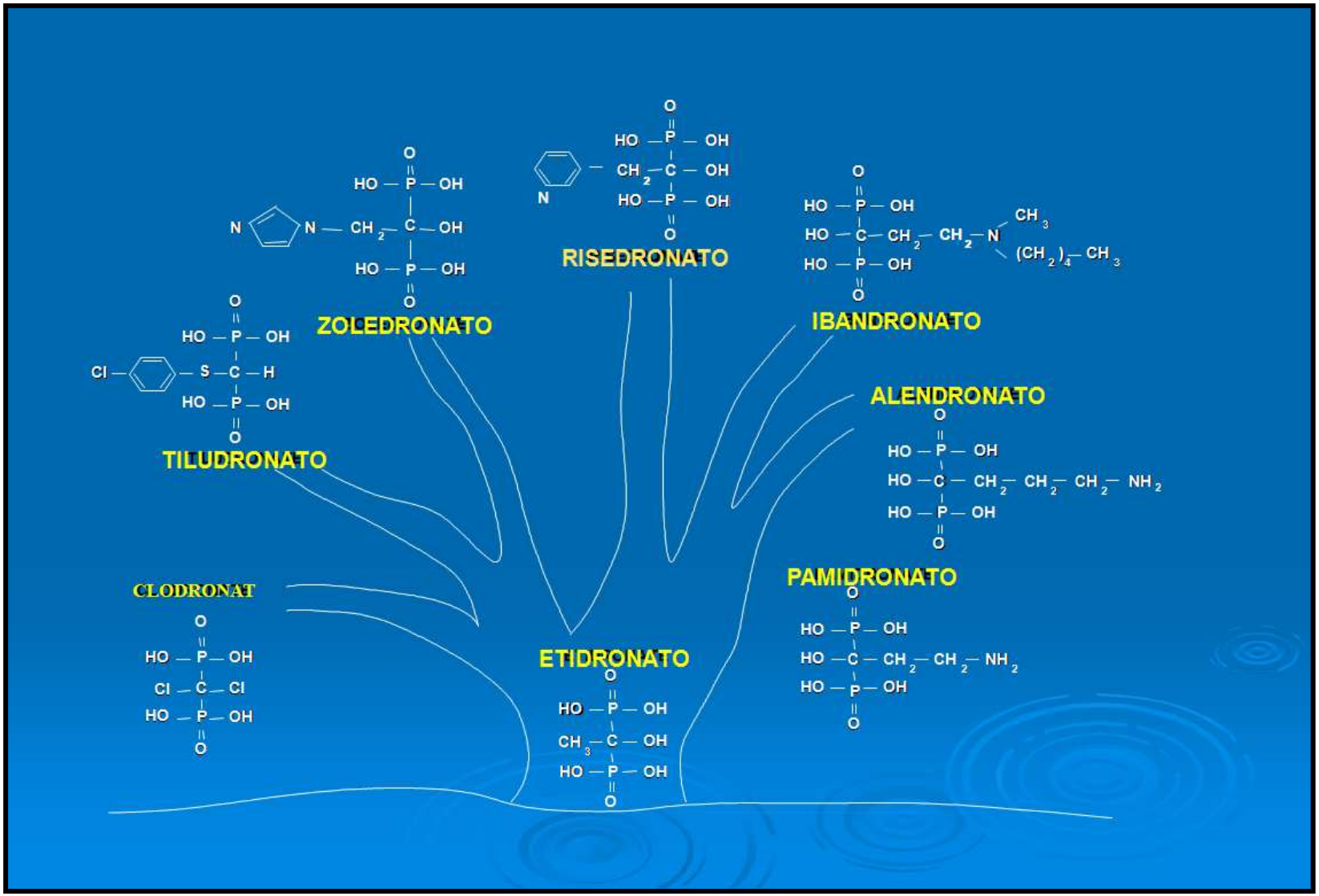
- Máximo efecto 3-5 primeros años
- Efectos de la suspensión



- Si no paramos tratamiento:
  - Continuar a dosis plenas?
  - Cambiar a bifosfonatos orales?
  - Continuar con mitad de dosis?

Reumatología

Bifosfonatos



Reumatología

Pamidronato

- "Protocolo Glorieux"

Dosage (maximum dose: 60 mg/day)

Age	Dosage	Frequency
<2.0 years	0.5 mg/kg/day for 3 days	2 months
2.1—3.0 years	0.75 mg/kg/day for 3 days	3 months
>3.1 years	1.0 mg/kg/day for 3 days	4 months

- Mayoría de publicaciones

Glorieux. Cyclic administration of pamidronate in childretn with sever OI. NEJM 1998



Otros bifosfonatos ev

- Zoledronato:
  - Estudios comparativos PAM vs ZOL:
    - No diferencias en DMO columna / fractura
  - Comodidad:
    - Una sola infusión en 30-45’
  - Por determinar:
    - Mejor dosis: 0.05-0.1 mg/kg/dosis
    - Intervalo: 6-12m

- Neridronato:
  - Estudio efectos similares a PAM



Bifosfonatos orales

- Aledronato / Risedronato

Lancet. 2013 Oct 26;382(9902):1424-32. doi: 10.1016/S0140-6736(13)61091-0. Epub 2013 Aug 6.

Risedronate in children with osteogenesis imperfecta: a randomised, double-blind, placebo-controlled trial.

Bishop N, Adami S, Ahmed SF, Antón J, Arundel P, Burren CP, Devogelaer JP, Hangartner T, Hosszú E, Lane JM, Lorenc R, Mäkitie O, Munns CF, Paredes A, Pavlov H, Plotkin H, Raggio CL, Reyes ML, Schoenau E, Semler O, Sillence DO, Steiner RD.

Academic Unit of Child Health, Department of Human Metabolism, University of Sheffield, Sheffield Children's Hospital, Sheffield, UK. Electronic address: n.j.bishop@sheffield.ac.uk.

Alendronate for the Treatment of Pediatric Osteogenesis Imperfecta: A Randomized Placebo-Controlled Study

L. M. Ward, F. Rauch, M. P. Whyte, J. D'Astous, P. E. Gates, D. Grogan, E. L. Lester, R. E. McCall, T. A. Pressly, J. O. Sanders, P. A. Smith, R. D. Steiner, E. Sullivan, G. Tyerman, D. L. Smith-Wright, N. Verbruggen, N. Heyden, A. Lombardi, and F. H. Glorieux

J Clin Endocrinol Metab, February 2011, 96(2):355–364

- Papel en:
  - Terapia de mantenimiento?
  - Casos leves?
  - Niños mayores



Denosumab

- Inhibidor RANKL

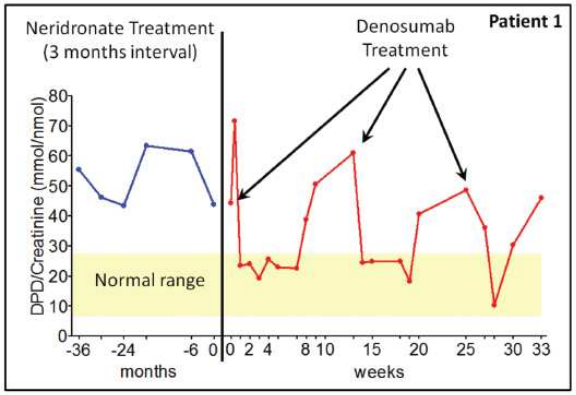
J Musculoskelet Neuronal Interact 2012; 12(3):183-188

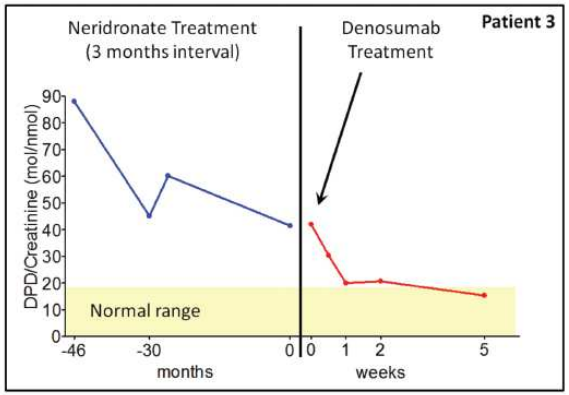
Original Article

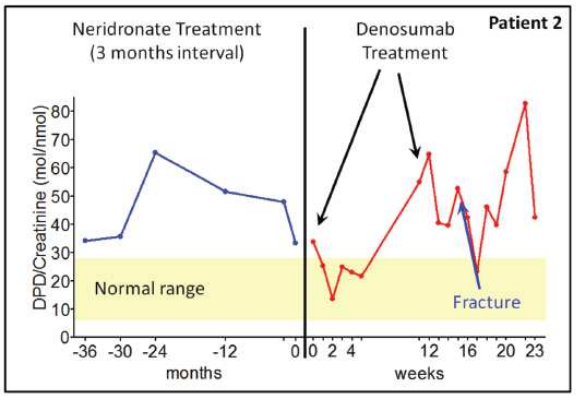
Hylonome

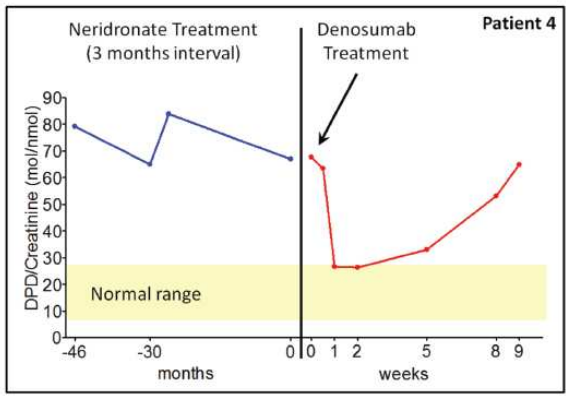
First use of the RANKL antibody denosumab in Osteogenesis Imperfecta Type VI

O. Semler[1*], C. Netzer[2*], H. Hoyer-Kuhn[1], J. Becker[2], P. Eysel[3], E. Schoenau[1]









DMO al año



Futuras terapias

- Estimulación osteoblastogénesis

J Bone Miner Res. 2013 Jan;28(1):73-80. doi: 10.1002/jbmr.1717.

Sclerostin antibody improves skeletal parameters in a Brtl/+ mouse model of osteogenesis imperfecta.

Sinder BP, Eddy MM, Ominsky MS, Caird MS, Marini JC, Kozloff KM.

Orthopaedic Research Laboratories, Department of Orthopaedic Surgery, University of Michigan Ann Arbor, MI, USA.

- Silenciación

Eur J Hum Genet. 2013 Sep 11. doi: 10.1038/ejhg.2013.198. [Epub ahead of print]

Allele-specific Col1a1 silencing reduces mutant collagen in fibroblasts from Brtl mouse, a model for classical osteogenesis imperfecta.

Rousseau J, Gioia R, Layrolle P, Lieubeau B, Heymann D, Rossi A, Marini JC, Trichet V, Forlino A.

1] INSERM, UMR 957, Nantes, France [2] Université de Nantes, Nantes Atlantique Universités, Laboratoire de Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Faculté de Médecine, Nantes, France.

- Trasplante cél. madre

Stem Cells Dev. 2013 Oct 16. [Epub ahead of print]

Potential of Human Fetal Chorionic Stem Cells for the Treatment of Osteogenesis Imperfecta.

Jones GN, Moschidou D, Abdulrazzak H, Kalirai BS, Vanleene M, Osatis S, Shefelbine SJ, Horwood NJ, Marenzana M, De Coppi P, Bassett JH, Williams GR, Fisk NM, Guillot PV.

1 Institute of Reproductive and Developmental Biology , Imperial College London, London, United Kingdom .



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