

# **ENFOQUE DIAGNÓSTICO DISCAPACIDAD CRÓNICA EN PACIENTES CON CUADROS NEUROGENÉTICOS CON FOCO EN DISPLASIAS ESQUELÉTICAS Y MUCOPOLISACARIDOSIS**

**DR. PATRICIO GUERRA  
NEURÓLOGO INFANTIL Y ADOLESCENTES**

**MAGÍSTER NEUROCIENCIAS**

**CLÍNICA UNIVERSITARIA PUERTO MONTT - CLÍNICA ALEMANA PUERTO VARAS  
ESCUELA DE MEDICINA UNIVERSIDAD SAN SEBASTIÁN SEDE PATAGONIA PUERTO MONTT**

## ORIGINAL ARTICLE

## A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency

B.K. Burton, M. Balwani, F. Feillet, I. Barić, T.A. Burrow, C. Camarena Grande, M. Coker, A. Consuelo-Sánchez, P. Deegan, M. Di Rocco, G.M. Enns, R. Erbe, F. Ezgu, C. Ficicioglu, K.N. Furuya, J. Kane, C. Laukaitis, E. Mengel, E.G. Neilan, S. Nightingale, H. Peters, M. Scarpa, K.O. Schwab, V. Smolka, V. Valayannopoulos, M. Wood, Z. Goodman, Y. Yang, S. Eckert, S. Rojas-Caro, and A.G. Quinn

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### ABSTRACT

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#### BACKGROUND

Lysosomal acid lipase is an essential lipid-metabolizing enzyme that breaks down endocytosed lipid particles and regulates lipid metabolism. We conducted a phase 3 trial of enzyme-replacement therapy in children and adults with lysosomal acid lipase deficiency, an underappreciated cause of cirrhosis and severe dyslipidemia.

#### METHODS

In this multicenter, randomized, double-blind, placebo-controlled study involving 66 patients, we evaluated the safety and effectiveness of enzyme-replacement therapy with sebelipase alfa (administered intravenously at a dose of 1 mg per kilogram of body weight every other week); the placebo-controlled phase of the study was 20 weeks long and was followed by open-label treatment for all patients. The primary end point was normalization of the alanine aminotransferase level. Secondary end points included additional disease-related efficacy assessments, safety, and side-effect profile.

#### RESULTS

Substantial disease burden at baseline included a very high level of low-density lipoprotein cholesterol ( $\geq 190$  mg per deciliter) in 38 of 66 patients (58%) and cirrhosis in 10 of 32 patients (31%) who underwent biopsy. A total of 65 of the 66 patients who underwent randomization completed the double-blind portion of the trial and continued with open-label treatment. At 20 weeks, the alanine aminotransferase level was normal in 11 of 36 patients (31%) in the sebelipase alfa group and in 2 of 30 (7%) in the placebo group ( $P=0.03$ ), with mean changes from baseline of  $-58$  U per liter versus  $-7$  U per liter ( $P<0.001$ ). With respect to pre-specified key secondary efficacy end points, we observed improvements in lipid levels and reduction in hepatic fat content ( $P<0.001$  for all comparisons, except  $P=0.04$  for triglycerides). The number of patients with adverse events was similar in the two groups; most events were mild and were considered by the investigator to be unrelated to treatment.

#### CONCLUSIONS

Sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in children and adults with lysosomal acid lipase deficiency. (Funded by Synageva BioPharma and others; ARISE ClinicalTrials.gov number, NCT01757184.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Burton at the Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Ave., Chicago, IL 60611, or at bburton@luriechildrens.org.

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# PROGRAMA PRESENTACIÓN

-INTRODUCCIÓN CAMBIOS DEMOGRÁFICOS Y BIOSOCIALES

-ENFERMEDADES RARAS

-ETIOLOGÍA GENERAL DISCAPACIDAD PSICOMOTORA

-ENFOQUE DIAGNÓSTICO INICIAL

-CAUSAS GENÉTICAS DISCAPACIDAD PSICOMOTORA

-ESTUDIOS DISPONIBLES GENÉTICA

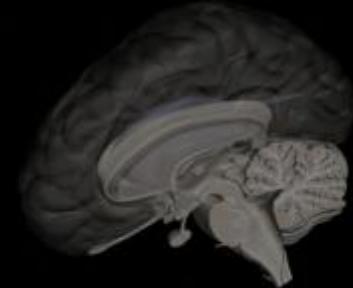
-ENFOQUE DIAGNÓSTICO CUADROS SOSPECHA ALTERACIONES GENÉTICAS

-CUADROS DE BASE GENÉTICA ASOCIADOS A TALLA BAJA Y ALTERACIONES ESQUELÉTICAS (DISPLASIAS ESQUELÉTICAS)

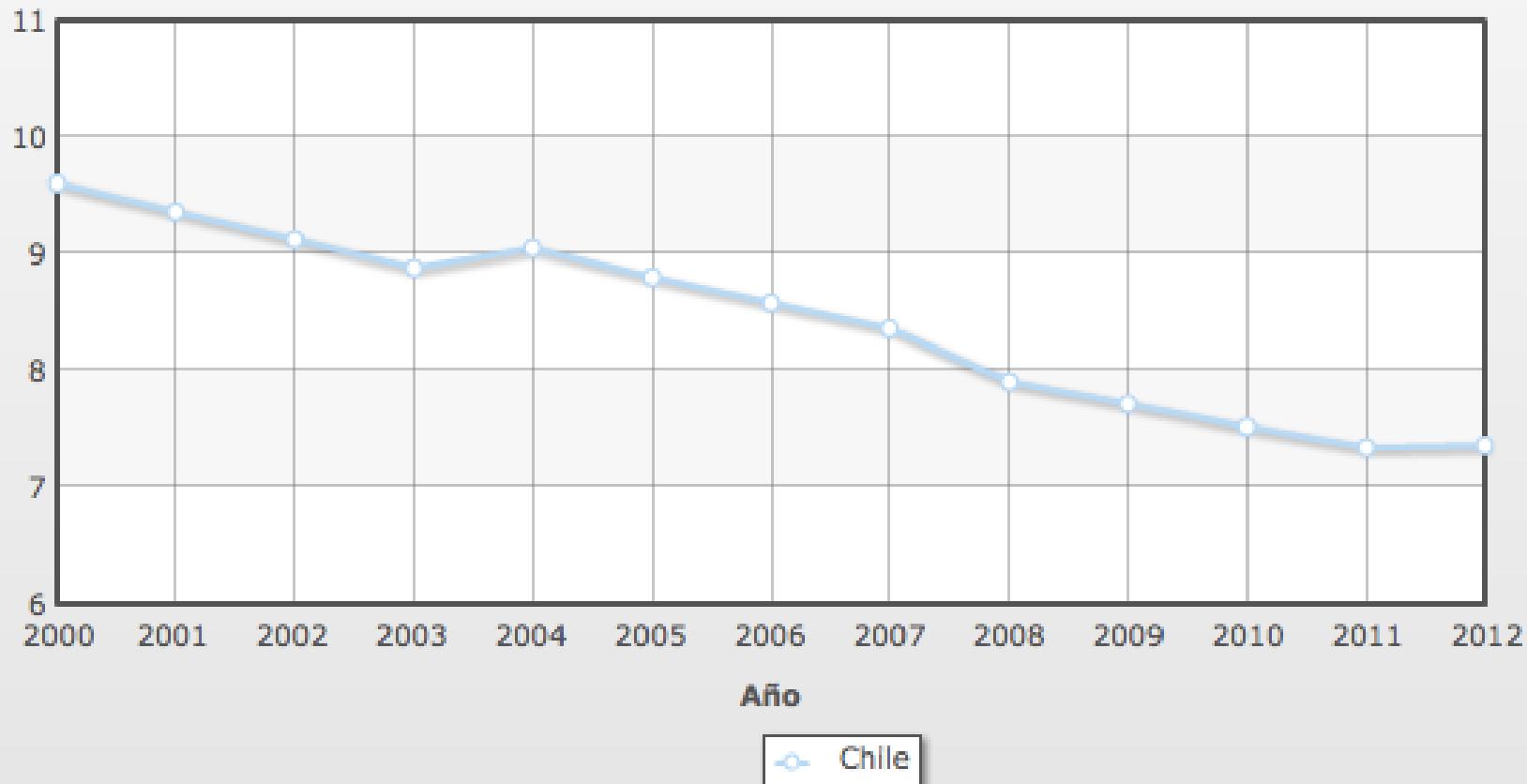
-DIAGNÓSTICO DIFERENCIAL DISPLASIAS ESQUELÉTICAS

-MUCOPOLISACARIDOSIS: ENFERMEDAD DE MORQUIO

-NUEVOS AVANCES TRATAMIENTO ENFERMEDADES LISOSOMALES



## Tasa de mortalidad infantil (muertes/1000 nacimientos normales)

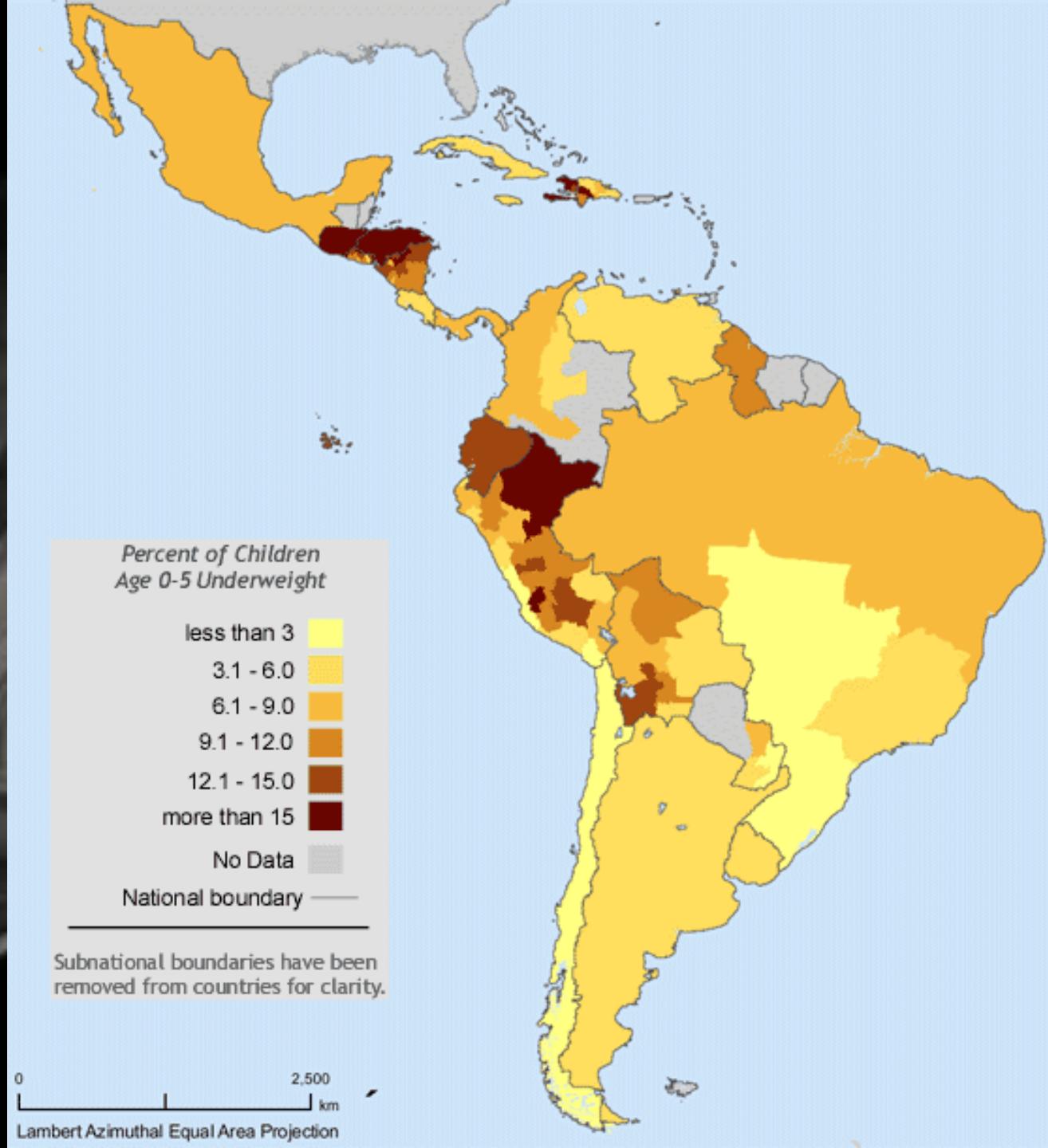


Waiting

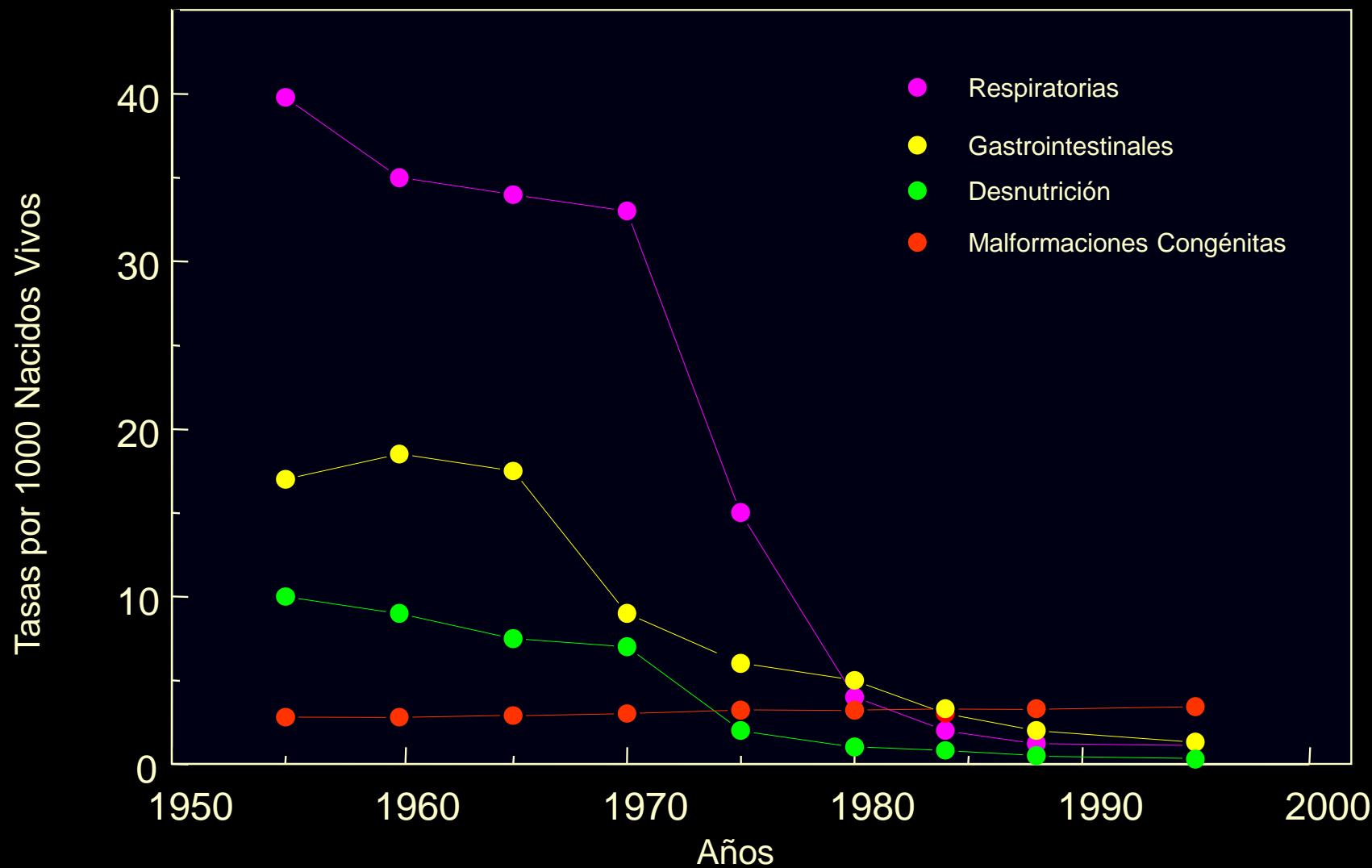
Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Chile	9,6	9,36	9,12	8,88	9,05	8,8	8,58	8,36	7,9	7,71	7,52	7,34	7,36

# DESNUTRICIÓN INFANTIL

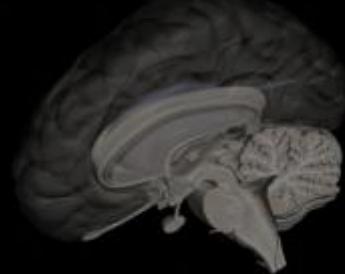
## ANÁLISIS A NIVEL LATINOAMERICANO



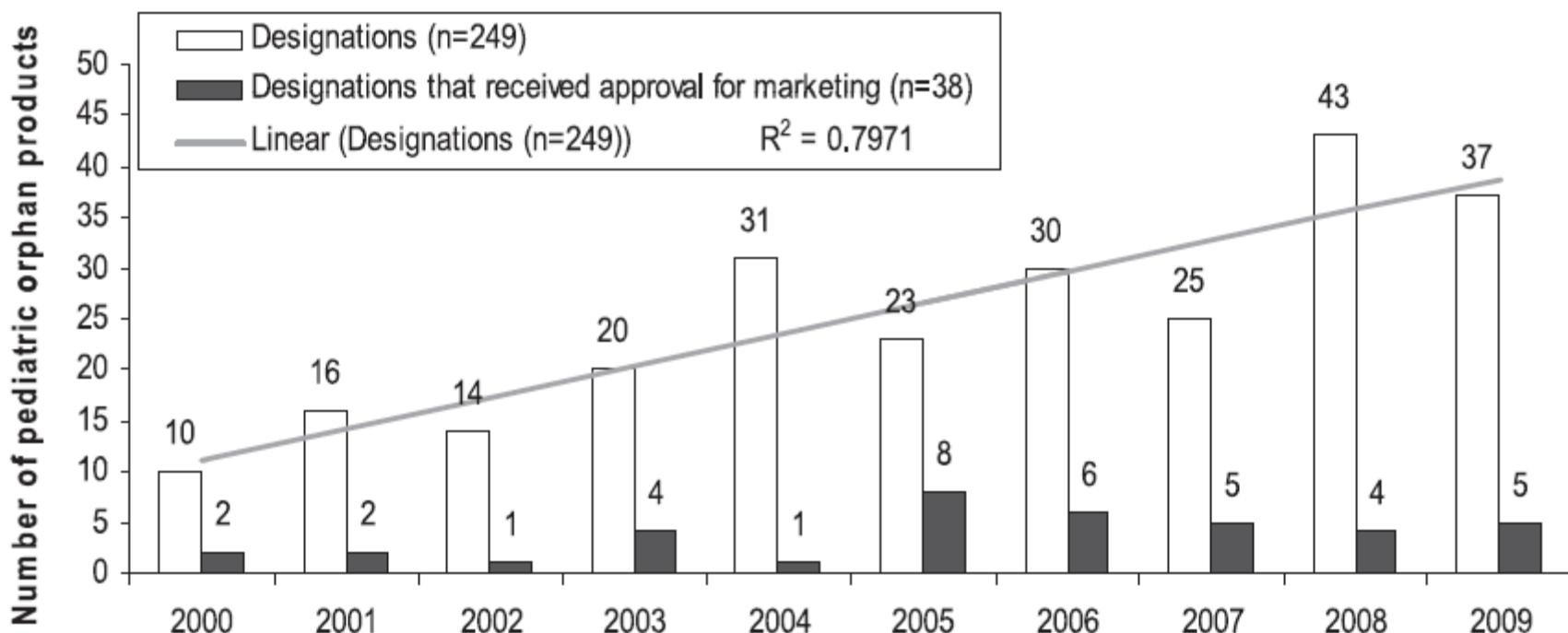
## MORTALIDAD INFANTIL EN CHILE GRUPOS DE CAUSAS SELECCIONADAS



# ENFERMEDADES POCO FRECUENTES (RARE DISORDERS)



- CONDICIONES QUE AFECTAN PEQUEÑOS GRUPOS DE PACIENTES
  - US: 1:200.000 HABITANTES
  - EU: 1:2.000
  - CHILE: 1:10.000
- REPRESENTAN UN SERIO PROBLEMA EN SALUD PÚBLICA
  - CONDICIONES CRÓNICAS, QUE PONEN EN PELIGRO LA VIDA
  - ESCAZO CONOCIMIENTO CIENTÍFICO
  - ESCAZA DISPONIBILIDAD DIAGNÓSTICOS DE CERTEZA
  - AUSENCIA DE TRATAMIENTOS
- DESAFÍOS ÉTICOS
  - JUSTICIA DISTRIBUTIVA
  - INVESTIGACIÓN EN HUMANOS
  - CONFLICTOS DE INTERESES



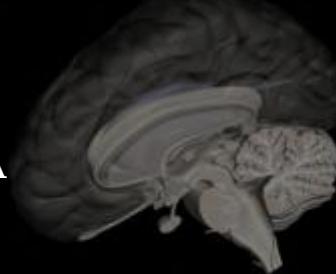
**FIGURE 1**

Pediatric (category 1) orphan product designations and approvals by year, from 2000 to 2009. Bars represent total number of designated (*white bar*) and approved (*dark bar*) products (both drugs and biologics) in each year from 2000 to 2009. The gray line shows the linear trend of increasing number of designations during the study period ( $R^2 = 0.797$ ).

What the Orphan Drug Act Has Done Lately for Children  
With Rare Diseases: A 10-Year Analysis

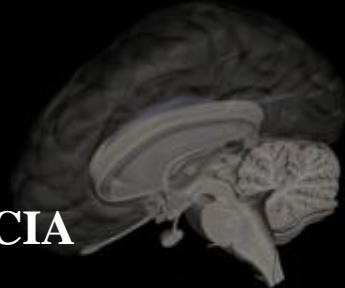
*Pediatrics* 2012;129:516–521

# **ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA**

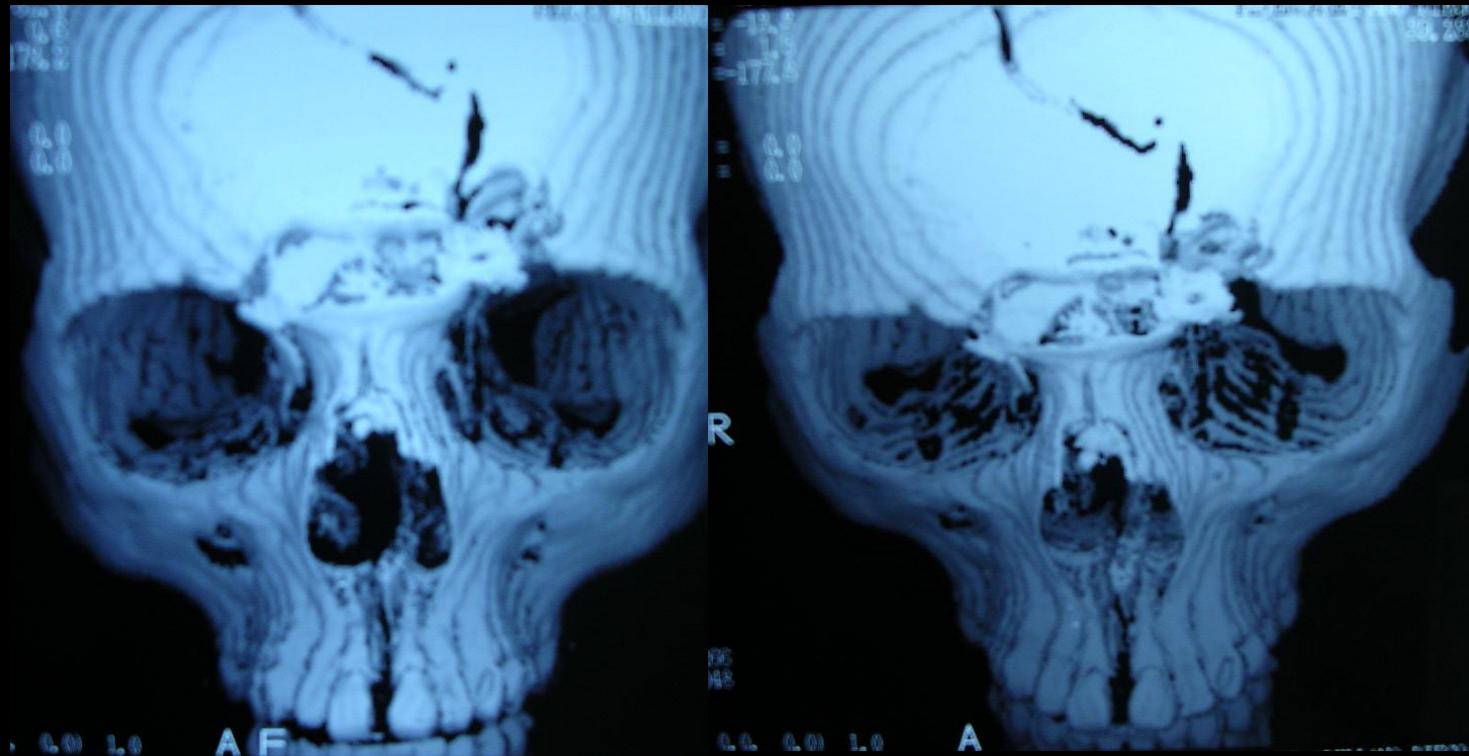


- PRODUCTO DE TRAUMATISMOS O ACCIDENTES**
- PRODUCTO DE PATOLOGÍA PERINATAL**
- PRODUCTO DE TÓXICOS U OTRAS NOXAS DURANTE GESTACIÓN**
- PRODUCTO DE ENFERMEDADES (TUMORES-AVC)**
- PRODUCTO DE ALTERACIONES GENÉTICAS DE BASE**
- PRODUCTO DE ERRORES INNATOS DEL METABOLISMO**
- FALTA DE ESTIMULACIÓN PSICOSOCIAL TEMPRANA**
- ASOCIADAS A AUTISMO**
- DE CAUSA DESCONOCIDA**

## ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA

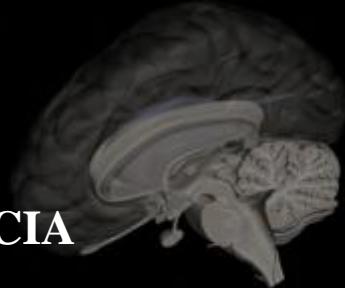


-PRODUCTO DE TRAUMATISMOS O ACCIDENTES



ESTUDIO RADIOLÓGICO ANATÓMICO Y FUNCIONAL  
FUNCIÓN COGNITIVA

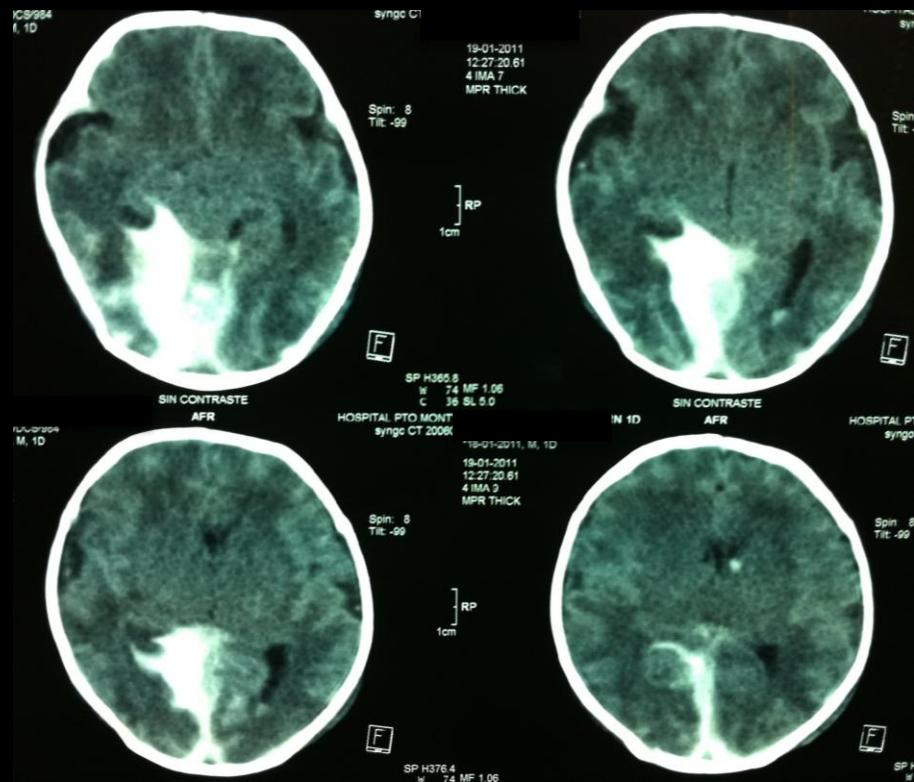
# ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA



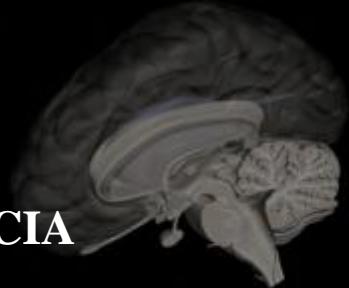
## -PRODUCTO DE PATOLOGÍA PERINATAL

### ESTUDIO

TAC  
RMN  
LCR  
Gases-ELP  
Ca-Glicemia  
Amonio  
Hemograma  
EEG  
Monitoreo EEG continuo  
PBQ



## ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA



-PRODUCTO DE TÓXICOS U OTRAS NOXAS DURANTE GESTACIÓN



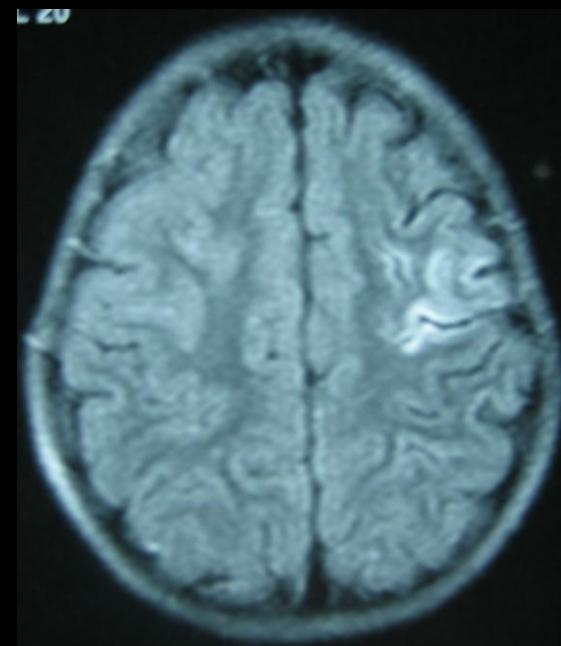
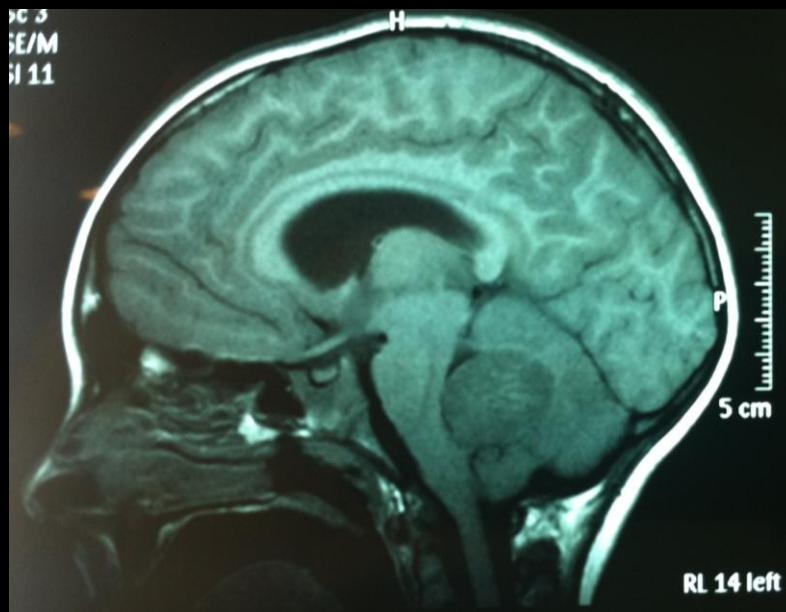
CARACTERIZACIÓN EN BASE A HISTORIA CLÍNICA Y DISMORFIAS

BASES DE DATOS DISMORFOLÓGICAS

## ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA



-PRODUCTO DE ENFERMEDADES (TUMORES-AVC-INFECCIONES-ETC)



ESTUDIO EN BASE A LA SOSPECHA CLÍNICA ESPECÍFICA

## **ETIOLOGÍA DISCAPACIDA PSICOMOTORA DE IMPORTANCIA**



**-PRODUCTO DE ERRORES INNATOS DEL METABOLISMO**



**TAMIZAJE NEONATAL + ESTUDIO ESPECÍFICO SEGÚN CLÍNICA**



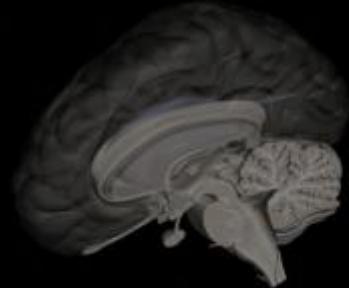
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Y TECNOLOGIA DE LOS ALIMENTOS  
Laboratorio Enfermedades Metabólicas



Universidad de las Naciones  
Unidas  
Unidad de Investigacion  
y Docencia



### RESULTADOS SCREENING ESPECTROMETRIA DE MASAS

Nombre :  
Fecha :  
Fecha Nacimiento :  
Procedencia :

Resultados :

Aminoacidos		Resultado	Rango	
	Símbolo	Obtenido ( $\mu\text{M}$ )	Normal ( $\mu\text{M}$ )	Condición
Acilcarnitinas				
Carnitina libre	C0	42.80	0-70	N
Acetilcarnitina	C2	32.40	0-27.0	ALTO
Propionilcarnitina	C3	1.95	0-4.7	N
Butirilcarnitina	C4	0.14	0-0.8	N
Isovalericarnitina	C5	0.14	0-0.4	N
Octanoilcarnitina	C8	0.06	0-0.3	N
Miristolcarnitina	C14	0.15	0-0.3	N
Palmitolcarnitina	C16	1.41	0-2.0	N
Alanina	Ala	143.00	19-514	N
Arginina	Arg	53.90	0-78	N
Aspartato	Asp	64.80	1-181	N
Citrulina	Cit	16.30	0-27	N
Fenilalanina	Fen	52.90	0-108	N
Glicina	Gli	234.00	0-450	N
Glutamato	Glu	328.00	0-484	N
Leucina	Leu	96.30	10-200	N
Metionina	Met	21.10	0-38	N
Oxitina	Orn	64.10	0-117	N
Tirosina	Tir	72.10	0-121	N
Valina	Val	102.00	43-243	N

Conclusión : Se observa un aumento en nivel de C2. Este metabolito no se asocia con patología, pero sin con un estado de cetosis del paciente.

L. LABORATORIO DE ENFE-MEJ D.S  
METABOLICAS - INTA  
UNIVERSIDAD DE CHILE

BQ. ALV Veniente G.

Lab. Enfermedades Metabólicas  
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Santiago 08 de Junio de 2005



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Laboratorio Enfermedades Metabólicas



Universidad de las Naciones  
Unidas  
Unidad de Investigacion  
y Docencia

### RESULTADOS SCREENING NEONATAL AMPLIADO

Nombre :  
Fecha :  
Fecha Nacimiento :  
Procedencia :  
Codigo INTA :

Test (técnica)	Resultado	Conclusion	Valor Normal
Perfil de Aminoácidos (EMT):	Normal	Normal	★
Perfil de Acilcarnitinas (EMT):	Normal	Normal	★
Fenilalanina o PKU (EMT):	53.1	Normal	< a 120 $\mu\text{mol/L}$ sangre
Hormona Tiroestimulante o TSH (RIA):	3.3	Normal	< a 20 $\mu\text{UI/ml}$ suero
Biotinidasa (AE):	79.5	Normal	> a 30% actividad
17- $\alpha$ -OH-progesterona o HAC (Fl):	0.7	Normal	< a 60.0 ng/ml
Galactosa Total (Abs)	4.5	Normal	< a 9 mg/dL
Galactosa 1P-Uridiltransferasa (Fl):	5.8	Normal	> a 3.5 U/g Hb
Tripsina Inmunoreactiva o FQ (Fl):	4.5	Normal	< a 90 ng/ml

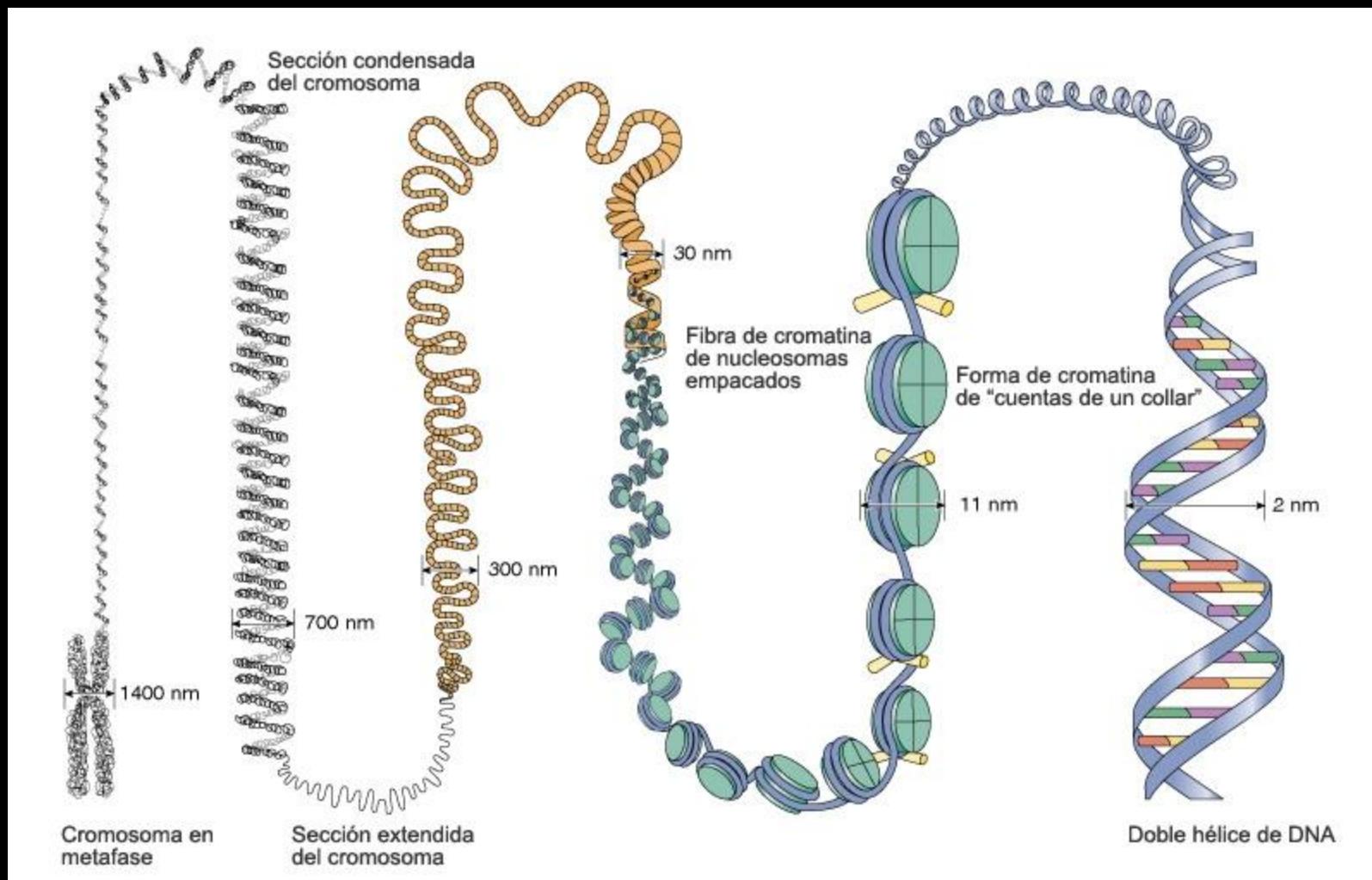
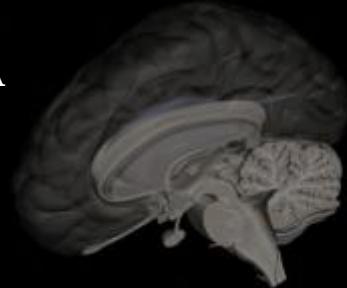
★ : Análisis que cuantifican varios metabolitos a la vez, por lo que no se entrega un detalle de los valores normales.

Comentario: Parámetros de Pesquisa Neonatal Ampliada dentro de rangos Normales.

# ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA

-FALTA DE ESTIMULACIÓN PSICOSOCIAL

-GRAVITANCIA FACTORES AMBIENTALES v/s GENÉTICOS  
(ESTUDIO GEMELOS)



Published in final edited form as:  
*Horm Behav.* 2011 March ; 59(3): 315–320. doi:10.1016/j.ybeh.2010.05.005.

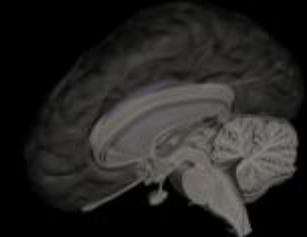
## Epigenetic marking of the BDNF gene by early-life adverse experiences

Tania L. Roth<sup>1,2</sup> and J. David Sweatt<sup>1,\*</sup>

<sup>1</sup> Department of Neurobiology and Evelyn F. McKnight Brain Institute, University of Alabama at Birmingham, Birmingham, AL 35294

### Abstract

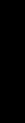
Studies over the past half-century have made it clear that environmental influences in development, particularly stress and traumatic experiences, can remain pervasive across the lifespan. Though it has been hypothesized for some time that the long-term consequences of early-life adversity represent epigenetic influences, it has not been until recently that studies have begun to provide empirical support of experience-driven epigenetic modifications to the genome. Here we focus on this theme, and review current knowledge pertaining to the epigenetics of behavioral development. At the center of our discussion is the brain-derived neurotrophic factor (BDNF) gene, as abnormal BDNF gene activity is a leading etiological hypothesis by which early-life adverse experiences persistently modify brain and behavioral plasticity.



## EXPERIENCIAS ADVERSAS EN LA INFANCIA



## MODIFICACIÓN EXPRESIÓN DEL GEN BDNF

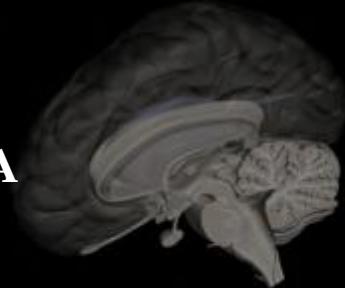


## RESPUESTA ANSIOGÉNICA EXAGERADA FRENTE A ESTRÉS



## EVIDENCIA MANTENCIÓN DE LA MODIFICACIÓN DE LA EXPRESIÓN DEL GEN BDNF AL MENOS HASTA LA TERCERA GENERACIÓN

# ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA



-ASOCIADAS A AUTISMO

-PATRÓN DE INTERESES Y CONDUCTAS RESTRICTIVAS

-TRASTORNO DE LA COMUNICACIÓN SOCIAL



Nº señales	1	2	3	Total
Señales verdes :	70			70
Señales naranjas :		70		140
TOTAL	70	140		210

**Observaciones :** En 70 metafases (100%) analizadas con hibridación in situ con fluorescencia se observó sólo una señal en 22q13 (SHANK3) y ambas señales en 22q11.2 (TUPLE1).

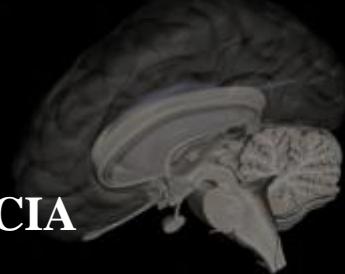
**Conclusiones:** En todas las metafases analizadas en una muestra de sangre se observó delección de SHANK3 en 22q13.

NOMENCLATURA ISCN 2013:ish del(22)(q13.3q13.3)(SHANK3-)

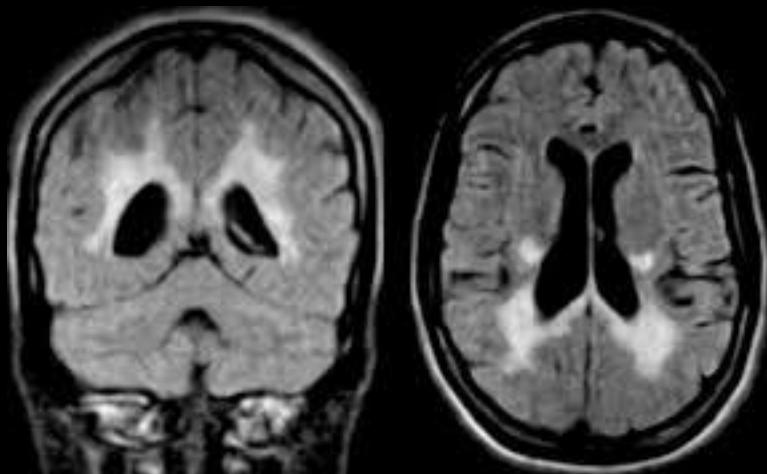
Fecha entrega: 23/07/2013

Este informe debe ser interpretado con los antecedentes clínicos.

## ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA



-PRODUCTO DE ALTERACIONES GENÉTICAS DE BASE





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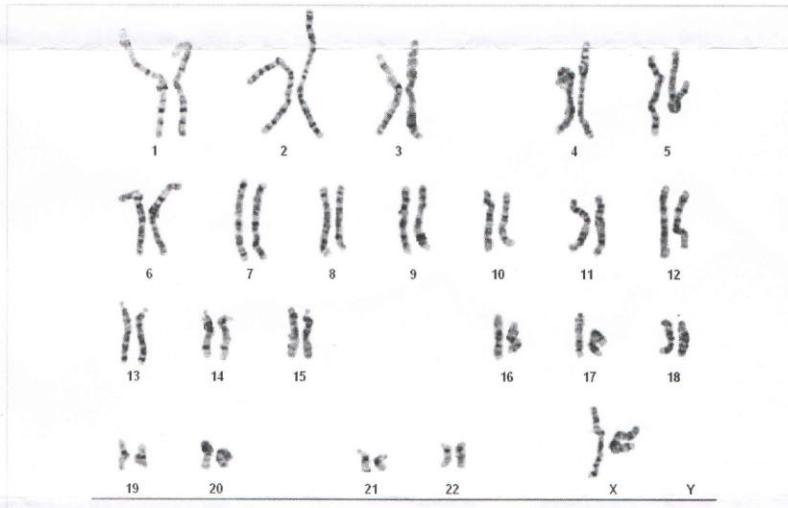


Instituto de Nutricion y  
Tecnologia de los Alimentos  
Universidad de Chile

Universidad de las  
Naciones Unidas

CASO: 331  
NOMBRE:   
APELLIDOS:  
RUT: 16448470-K  
EDAD: 27 AÑOS  
FECHA INGRESO: 25-07-2013

MUESTRA: SANGRE PERIFERICA  
PROTOCOLO: MEDIO COMPLETO CON TIMIDINA 10 -1 M  
DIAGNOSTICO: S/A  
REFERIDO POR: S/A

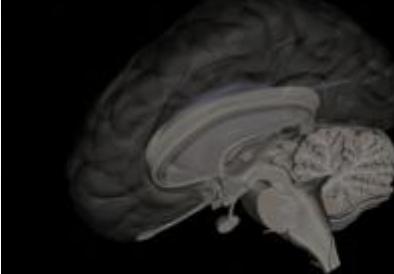


CARIOTIPO: 47,XXX/46,XX

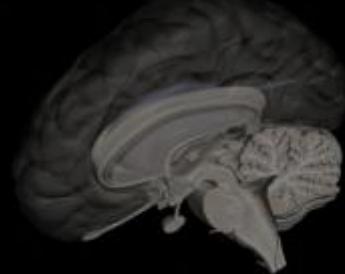
COMENTARIOS: EN EL ANALISIS DE 50 METAFASES CON BANDEO GTG (625 BANDAS) SE DETECTO UN MOSAICO BAJO DE ANEUPLOIDIA DEL CROMOSOMA X, COMPUESTO POR DOS LINEAS CELULARES: UNA NORMAL 46,XX EN 96% DE LAS MITOSIS Y OTRA ALTERADA, CON UN CROMOSOMA X EXTRA EN EL 4% RESTANTE.  
NOTA: SE SUGIERE REALIZAR FISH PARA EL CROMOSOMA X EN NUCLEOS INTERFASICOS, PARA ANALIZAR UN MAYOR NUMERO DE CELULA, SI LA CLINICA, ASI LO INDICA.

T.M. BIANCA CUROTO  
Citogenetista

M.Sc. M. ANGELICA ALLIENDE  
Citogenetista

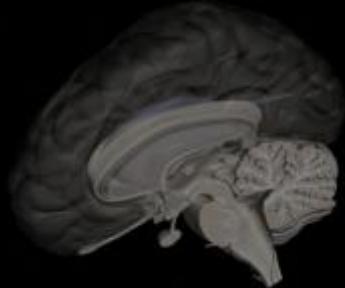


# **DISCAPACIDAD ASOCIADA A ETIOLOGÍA GENÉTICA**



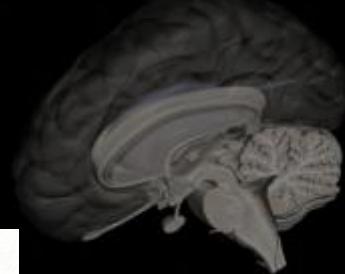
- ALTERACIONES CROMOSÓMICAS**
- ALTERACIONES DE DELECIÓN DE GENES CONTIGUOS**
- ALTERACIÓN DE UN GEN ÚNICO**
- ALTERACIONES POR REPETICIÓN DE TRIPLETES**
- ALTERACIONES POR ALTERACIÓN DE LA IMPRONTA**
- ALTERACIONES POR ASOCIACIÓN DE VARIANTES GENÉTICAS**
- ALTERACIONES EPIGENÉTICAS**

# DISCAPACIDAD ASOCIADA A ETIOLOGÍA GENÉTICA



## -ALTERACIONES CROMOSÓMICAS NUMÉRICAS





Preinforme

CARIOGRAMA

Diagnóstico:				Nº interno:	A 2224
Técnica:	PB-MAX			Cultivo:	Linfocitos
Análisis en:	13	Mitosis		Bandeo:	GTG

NÚMERO MODAL

2n 44	2n 45	2n 46	2n 47	2n 48	OTROS
				13	

OBSERVACIONES: En todas las metáfases analizadas se observó un cromosoma X y un cromosoma 21 adicionales.

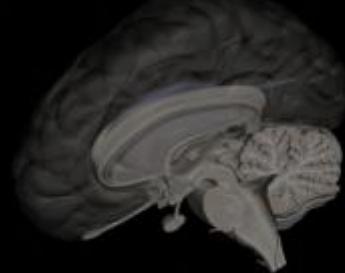
CONCLUSIONES:Cariotipo: 48,XXY,+21

Nota: Es muy importante el consejo genético.

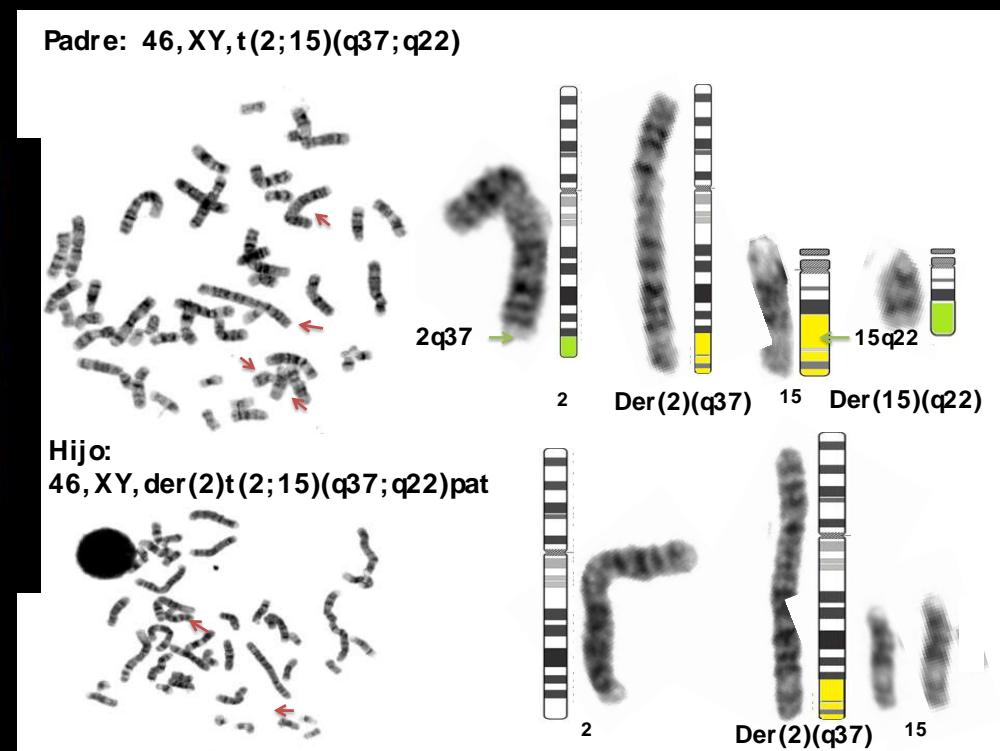
Informado: 26/01/2010

Este informe debe interpretarse con los antecedentes clínicos

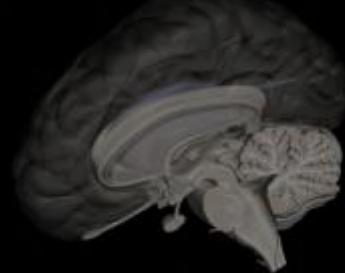
# DISCAPACIDAD ASOCIADA A ETIOLOGÍA GENÉTICA



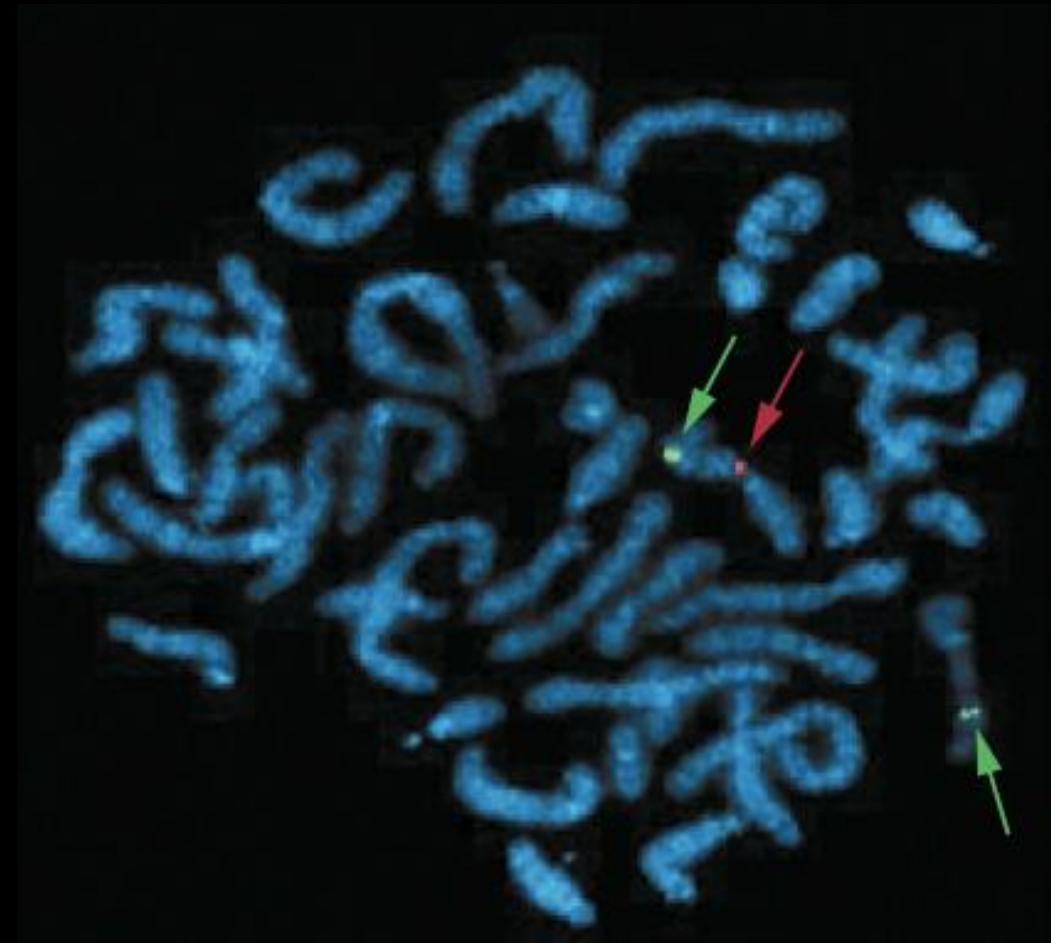
## -ALTERACIONES CROMOSÓMICAS ESTRUCTURALES TRASLOCACIONES

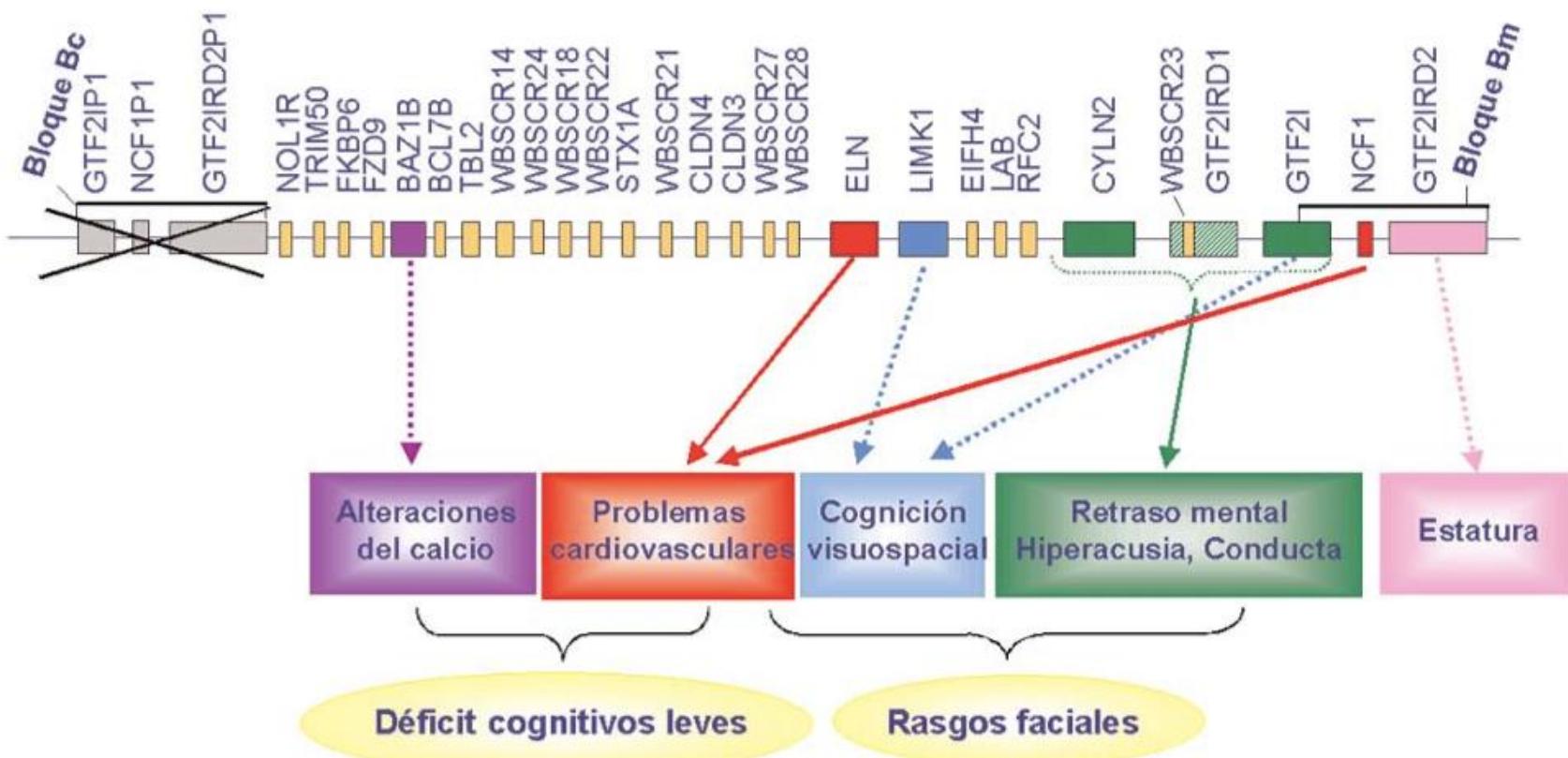
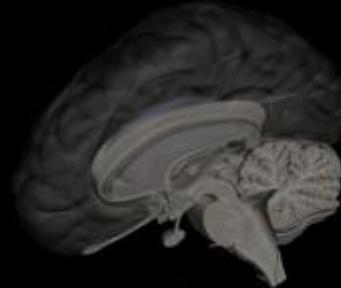


## DISCAPACIDAD ASOCIADA A ETIOLOGÍA GENÉTICA



-ALTERACIONES DE DELECIÓN DE GENES CONTIGUOS: WILLIAMS





# DISCAPACIDAD ASOCIADA A ETIOLOGÍA GENÉTICA



-ALTERACIÓN DE UN GEN ÚNICO

GEN 22q11.2



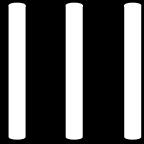
HIBRIDACION IN SITU CON FLUORESCENCIA (FISH) PARA DELECIÓN DEL CROMOSOMA 22	
Se realizo FISH con la sonda LSI DiGeorge/velocardiofacial (VCFS), Vysis, Inc., que identifica el gen TUPLE1.	
MUESTRA:	: SANGRE PERIFERICA
NUMERO INTERNO:	: F481
INDICACIÓN CLINICA:	: Obs. DiGeorge.
NUMERO DE METAFASES ANALIZADAS:	: 30
NUCLEOS INTERFASTICOS:	: 300
COMENTARIO:	: 2 señales en las metafases y 3 señales en 73% de los nucleos interfasicos.
RESULTADO:	: 1 ish 22q11.2(TUPLE 1x2) nuc ish 22q11.2(TUPLE 1x3)(73)/nuc ish 22q11.2(TUPLE 1x2)(27)
CONCLUSION:	: En 73% de los nucleos interfasicos se observaron 3 señales TUPLE 1, lo que corresponderia a una duplicacion de esta region en uno de los cromosomas.
OBSERVACIONES:	: Se sugiere realizar FISH cromosoma 22 a ambos padres.



NORMAL



DI GEORGE



VARIANTE DI GEORGE

# ESTUDIO CROMOSÓMICO POR HIBRIDACIÓN GENÓMICA COMPARATIVA (aCGH-SNP)

Muestra : Sangre periférica  
Código Interno : A5314  
Indicación clínica : Retraso pondopostural, Talla baja, Retraso del desarrollo moderado, Hipertonia, Dismorfias, Malformación del pabellón auricular, Hipotiroidismo, 46,XX

Se utilizó la técnica de hibridación genómica Comparada (aCGH) usando la plataforma 4x180K Agilent SurePrint G3 CGH+SNP Microarray con las referencias Agilent technologies. El Array contiene 120.000 sondas CGH con un espacio medio de 25Kb y 60.000 sondas SNP con una resolución LOH/UPD de 5-10 Mb. Las sondas CGH cubren toda la zona ISCA (Internacional Standards For Cytogenomics Arrays) y en estas regiones es posible detectar pérdidas y ganancias de material genómico de <25 Kb. Control de Calidad validado DLRS (Derivative Log Ratio Spread) <0.3.

## **RESULTADOS:**

Alteración	Cromosoma	Intervalo	Tamaño Kb	Nº Sondas
Amplificación	1p36.11	25,068,888-27,133,562	2.064	67

**RefSeq Genes:** RUNX3, SYF2, RHD, RHCE, LDLRAP1, SEPN1, PAQR7, STMN1, EXTL1, SLC30A2, PDIK1L, LIN28A, DHDDS, HMGN2, RPS6KA1, PIGV

## **FORMULA:**

arr[hg19] 1p36.11(25,068,888-27,133,562)X3



**(a)**



**(b)**



**(c)**

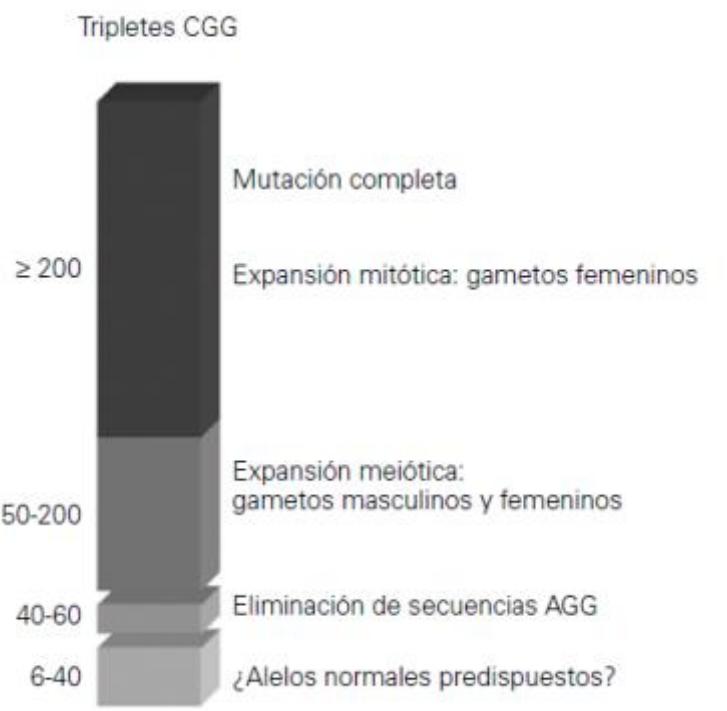
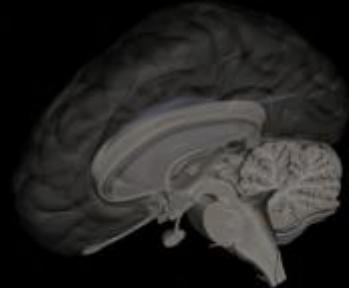


**(d)**



# DISCAPACIDAD ASOCIADA A ETIOLOGÍA GENÉTICA

## -ALTERACIONES POR REPETICIÓN DE TRIPLETES FENÓMENO DE ANTICIPACIÓN



## DISTROFIA MIOTÓNICA X FRÁGIL HUNTINGTON



TEST: Direct analysis of the CTG repeat region of the DM gene with polymerase chain reaction (PCR)/ capillary electrophoresis and analyzed with restriction enzymes by the Southern blot technique.

RESULTS:

NAME		CTG RPT#	Significance
[REDACTED]	Allele 1	2500	(DM)
	Allele 2	13	

INTERPRETATION:

Thomas Schwerter has an expanded repeat sequence, which is consistent with a myotonic disease gene. The parents of the patient should be examined to determine the source of the gene and to estimate the risk of reoccurrence of the disease in any other children they may have. Furthermore, the implications of genetic testing can be complicated and genetic counseling can be a valuable aid in understanding the results.

If you or the family has any questions, please do not hesitate to contact me.

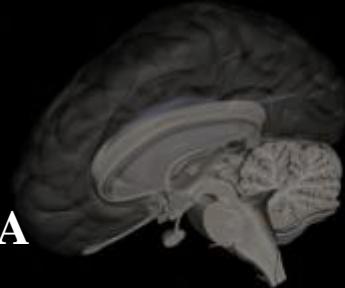
Sincerely yours,

Frederick V. Schaefer, Ph.D.  
Director, Molecular Genetics

Southern blot analysis performed by Greenwood Genetic Center 125 Gregor Mendel Circle Greenwood, SC 29646

This test was developed and its performance determined by the Center for Genetic Testing at Saint Francis. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary and to our knowledge no laboratory in the world has FDA approval for this class of testing. This test is used for clinical purposes. Pursuant to the requirements of CLIA '88, this laboratory has established and verified the test's accuracy and precision.

# **ETIOLOGÍA DISCAPACIDAD PSICOMOTORA DE IMPORTANCIA**



**-DE CAUSA DESCONOCIDA**

**CADA VEZ MENOR EN MEDIDA QUE TECNOLOGÍA AVANZA**

**IMPORTANTE PESO DE CAUSA GENÉTICA**

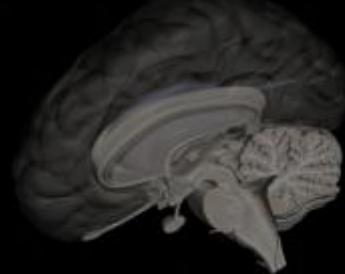
**NO DEBE INMOVILIZAR LAS ESTRATEGIAS TERAPÉUTICAS**

**IMPORTANTE SIEMPRE REPLANTEAR ETIOLOGÍA**

**BUSCAR CAUSA PERMITE**

**CONSEJO GENÉTICO  
BUSCAR POSIBLES TERAPIAS  
CONOCER CURSO DEL CUADRO  
PREVENIR COMPLICACIONES**

# **RETRASO DEL DESARROLLO PSICOMOTOR**



**ADECUADA HISTORIA FAMILIAR**

**HISTORIA GESTACIONAL**

**HISTORIA PERINATAL**

**DETALLE DE HITOS LOGRADOS Y NO LOGRADOS**

**EXAMEN FÍSICO GENERAL (PIEL)**

**BÚSQUEDA DE DISMORFIAS**

**CIRCUNFERENCIA CRANEALES**

**EXAMEN NEUROLÓGICO**

**TONO MOTOR**

**REFLEJOS DEL DESARROLLO**

**FONDO DE OJO**

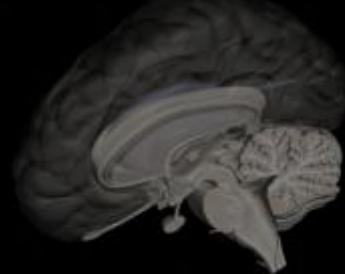
**EXÁMENES DE SER PERTINENTE**

# **DISCAPACIDAD PSICOMOTORA : ENFOQUE DIAGNÓSTICO**



- SINDRÓMICA**
- NO SINDRÓMICA**
- CON ANTECEDENTES FAMILIARES**
- SIN ANTECEDENTES FAMILIARES**
- CON EXAMEN NEUROLÓGICO NORMAL**
- CON EXAMEN NEUROLÓGICO ALTERADO**

# **DISCAPACIDAD PSICOMOTORA: ENFOQUE DIAGNÓSTICO**



**ASOCIA CUADRO CLÍNICO A DISMORFIAS O ALTERACIONES CLÍNICAS ESPECÍFICAS QUE PERMITAN ACOTAR ALTERNATIVAS DIAGNÓSTICAS**

- TALLA BAJA**
- TALLA ALTA**
- FACIES ESPECIAL**
- ALTERACIONES CUTÁNEAS**
- ALTERACIONES ESQUELÉTICAS**
- MALFORMACIONES ESPECÍFICAS (CARDIACAS, RENALES, ETC)**
- ALTERACIONES SISTEMA NERVIOSO CENTRAL**
- ETC**

## **ALTERACIONES PSICOMOTORAS ASOCIADAS A:**

**-TALLA BAJA**

**-DESPROPORCIÓN DE SEGMENTOS CORPORALES**

**-ALTERACIONES ESQUELÉTICAS**



**DISPLASIAS ESQUELÉTICAS  
(OSTEOCONDRODISPLASIAS)**



**CAUSA GENÉTICA  
BAJA FRECUENCIA  
DIFICULTAD DIAGNÓSTICA  
DESAFÍO TERAPÉUTICO**

# DISPLASIAS ESQUELÉTICAS

-ENFERMEDADES MONOGÉNICAS

-456 ENTIDADES

-INCIDENCIA 1 EN 4.000-5.000 RN VIVOS

-REPRESENTAN EL 2-3% DE CONSULTAS POR TALLA BAJA

-PLANTEAR SIEMPRE EN TALLA BAJA DESPROPORCIONADA

-ACORTAMIENTO DE EXTREMIDADES: RIZO PROXIMAL  
MESO MEDIAL  
ACRO DISTAL



# **DISPLASIAS ESQUELÉTICAS**

**ESTUDIO RX**

**CRÁNEO AP-LAT**

**COLUMNA AP-LAT**

**EXTREMIDADES SUPERIOR FRONTAL**

**EXTREMIDADES INFERIORES FRONTAL**

**PIE**



**A EVALUAR EN RADIOLOGÍA (RX) DE HUESOS LARGOS:**

**INTEGRIDAD**

**LONGITUD**

**DEFORMIDAD**

**DENSIDAD**

**ESTRUCTURA**

**FISIS**

**CLÍNICA (FENOTIPO)+RADIOLOGÍA: PLANTEAMIENTO DIAGNÓSTICO**

**OSTEO GEN PROFILE: 229 GENES PARA DISPLASIA ESQUELÉTICA**



## **ACORTAMIENTO DE EXTREMIDADES:**

**ACONDROPLASIA**

**HIPOCONDROPLASIA**

**DISPLASIA DIASTRÓFICA**

**PSEUDOACONDROPLASIA**

**CONDRODISPLASIA METAFISIARIA**

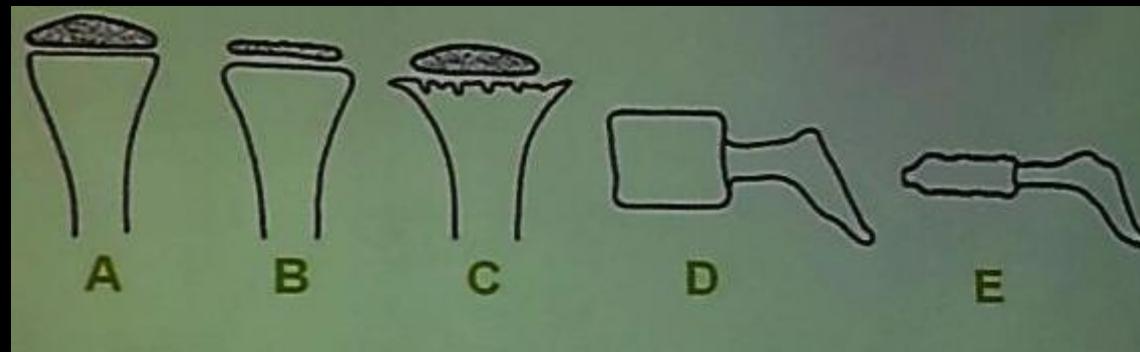
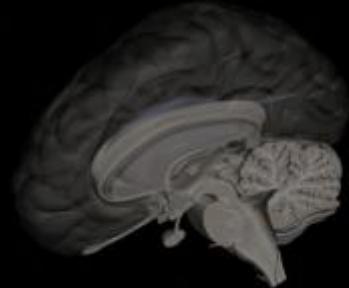
**CONDRODISPLASIA PUNCTATA**

**DISPLASIA CONDROECTODÉRMICA**

## **ACORTAMIENTO DE TRONCO**

**DISPLASIA ESPONDILOEPIFISIARIA**

**DISPLASIA ESPONDILOMETAFISIARIA**



**A+D= NORMAL**

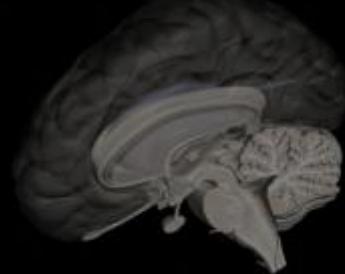
**B+D= DISPLASIA EPIFISIARIA**

**C+D= DISPLASIA METAFISIARIA**

**B+E= DISPLASIA ESPÓNDILO-EPIFISIARIA**

**C+E= DISPLASIA ESPÓNDILO-METAFISIARIA**

**B+C+E= DISPLASIA ESPÓNDILO-EPIMETAFISIARIA**



RESEARCH ARTICLE

AMERICAN JOURNAL OF  
medical genetics PART  
**A**

## Nosology and Classification of Genetic Skeletal Disorders: 2010 Revision

Matthew L. Warman,<sup>1</sup> Valerie Cormier-Daire,<sup>2</sup> Christine Hall,<sup>3</sup> Deborah Krakow,<sup>4,5</sup> Ralph Lachman,<sup>4</sup> Martine LeMerrer,<sup>2</sup> Geert Mortier,<sup>6</sup> Stefan Mundlos,<sup>7</sup> Gen Nishimura,<sup>8</sup> David L. Rimoin,<sup>4</sup> Stephen Robertson,<sup>9</sup> Ravi Savarirayan,<sup>10</sup> David Sillence,<sup>11</sup> Juergen Spranger,<sup>12</sup> Sheila Unger,<sup>12,13</sup> Bernhard Zabel,<sup>12</sup> and Andrea Superti-Furga<sup>12,14\*</sup>

DIAGNÓSTICO DISPLASIA ESQUELÉTICA EN BASE A:

- CLÍNICA
- RADIOLOGÍA
- ESTUDIO GENÉTICO
- EVALUACIÓN DE EXPERTOS

# **DISPLASIAS ESQUELÉTICAS**



**-POSIBILIDADES TERAPÉUTICAS PALIATIVAS**

**-USO DE BIFOSFONATOS**

**-CORRECCIONES QUIRÚRGICAS**

**-USO DE HORMONA DE CRECIMIENTO (DEFICIENCIA SHOX)**

**-REEMPLAZO ENZIMÁTICO:**      **HURLER-SCHEIE**

**HUNTER**

**MORQUIO**

**MAROTEAUX-LAMY**



MPS I

MPS VI

HURLER-SCHEIE



MPS II

HUNTER



MPS III

SANFILIPPO



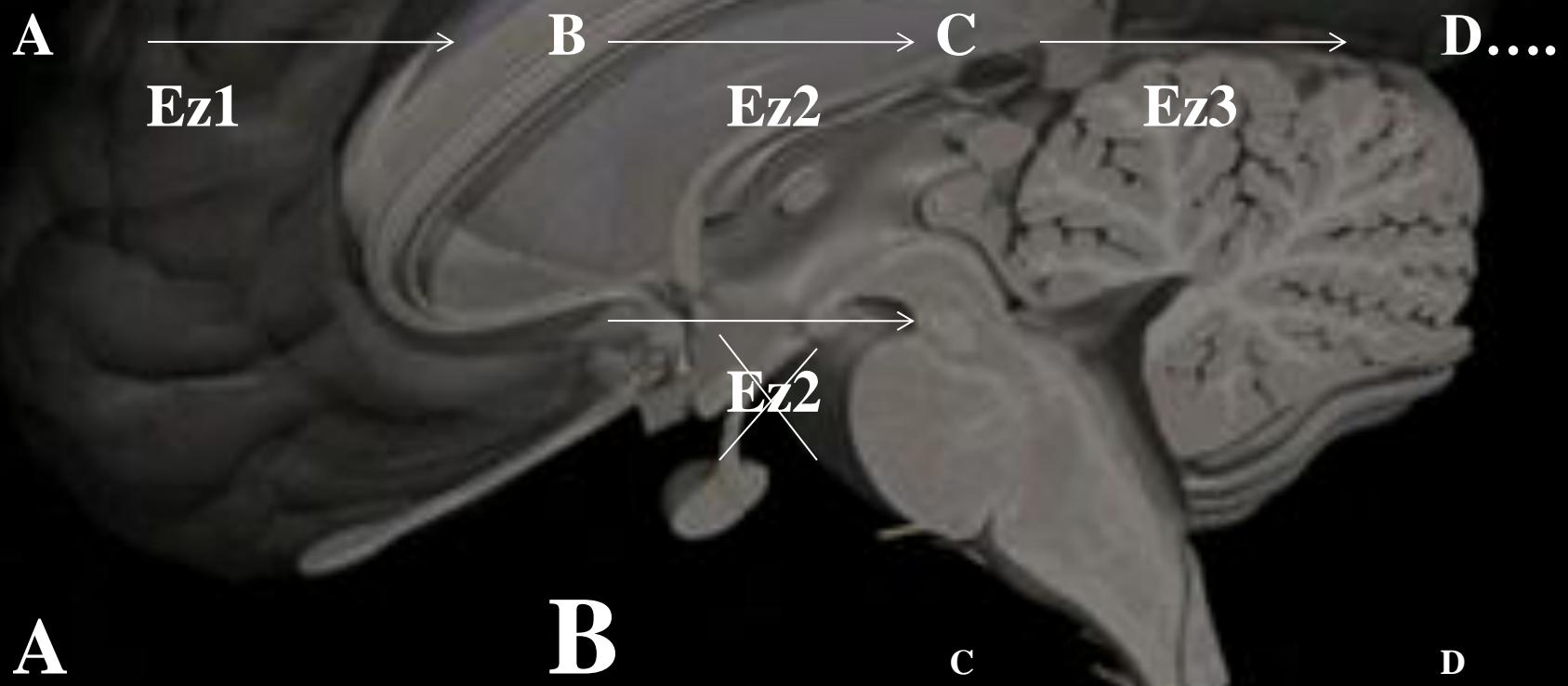
MPS IV

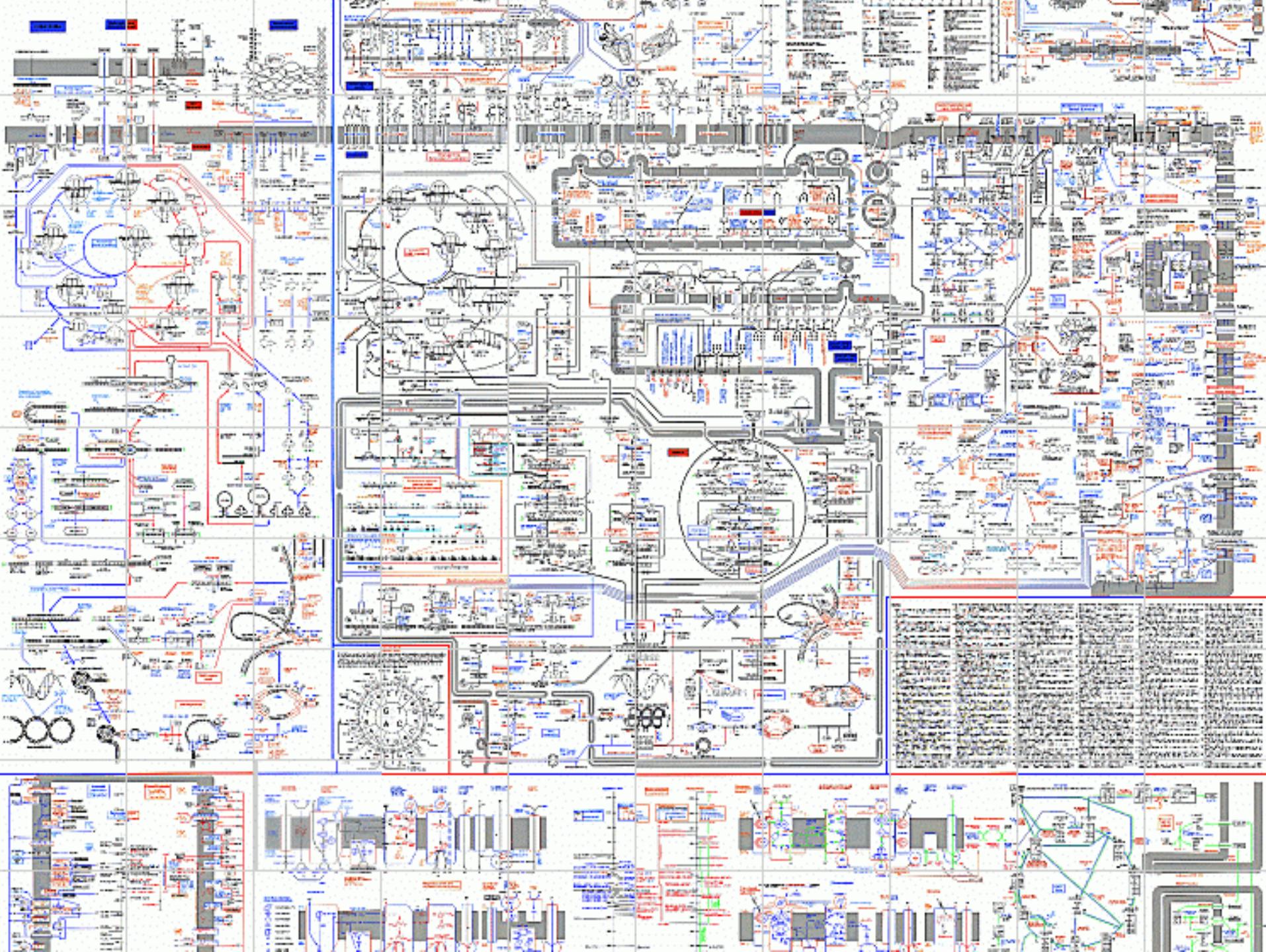
MORQUIO



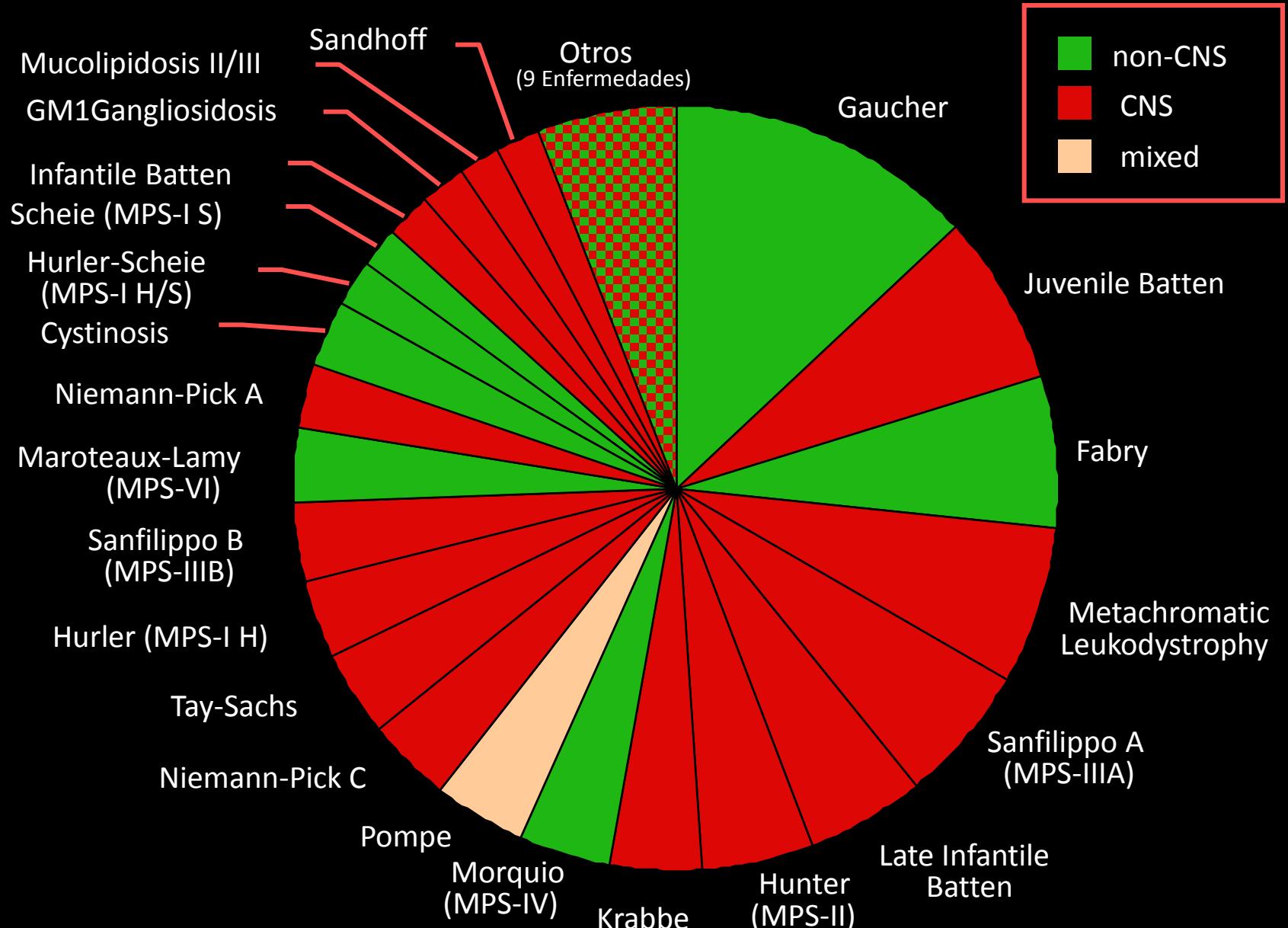
## ALTERACIONES GENÉTICAS FUNCIONALES

-ERROR GENÉTICA HABITUALMENTE EN UN GEN ÚNICO CAUSANDO  
AUSENCIA TOTAL O PARCIAL O FALLA DE FUNCIONAMIENTO ENZIMÁTICO









from Meikle et al, JAMA 281:249-254, 1999; Batten data mapped from worldwide estimates



# Caracterización citogenético-molecular de enfermedades genéticas en el Hospital Base de Puerto Montt

M. ANGÉLICA ALLIENDE<sup>1,a</sup>, BIANCA CUROTO<sup>1,b</sup>, PATRICIO GUERRA<sup>2</sup>, LORENA SANTA MARÍA<sup>1,c</sup>, REINERÍA HERMOSILLA<sup>3</sup>, DORIS ORPHANÓPOULOS<sup>4</sup>, JORGE VILLANUEVA<sup>2</sup>, ELIZABETH WETTIG<sup>5,7</sup>, XIMENA BARRAZA<sup>6</sup>

## Cytogenetic and molecular profile of genetic diseases in Puerto Montt main hospital

**Background:** Chromosome aberrations (CA) are the main etiology of multiple congenital malformations, recurrent abortions and intellectual disability (ID) specifically of moderate and severe degree. They account for 0.3 to 1% of newborns (NB) and 6 of 10,000 NB have chromosome imbalances with submicroscopic deletions or duplications smaller than 10 MB that are overlooked by conventional cytogenetic studies. **Aim:** To report the results of cytogenetic and molecular studies performed in patients with a congenital malformation disease or ID with or without dysmorphic features, attended in a regional hospital. **Patients and Methods:** One hundred and eighty patients, 27 with a clinical diagnosis of Down syndrome, derived for the suspicion of a genetic disease, were studied. A karyogram was performed in all of them and in 30 cases additional molecular studies, such as fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) were carried out. **Results:** Among the 153 patients without Down syndrome, 20 (13%) had a genetic abnormality responsible for the altered phenotype. Sixteen had a chromosome aberration (structural and numerical aberrations in 75 and 25% respectively) and four had genetic molecular alterations. Additional studies were performed to confirm or better characterize the chromosome aberration in 13 of the 30 patients in whom these were requested. **Conclusions:** Chromosome and specific genetic molecular studies in selected cases help to characterize patients with genetic diseases. The collaboration between academic and health care facilities is crucial.

(Rev Med Chile 2011; 139: 298-305).

**Key words:** Chromosome Abnormality disorders; Cytogenetic analysis; Molecular genetics.

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<sup>2</sup>Servicio de Pediatría, Hospital Base de Puerto Montt.

<sup>3</sup>Laboratorio Clínico, Hospital Base de Puerto Montt.

<sup>4</sup>Servicio de Gineco-Obstetricia, Hospital Base de Puerto Montt.

<sup>5</sup>Servicio de Neonatología, Hospital Base de Puerto Montt.

<sup>6</sup>Servicio de Pediatría, Hospital Regional de Valdivia.

<sup>7</sup>Estudio Colaborativo Latinoamericano de Malformaciones Congénitas (ECLAMC).

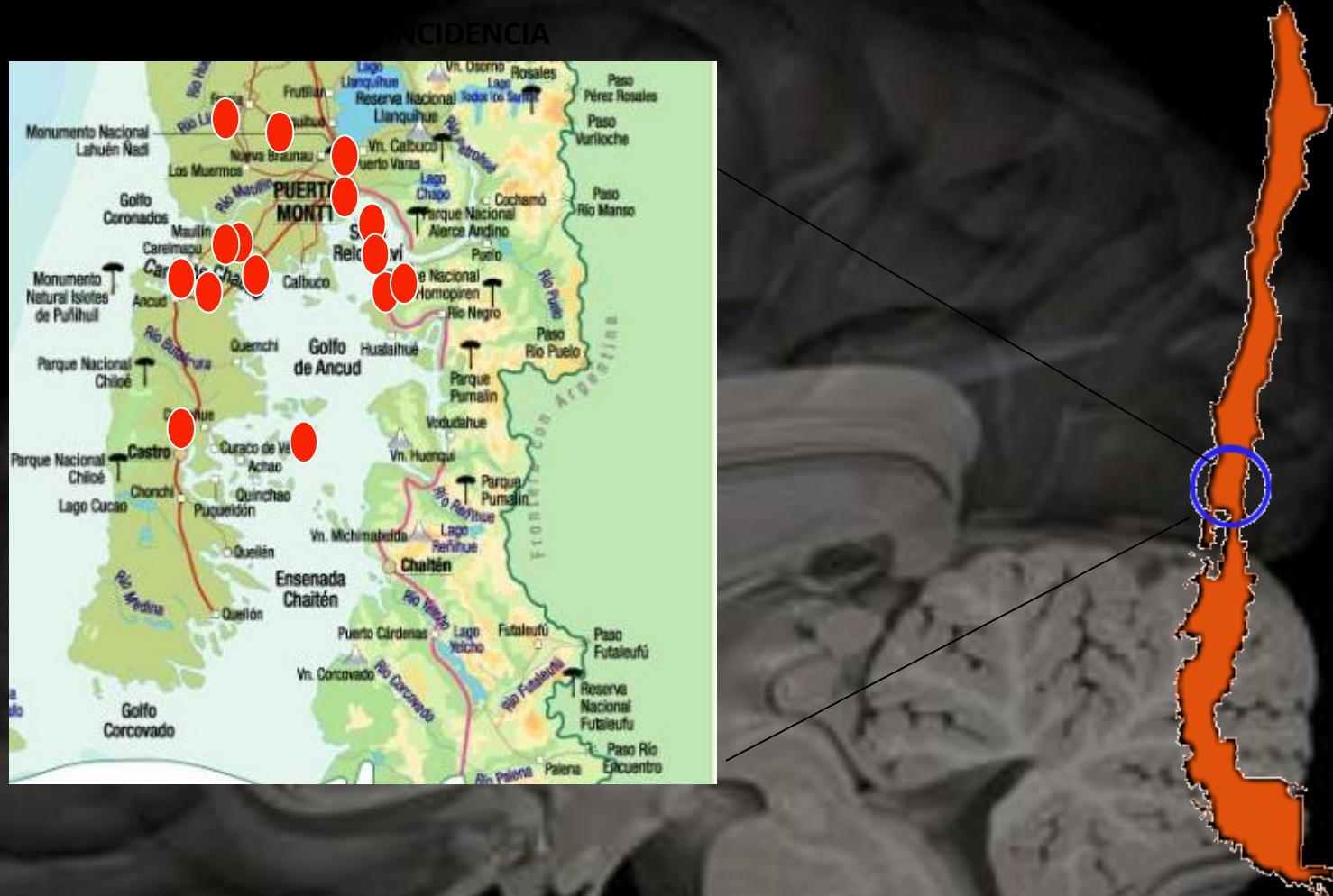
<sup>a</sup>Magíster en Ciencias Biológicas c/m en Genética. Universidad de Chile.

<sup>b</sup>Tecnólogo Médico. Universidad de Chile.

<sup>c</sup>Doctor en Ciencias c/m en Biología Celular, Molecular y Neurociencias. Universidad de Chile.

Recibido 9 de junio de 2010, aceptado el 17 de enero de 2011.

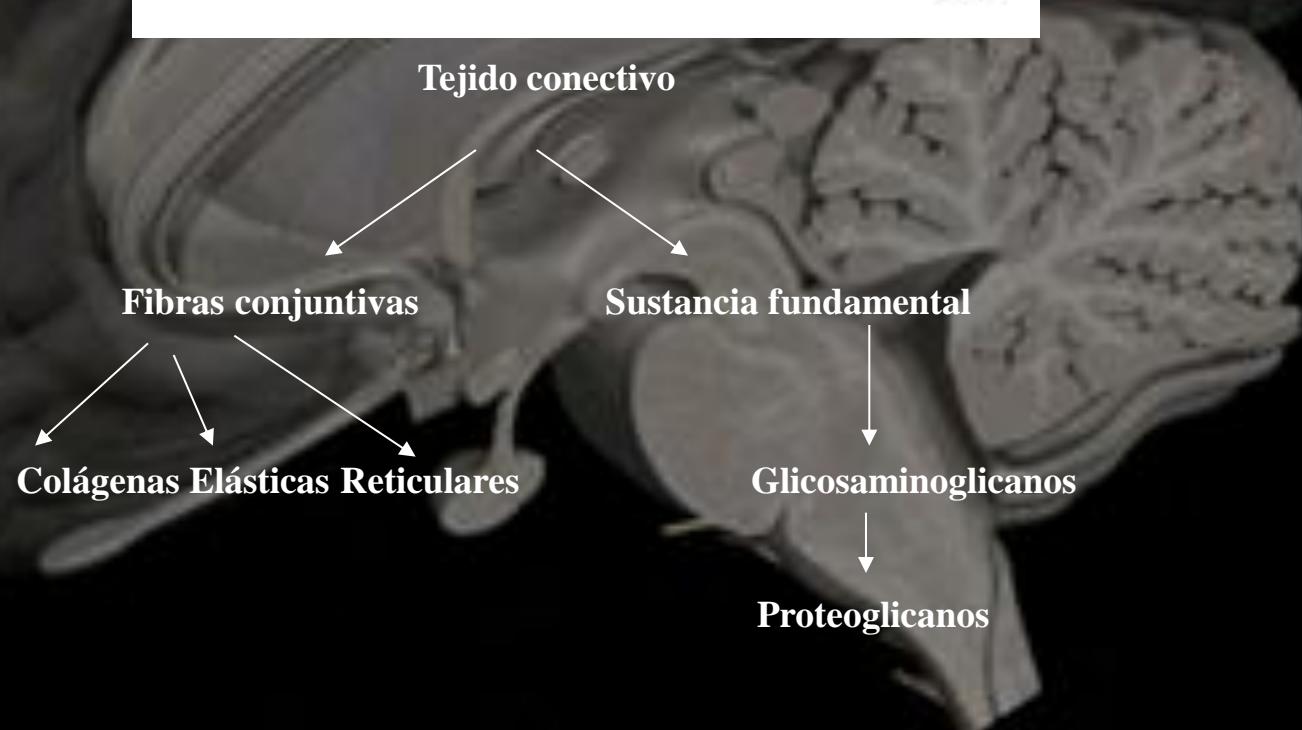
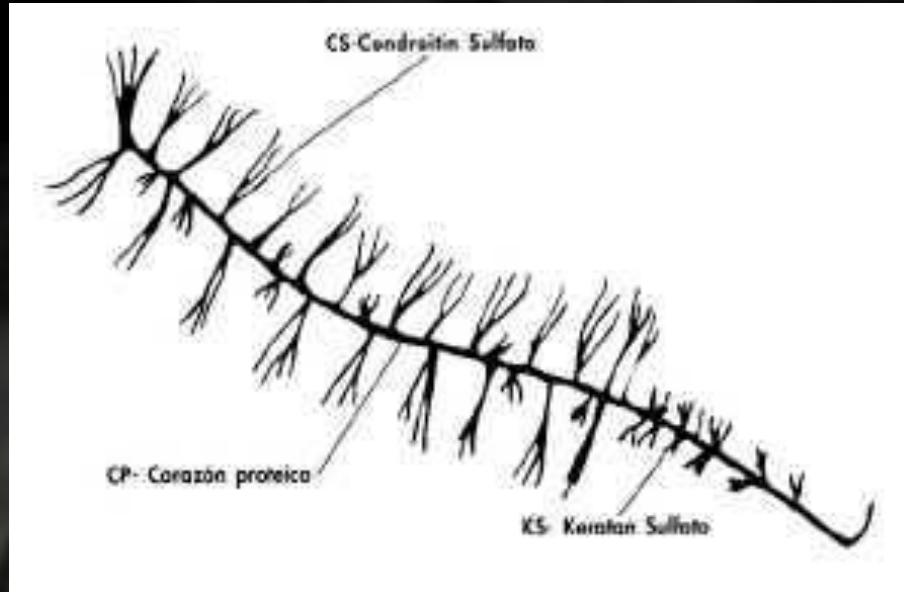
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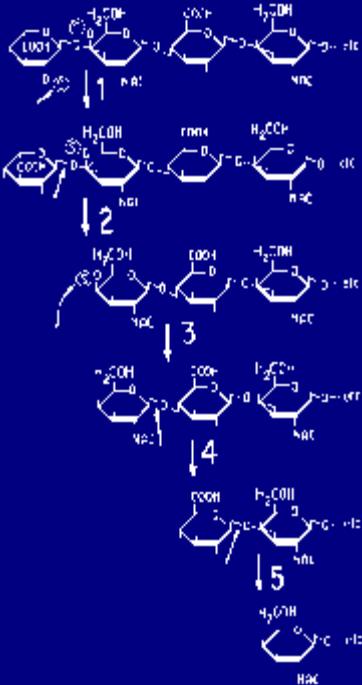


Incidencia MPS: Hungría 1/10.000

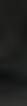
Irlanda 1/25.000

## MUCOPOLISACÁRIDOS-GLICOSAMINOGLICANOS

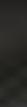




HIALURONIDASAS



ROMPE CADENAS LARGAS DE POLISACÁRIDOS  
EN UNIDADES MENORES



GLICOSAMINOGLICANOS PARCIALMENTE DEGRADADOS



HIDROLASAS ESPECÍFICAS  $\longleftrightarrow$  DEFICIENCIA ESPECÍFICA

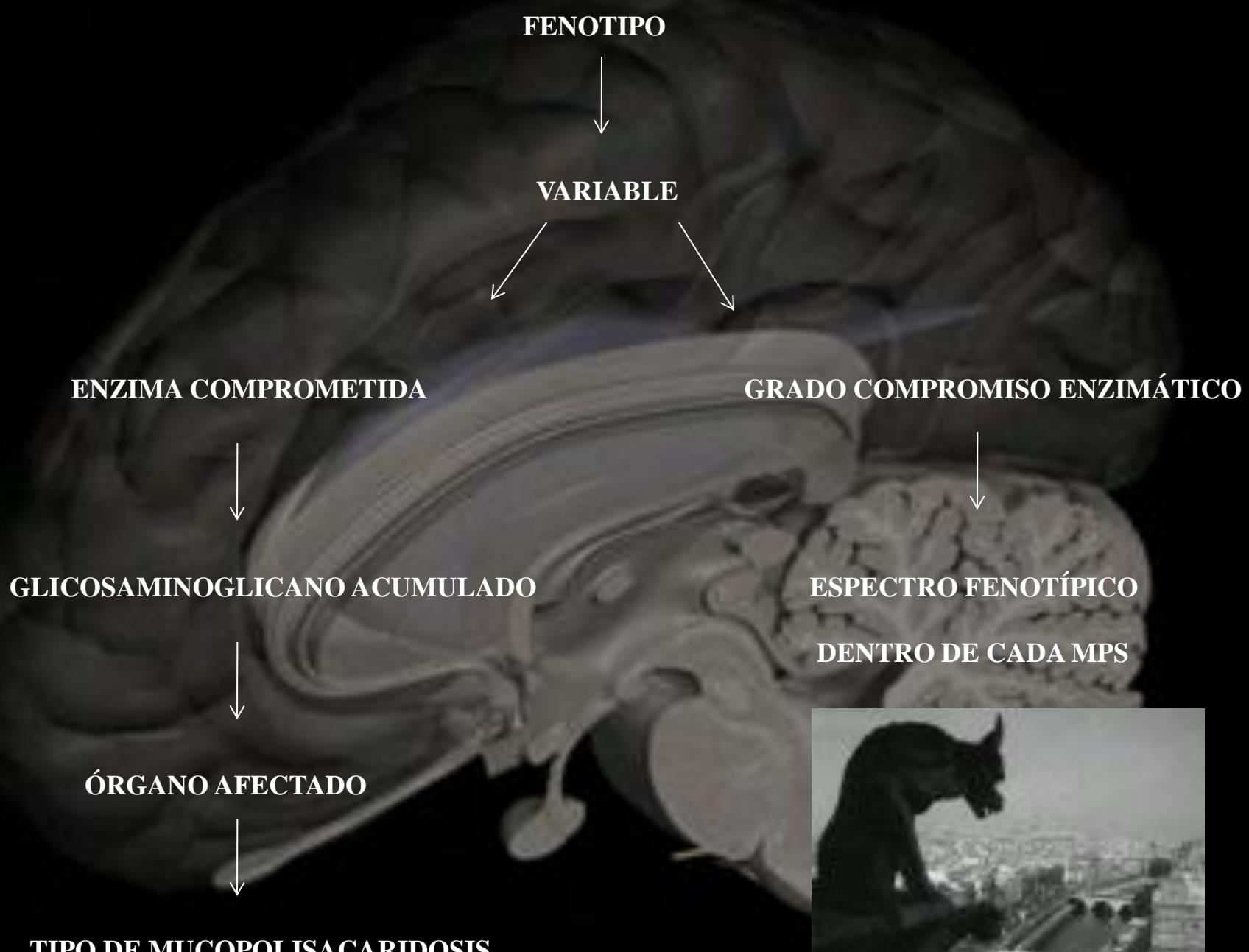


ACUMULACIÓN INTRALISOSOMAL DE MOLÉCULAS DE GLICOSAMINOGLICANOS  
PARCIALMENTE DEGRADADOS



ALTERACIÓN METABOLISMO CELULAR CON FENOTIPO ESPECÍFICO

<b>Tipo de MPS</b>	<b>Nombre Común</b>	<b>Deficiencia enzimática</b>	<b>GAG Afectado</b>
MPS I	Hurler, Hurler Scheie, Scheie	$\alpha$ -L-iduronidasa	DS, HS
MPS II	Hunter	Iduronato sulfatasa	DS, HS
MPS III A-D	Sanfilippo A Sanfilippo B Sanfilippo C Sanfilippo D	Heparán N-sulfatsa N-acetilglucosaminidasa Acetil-CoAlfa-glucosaminida acetiltransferasa N-acetilglucosamina-6-sulfatasa	HS HS HS HS HS
MPS IV A	<b>Morquio A</b>	<b>N-acetíl galactosamina-6-sulfatasa (GALNS)</b> á-galactosidasa	KS,CS
MPS IV B	Morquio B		KS
MPS VI	Maroteaux-Lamy	N-acetilgalactosamina 4-sulfatasa (arilsulfatasa B)	DS
MPS VII	Encubierto	á-glucuronidasa	DS, HS, CS
MPS IX	Deficiencia de Hialuronidasa	Hialuronidasa	HA



# MUCOPOLISACARIDOSIS ÓRGANOS COMPROMETIDOS

SISTEMA NERVIOSOS CENTRAL

SISTEMA NERVIOSO PERIFÉRICO

GLOBO OCULAR-NERVIO ÓPTICO

PIEL

ESQUELETO

HÍGADO-BAZO

OIDO

CORAZÓN

APARATO RESPIRATORIO

# MUCOPOLISACARIDOSIS: MANIFESTACIONES CLÍNICAS

## SISTEMA NERVIOSO CENTRAL Y PERIFÉRICO

**RETARDO MENTAL (RDSM-DETERIORO)**

**HIDROCEFALIA COMUNICANTE**

**COMPRESIÓN NERVIO ÓPTICO**

**COMPRESIÓN MEDULAR**

**COMPRESIÓN NERVIOS PERIFÉRICOS**

**EPILEPSIA**



# MUCOPOLISACARIDOSIS: MANIFESTACIONES CLÍNICAS

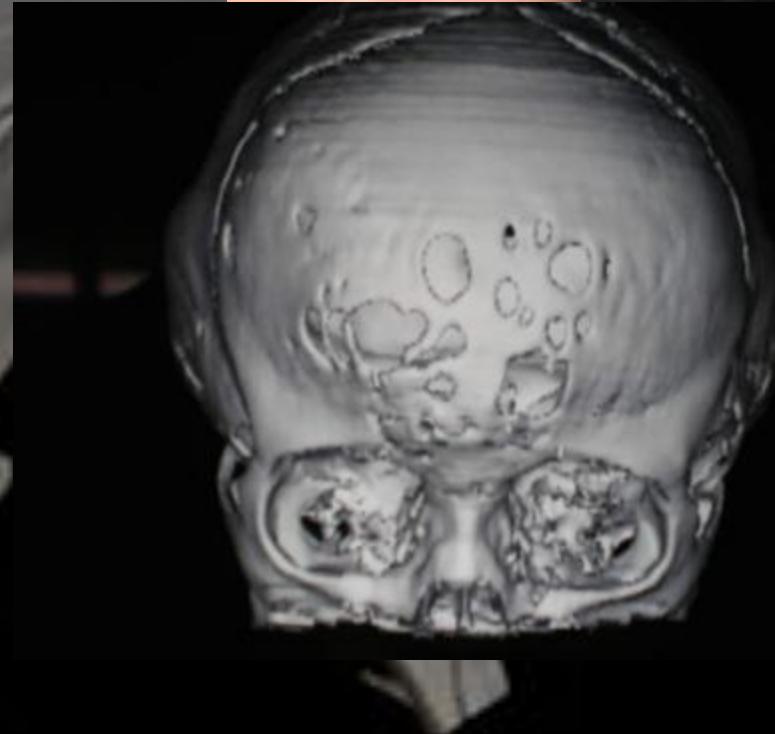
## VISIÓN

OPACIDADES CORNEALES

GLAUCOMA

COMPRESIÓN NERVIO ÓPTICO

DEGENERACIÓN RETINIANA



Spin  
Tilt

## MUCOPOLISACARIDOSIS: MANIFESTACIONES CLÍNICAS

### SISTEMA CARDIOVASCULAR

HIPERTENSIÓN ARTERIAL

MIOCARDIOPATÍA

CARDIOPATÍA CORONARIA

VALVULOPATÍAS



# MUCOPOLISACARIDOSIS: MANIFESTACIONES CLÍNICAS

## SISTEMA RESPIRATORIO

PATOLOGÍA PULMONAR RESTRICTIVA

EXCURSIÓN DIAFRAGMÁTICA LIMITADA

IRA A REPETICIÓN

ESPESAMIENTO SECRECIONES

VÍA ÁREA ALTA ESTRECHA

HIPERTENSIÓN PULMONAR

APNEAS OBSTRUCTIVAS

## MUCOPOLISACARIDOSIS: MANIFESTACIONES CLÍNICAS

### SISTEMA DIGESTIVO

HEPATOMEGLIA

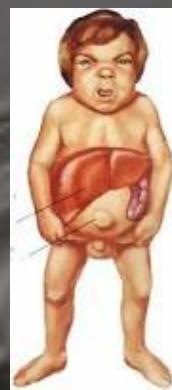
ESPLENOMEGLIA

DIARREA INTERMITENTE

HERNIA INGUINAL

HERNIA UMBILICAL

HERNIA LINEA MEDIA



# MUCOPOLISACARIDOSIS: MANIFESTACIONES CLÍNICAS

## SISTEMA ESQUELÉTICO

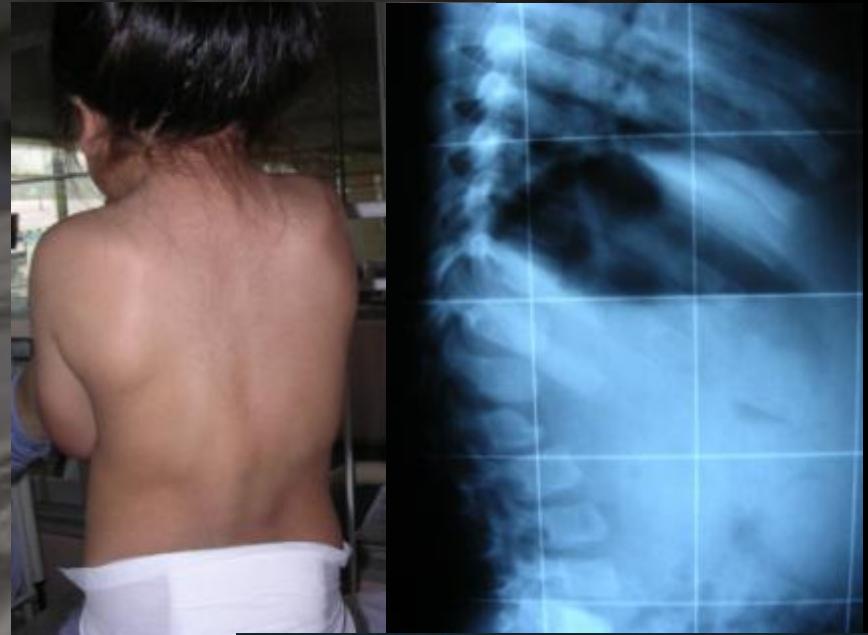
DWARFISMO

ESCOLIOSIS

LUXACIÓN CADERA

RIGIDEZ ARTICULAR

XIFOSIS



ARCHIVO PERSONAL  
AUTORIZADO USO ACADÉMICO



# MUCOPOLISACARIDOSIS: DIAGNÓSTICO

SOSPECHA CLÍNICA

TALLA BAJA

RDSM

ALTERACIONES ESQUELÉTICAS

FENOTIPO TOSCO

OPACIDADES CORNEALES

MACROCEFALIA RELATIVA

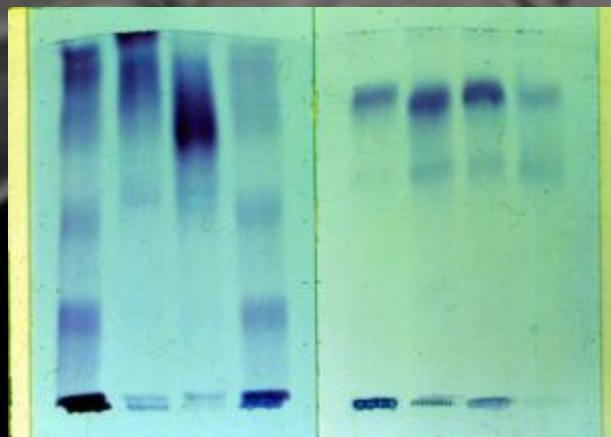
HEPATOESPLENOMEGALIA

# MUCOPOLISACARIDOSIS: DIAGNÓSTICO LABORATORIO

TEST DE BERRY



CUANTIFICACIÓN-CROMATOGRAFÍA  
GLICOSAMINOGLICANOS EN ORINA



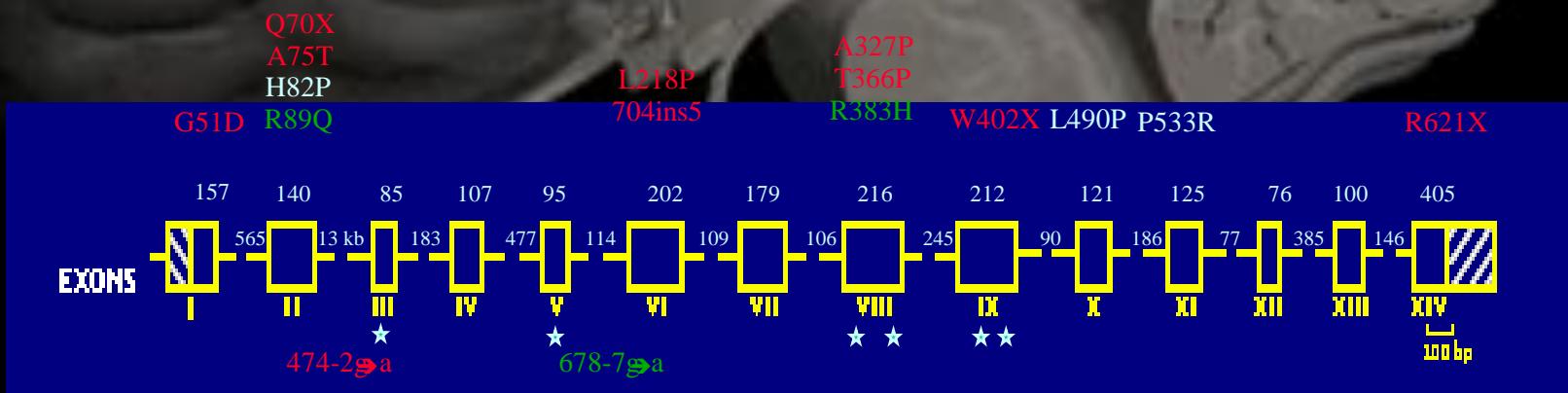
# MUCOPOLISACARIDOSIS: DIAGNÓSTICO

## LABORATORIO

### ESTUDIO ENZIMÁTICO EN LEUCOCITOS

### ESTUDIO ENZIMÁTICO EN TARJETAS DE PAPEL FILTRO

### ESTUDIO GENOTIPO



# MUCOPOLISACARIDOSIS

## MÉTODOS DIAGNÓSTICOS



## DBS (GOTA DE SANGRE SECA EN PAPEL FILTRO)

FÁCIL DE TOMAR

EXAMEN VALIDADO

SENSIBILIDAD SIMILAR PARA DISTINTAS PRESENTACIONES

NO DISTINGUE FORMAS CLÍNICAS

USO EN TAMIZAJE

# MUCOPOLISACARIDOSIS: ESTUDIO BÁSICO

Rx CRÁNEO

ECO ABDOMINAL

RX COLUMNA-ESQUELETO TOTAL

EVALUACIÓN OFTALMOLÓGICA

AUDIO-IMPEDANCIOMETRÍA-EOA-PEA

ECOCARDIOGRAFÍA 2D DOPPLER COLOR

TAC CEREBRAL SIN CONTRASTE

RMN COLUMNA CERVICAL

ESPIROMETRÍA-SATUROMETRÍA NOCTURNA-PSG



# ENFERMEDADES LISOSOMALES CON TRE

MPS I

MPS II

MPS VI

MPS III (\*)

MPS IV-A

POMPE

GAUCHER

FABRY

WOLMAN (\*)

# TERAPIA DE REEMPLAZO ENZIMÁTICO EN ENFERMEDADES LISOSOMALES APROBACIÓN FDA

**Table 2 Current approved ERT for LSD**

Enzyme	Disease	Brand name	Generic name	Year approved	Antibody <sup>a</sup>	
					Status (%)	Treatment effect
Acid β-glucosidase	Gaucher	Ceredase, Cerezyme	algucerase, imiglucerase	1991 1993	~12	none/rare
α-GAL A	Fabry	Fabrazyme, Replagal (not in US)	agalsidase β agalsidase α	2003 2003	>50–90	? dose-dependent
α-L-Iduronidase	MPS I	Aldurazyme	laronidase	2003	>59–90	?
Iduronate-2-sulfatase	MPS II	Elaprase	idursulfase	2006	>50	?
N-acetylgalactosamine 4-sulfatase	MPS VI	Naglazyme	galsulfase	2005	~90	?
Acid α-glucosidase	glycogen storage disease II, Pompe	Myozyme	alglucosidase α	2006	~50–90	+

MPS, mucopolysaccharidosis.

<sup>a</sup> Status indicates antibody positivity rate. Treatment effect: + means that there is a significant effect on the efficacy of the ERT. For Myozyme, there is a significant effect to decrease efficacy in infantile Pompe patients. For the other drugs, the question mark indicates that the effect on efficacy is unknown. All of the drugs, except acid β-glucosidase, produce significant adverse effects in antibody-positive patients in addition to any other effects on efficacy.

**Enzyme reconstitution/replacement therapy for lysosomal storage diseases**  
**Curr Opin Pediatr 19:628-635**

# TERAPIA DE REEMPLAZO ENZIMÁTICO EN ENFERMEDADES LISOSOMALES

## COSTOS ECONÓMICOS

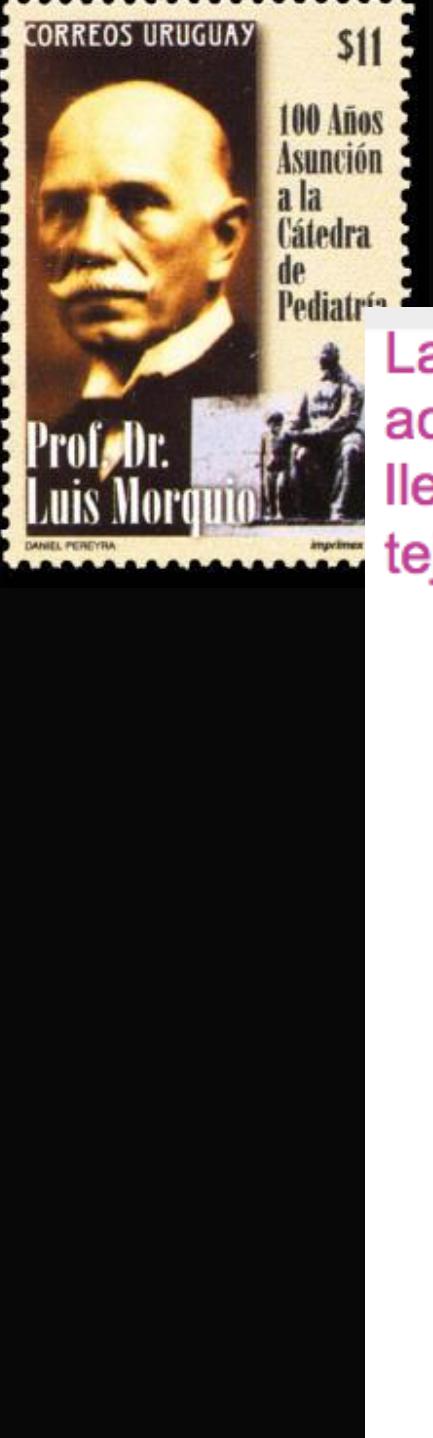
**Table 3 Cost of enzyme reconstitution therapy by disease<sup>a</sup>**

Disease	Product	Dose/kg	Drug average wholesale price (US\$/vial)	Annual cost (US\$)
Pompe disease	Myozyme 50 mg/vial (Genzyme)	20 mg/kg every 14 days	720.00	224 640.00
Gaucher disease	Cerezyme 200 U/vial (Genzyme)	60 U/kg every 14 days	790.00	184 860.00
MDS I	Aldurazyme 2.9 mg/vial (Genzyme)	0.58 mg/kg every 7 days	783.60	162 988.80
MDS II	Elaprase 6 mg/vial (Shire TKT Pharmaceuticals)	0.5 mg/kg every 7 days	3153.84	491 999.04
MDS VI	Naglazyme 5 mg/vial (Biomarin Pharmaceuticals)	1 mg/kg every 7 days	1812.00	565 344.00
Fabry disease	Fabrazyme 5 mg/vial (Genzyme)	1 mg/kg every 14 days	720.00	112 320.00
	Replagal <sup>b</sup> 3.5 mg/vial (Shire TKT Pharmaceuticals)	0.2 mg/kg every 14 days	2540.96	132 129.92

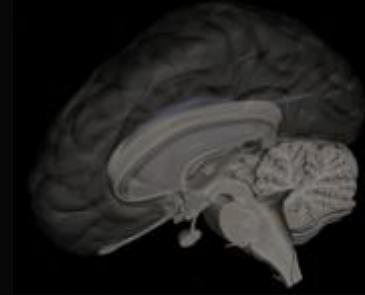
MPS, mucopolysaccharidosis.

<sup>a</sup> Annual cost of enzyme reconstitution therapy based upon a 30-kg child receiving therapy according to dosing recommendations provided by the manufacturers in package inserts. Average wholesale prices of the drugs, except Replagal ([http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4118404](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4118404)) were obtained from the Red Book Database (<http://www.micromedex.com/products/redbook/database>). The annual cost calculation does not account for other fees, including markup on the drug from hospitals, private offices, and infusion centers, and cost of supplies, among others.

<sup>b</sup> Replagal is licensed for use in Europe, Asia and Canada, but not the US.



# ENFERMEDAD DE MORQUIO



La deficiencia de actividad enzimática resulta en la acumulación de glucosaminoglicano (GAG), que lleva a una disfunción generalizada de células, tejidos y órganos

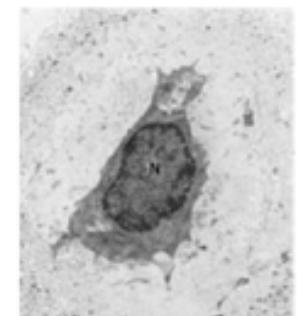
La actividad enzimática deficiente de GALNS altera la degradación lisosómica de keratán sulfato (KS) y condroitín sulfato 6 (CS6) (GAGs).



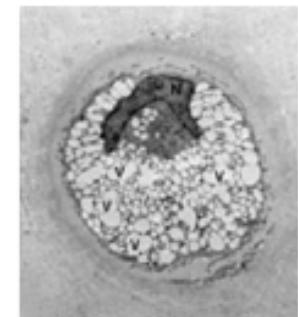
La acumulación de estos GAGs en los lisosomas llevan a la alteración de la función normal de la célula.



La disfunción celular resulta en trastornos multisistémicas progresivas que son la características de este trastorno.



Células normales sin acumulación de GAG en los lisosomas



Células en Morquio A con acumulación de GAG en los lisosomas

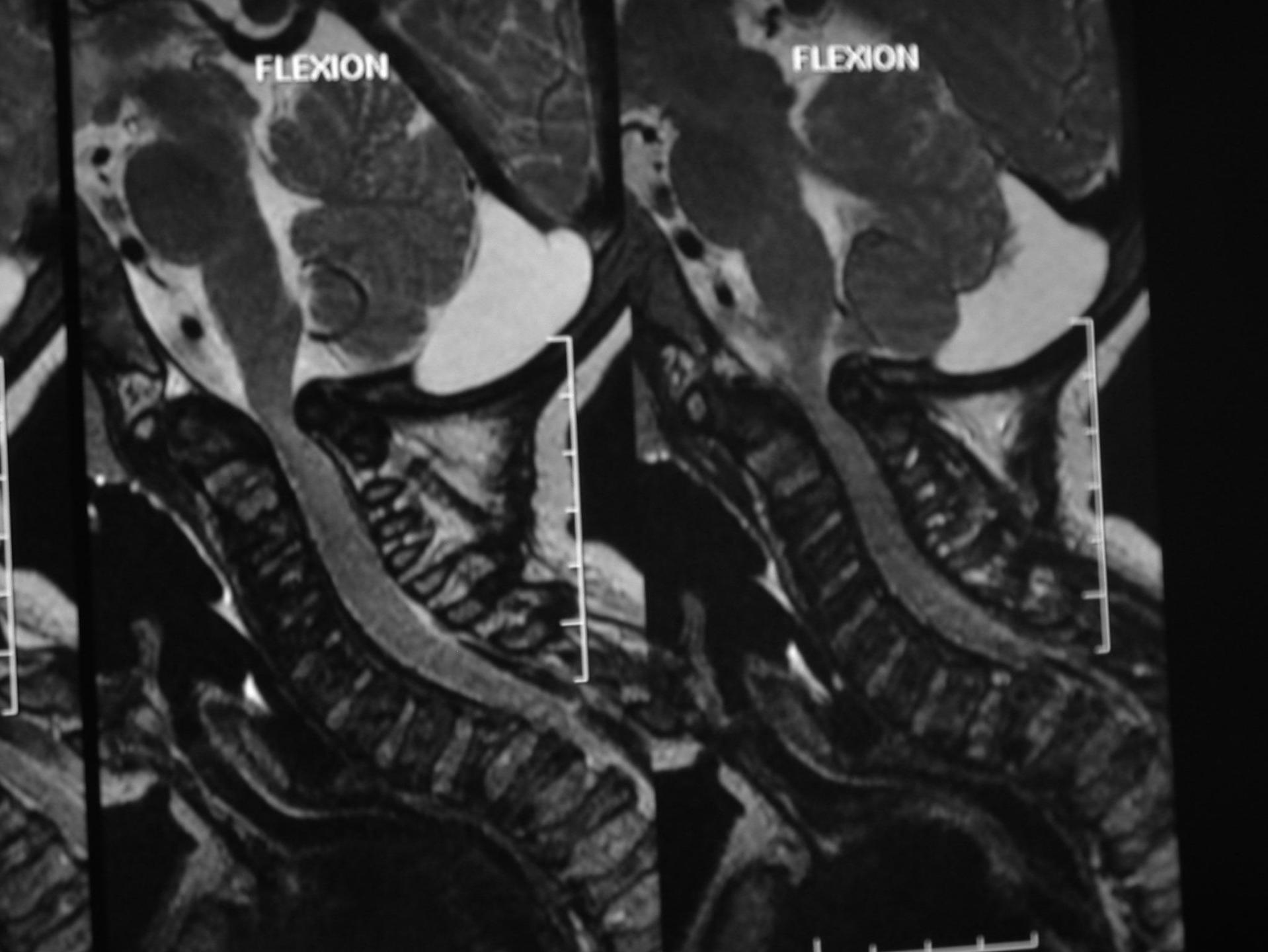


## MARCHA EN PACIENTE MORQUIO



FLEXION

FLEXION





## Síndrome de Morquio A - información importante

- También llamada MPS IVA o mucopolisacaridosis IVA
- Trastorno lisosomal recesivo autosómico
  - Hay más que 40 Enfermedades por Depósito Lisosomal (EDLs) distintas y que afectan cerca de 1 en cada 5.000 nacidos vivos
- La incidencia de Morquio varía de 1 en cada 76.000 nacidos vivos (Irlanda del Norte) a 1 en cada 640.000 nacidos vivos (Australia Occidental)
- Causado por una actividad deficiente de la enzima Sulfatasa-6-n-acetílgalactosamina (GALNS, por sus siglas en inglés), implicada en la descomposición de dos glucosaminoglicanos (GAGs):
  - Queratán Sulfato (KS)
  - Condroitín Sulfato 6 (CS6)



# Morquio A es clínicamente heterogéneo

- Más de 220 mutaciones en el gen GALNS dan lugar a una extensa diversidad genotípica y fenotípica
- Independientemente del genotipo o fenotipo específico, Morquio A causa daños progresivos a órganos blanco, resultando en complicaciones que pueden ser incluso letales
- La esperanza de vida en la mayoría de los pacientes con Morquio A está limitada a la segunda o tercera década de la vida



16 años



17 años



17 años



18 años



19 años

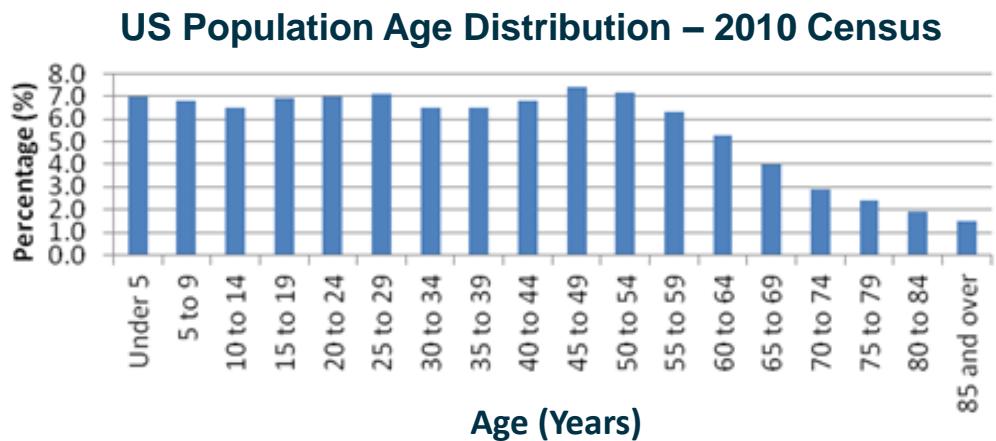
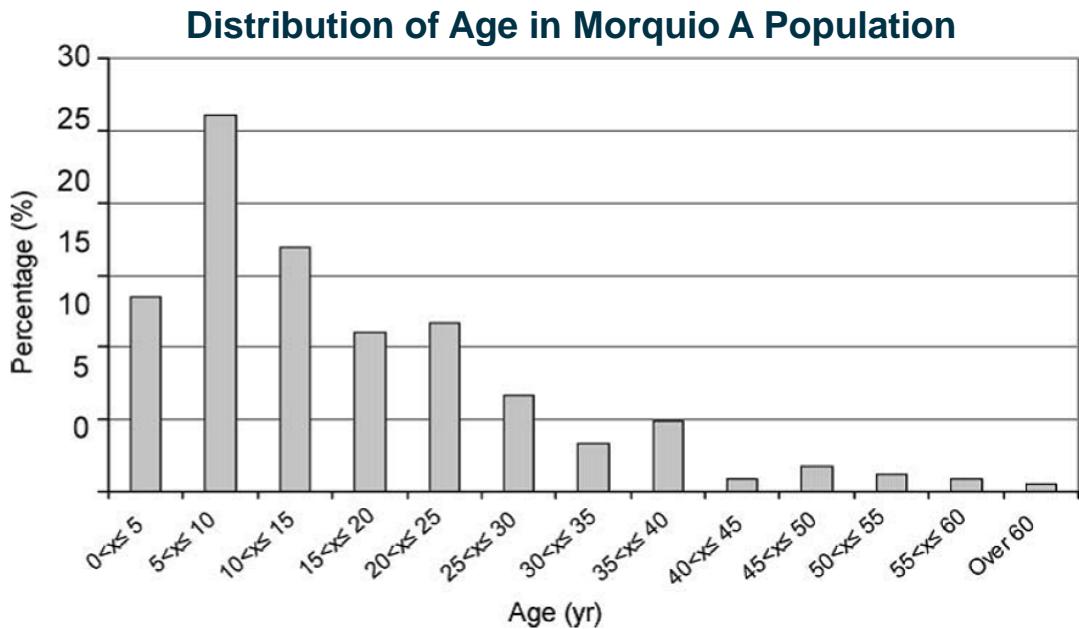
# Morquio A: un trastorno progresivo multisistémico

- La deficiencia sistémica en la actividad enzimática de *N*-acetilgalactosamina-6-sulfatasa (GALNS) puede llevar a un daño progresivo de algunos órganos, resultando en manifestaciones sistémicas complejas con consecuencias potencialmente letales.



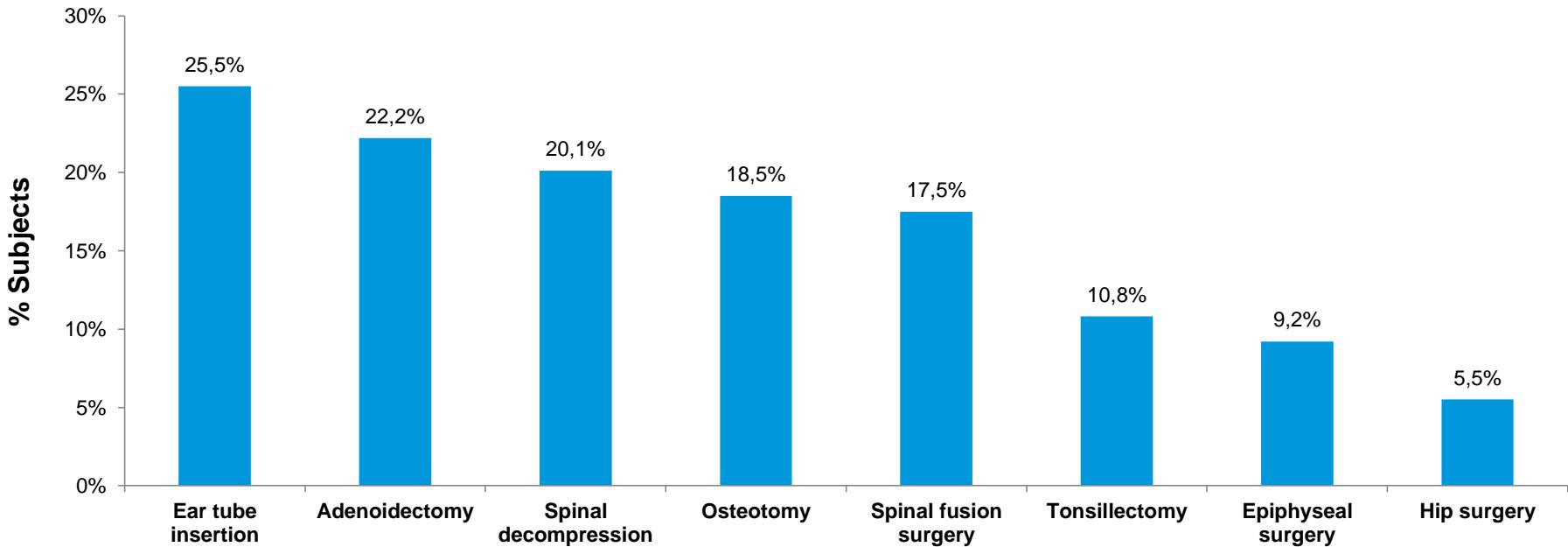
# La expectativa de vida es reducida

- Most patients usually do not survive beyond 30s
- Major causes of mortality:
  - Pulmonary complications
  - Cervical instability and myelopathy
  - Cardiac complications
  - Complications associated with surgery and general anesthesia



Harmatz P, et al. The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects. Mol Genet Metab. 2013. US Census 2010

# Los pacientes requieren de multiples cirugías



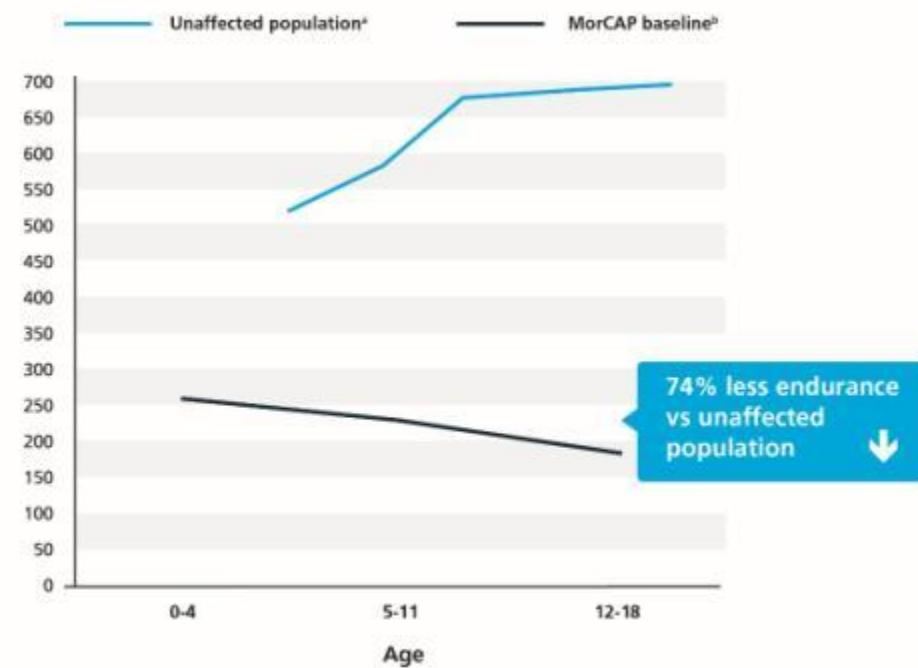
n = 325 subjects (mean age= 14.5 years)

- >70% of 325 Morquio A patients required at least one surgical procedure

# La Resistencia (6MWT) es severamente limitada en pacientes con Morquio A

- The 6MWT evaluates the global and integrated responses and functional reserves of cardiovascular, pulmonary and musculoskeletal systems
- Comparing 12-18 year olds with and without Morquio A, those with Morquio A exhibit **up to 74% less endurance** as demonstrated by 6MWT 87.7 vs. 181.2 meters
- Reduced endurance progresses over time for individuals with Morquio A

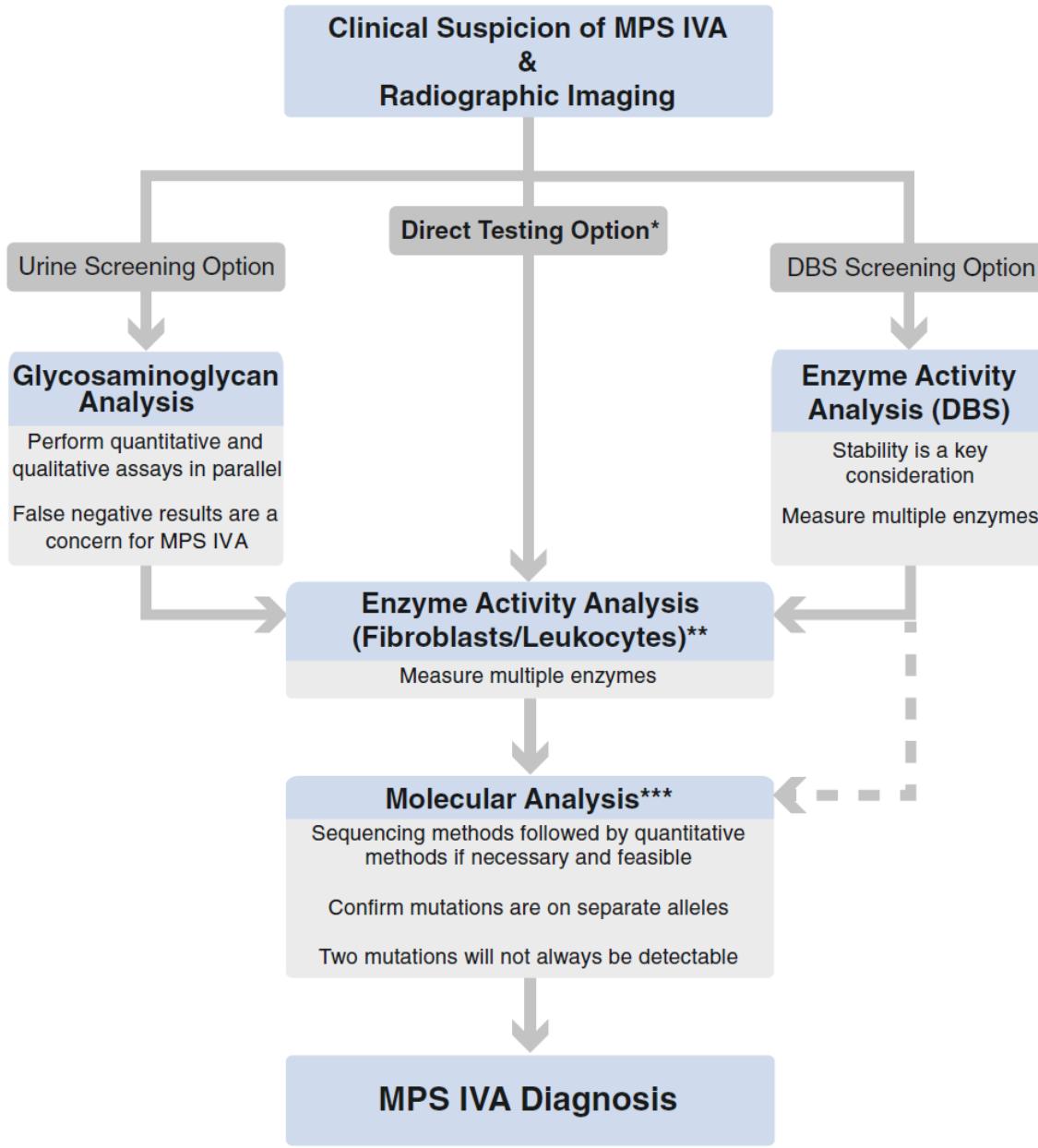
6MWT Distance in Untreated Morquio A Patients and Age-matched Healthy Controls



Harmatz P, et al. The Morquio A Clinical Assessment Program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects. *Mol Genet Metab*. 2013.

<sup>a</sup>Adapted from Geiger et al, study provides reference values for 6MWT based on and limited to demographics for 528 healthy children and adolescents ages 3 to 18.

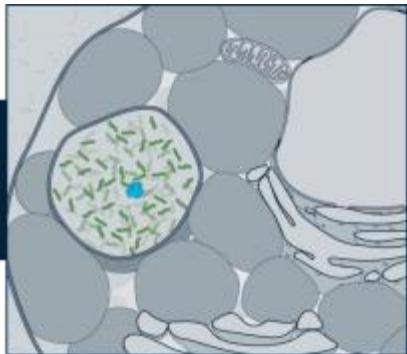
<sup>b</sup>Baseline data for MorCAP, a multicenter, multinational, cross sectional longitudinal study of 325 patients with Morquio A.



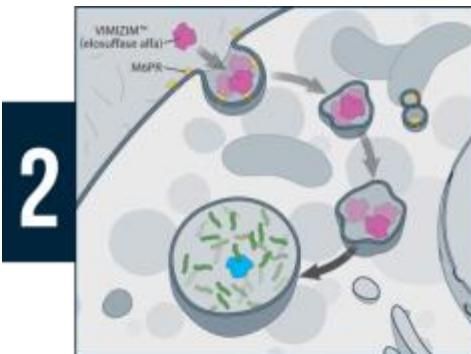
# (Elosulfase alfa) reemplaza la GALNS deficiente

The goal of ERT in Morquio A is to reduce GAG accumulation in order to restore cellular function.<sup>28</sup>

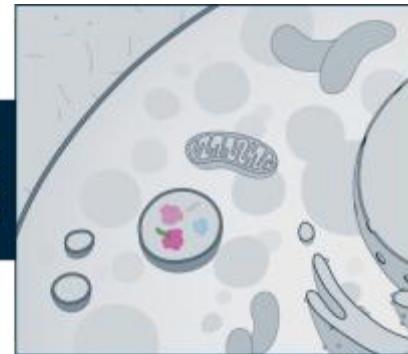
1



2



3

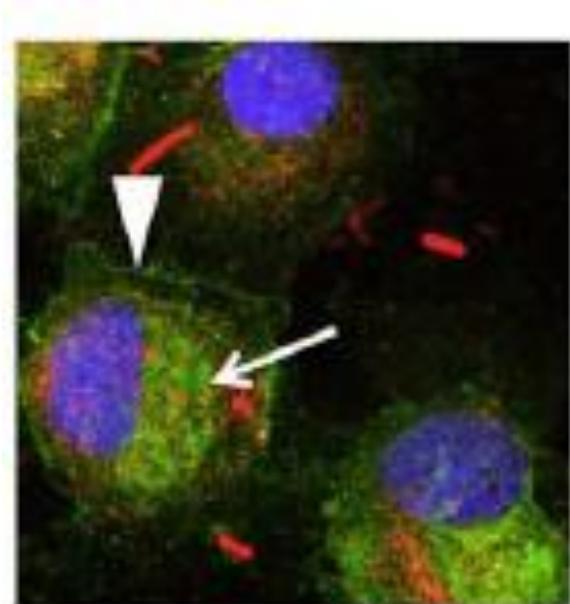


At a cellular level, GAGs accumulate in the lysosomes and occupy an increasingly greater area of the cytoplasm which disrupts normal cell function and activates secondary pathogenic cascades.<sup>28</sup>

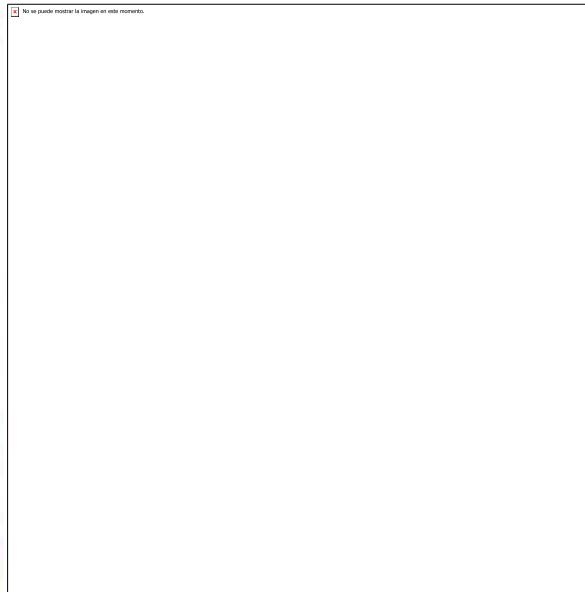
VIMIZIM™ (elosulfase alfa) is an exogenous recombinant human enzyme that replaces deficient GALNS.<sup>4,19</sup>

Within the lysosome, VIMIZIM increases catabolism of GAGs (KS and C6S)—restoring cell function.<sup>28,29</sup>

## VIMIZIM (elosulfase alfa) – Actividad farmacológica



Untreated



10 nM elosulfase alfa

- [Blue square] KS
- [Red square] Lysosomes
- [Orange square] Co-localization
- [White triangle] Extracellular KS
- [White arrow] Intracellular KS
- [Blue square] Nucleus

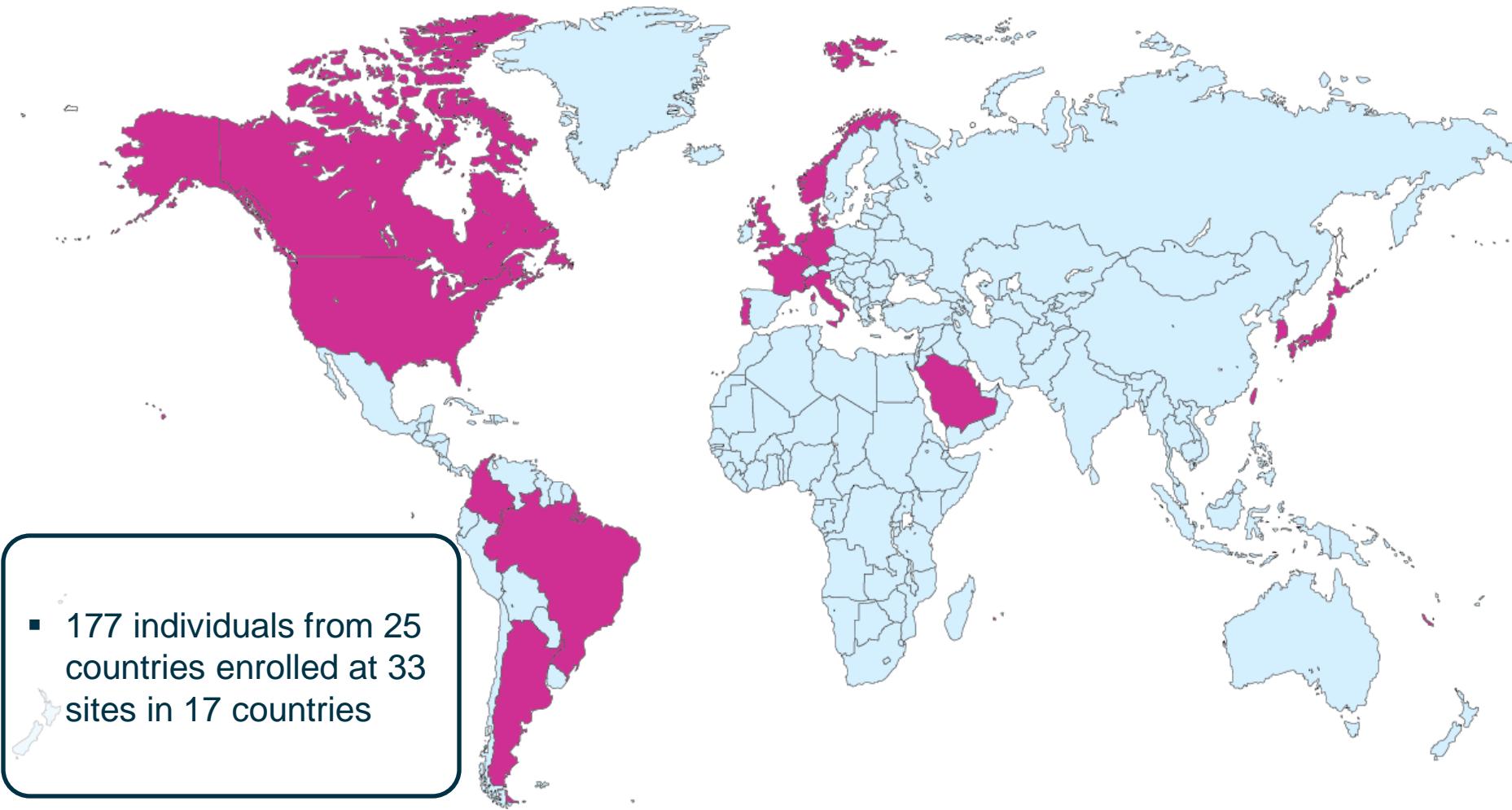
- Elosulfase alfa clears intracellular GAGs (KS) in MPS IVA chondrocytes
- Restores normal chondrocyte enzymatic function

Dvorak-Ewell et al, PLoS 2010.

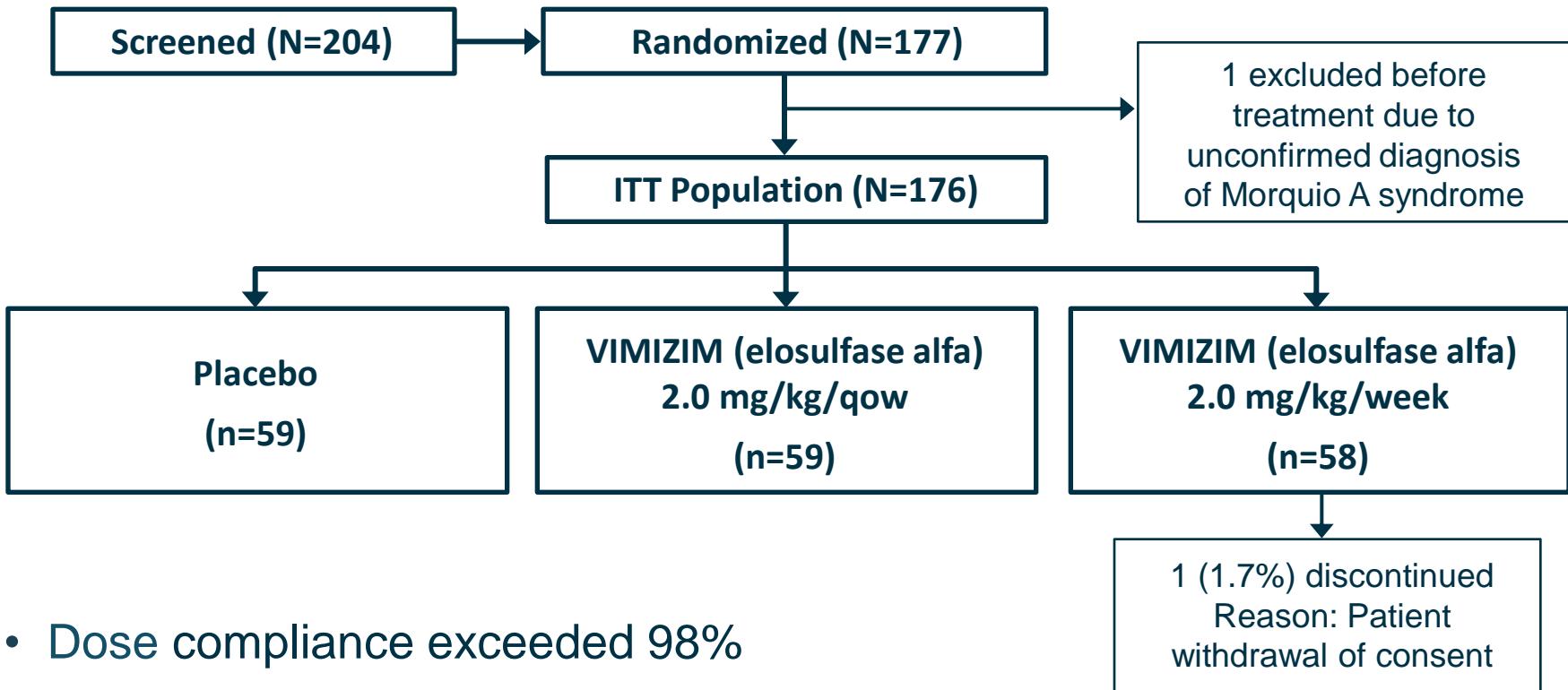
## VIMIZIM (elosulfase alfa) – resumen de estudios clínicos

MOR-002	Phase 1/2, multicenter, open-label dose-escalation study to evaluate the safety, tolerability and efficacy of VIMIZIM in patients with Morquio A (n=20) Initiated October 2008
MOR-100	Multicenter, open-label extension study enrolling patients from MOR-002 to evaluate the long term safety and efficacy of VIMIZIM in patients with Morquio A (n=17)
MOR-004	Phase 3, randomized, double-blind, placebo-controlled, multinational clinical study to evaluate the efficacy and safety of VIMIZIM 2mg/kg/wk and 2mg/kg/qow in patients with Morquio A. (n=176) Initiated January 2011
MOR-005	Multinational, multicenter extension study to evaluate the long-term efficacy and safety of VIMIZIM in patients with Morquio A. (n=173)
MOR-006	Phase 2 open-label multinational clinical study to evaluate the safety and efficacy of VIMIZIM in Morquio A patients with limited ambulation (n=13)
MOR-007	Phase 2 open-label multinational clinical study to evaluate the safety and efficacy of VIMIZIM in pediatric patients less than 5 years of age with Morquio A (n=15)
MOR-008	Phase 2, randomized, double-blind pilot study of safety and physiological effects of 2 doses of VIMIZIM in patients with Morquio A (n=25)

## Fase 3 - centros de investigación MOR-004



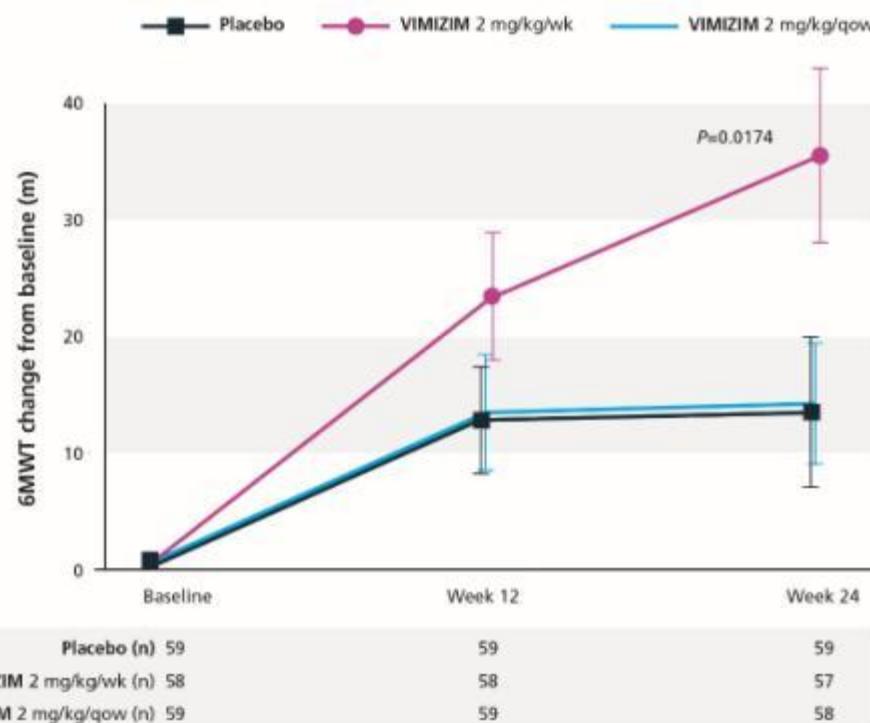
## Diseño Estudio fase 3



- Dose compliance exceeded 98%
- 99% rate of study completion

## Desenlace principal:

# VIMIZIM (elosulfase alfa) mejora significativamente la Resistencia medida con el 6MWT

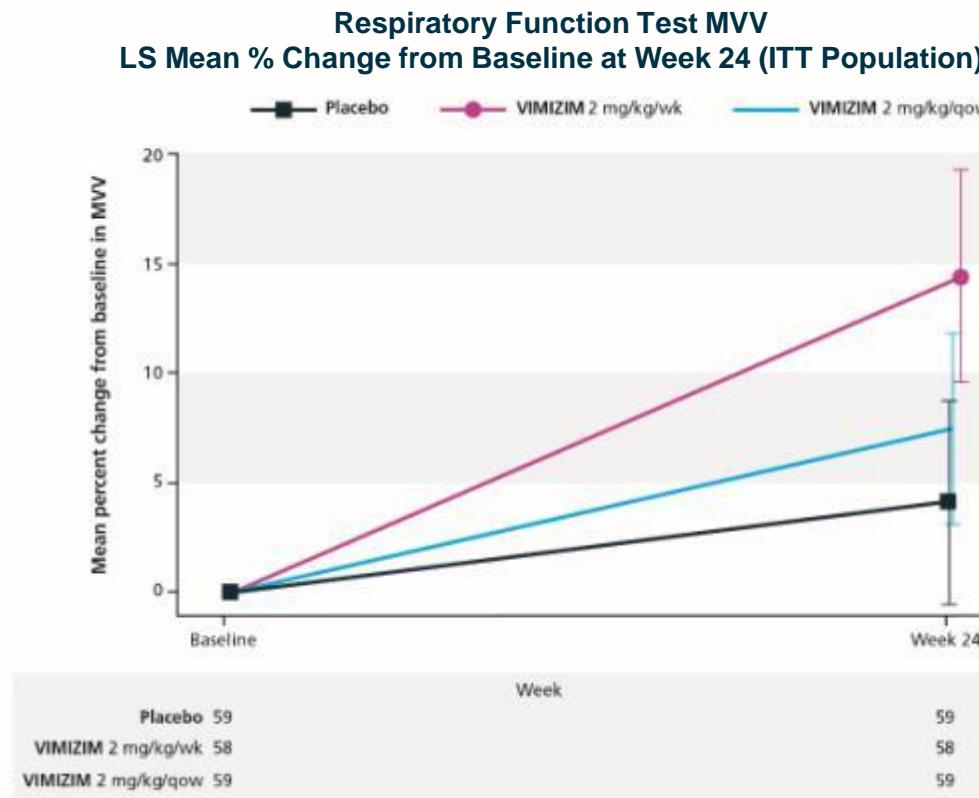


- 175 of 176 (99.4%) completed the 24-week study in the Intent-to-Treat group.
- Compared with placebo, VIMIZIM™ (elosulfase alfa) 2 mg/kg/wk demonstrated a statistically significant improvement in 6MWT distance in only 24 weeks ( $P=0.0174$ )
- Patients walked farther at Week 24 than at baseline, with a mean 23.8% improvement over baseline in the 6MWT
- Patients who continued receiving VIMIZIM through the extension trial stabilized walking ability after 72 weeks in extension study

## VIMIZIM desenlaces terciarios a la semana 24

### Maximum Voluntary Ventilation - MVV

- At Week 24, patients administered VIMIZIM™ (elosulfase alfa) 2 mg/kg/wk trended toward improvement in MVV percent change from baseline vs placebo



# VIMIZIM™ (elosulfase alfa) - seguridad y tolerabilidad

Adverse reactions were collected from 176 patients ages 5 to 57 who were enrolled in the 24-week, phase 3 pivotal study. The most common adverse reactions ( $\geq 10\%$ ) were pyrexia, vomiting, headache, nausea, abdominal pain, chills, and fatigue.

- Acute reactions requiring intervention were managed by
  - Temporarily interrupting or slowing the infusion
  - Administering additional antihistamines, antipyretics, or corticosteroids

Adverse reactions reported by  $\geq 10\%$  of patients treated with VIMIZIM™ (elosulfase alfa) (2 mg/kg/wk) and with a greater incidence than placebo.

Adverse reaction	VIMIZIM™ (elosulfase alfa) 2 mg/kg/wk n=58 (%)	Placebo n=59 (%)
Pyrexia	<b>19</b> (33%)	<b>8</b> (14%)
Vomiting	<b>18</b> (31%)	<b>4</b> (7%)
Headache	<b>15</b> (26%)	<b>9</b> (15%)
Nausea	<b>14</b> (24%)	<b>4</b> (7%)
Abdominal pain	<b>12</b> (21%)	<b>1</b> (1.7%)
Chills	<b>6</b> (10.3%)	<b>1</b> (1.7%)
Fatigue	<b>6</b> (10.3%)	<b>2</b> (3.4%)

<sup>a</sup>Safety and effectiveness in pediatric patients <5 years of age has not been established and is currently being evaluated.

# **VIMIZIM (elosulfase alfa) es el major abordaje terapéutico para los pacientes con Morquio A (MPS IV A)**

**VIMIZIM™ (elosulfase alfa) is the only ERT to treat the underlying cause of Morquio A.**



- VIMIZIM™ (elosulfase alfa) replaces the deficient enzyme (GALNS) that causes cellular, tissue, and organ dysfunction
- VIMIZIM slows the progressive loss of endurance as demonstrated by significant improvement in the 6MWT ( $p=0.0174$ )
- The 6MWT is a validated measure of endurance which evaluates the global and integrated responses of the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism

# **¿MUCOPOLISACARIDOSIS?**

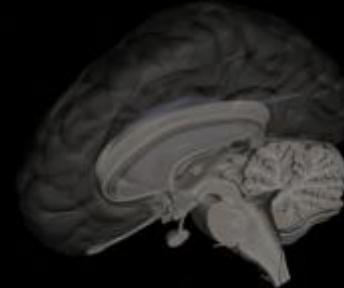
**NIÑOS**

**TALLA BAJA  
RETRASO PSICOMOTOR  
RIGIDEZ O DEFORMIDAD ARTICULAR  
FACIES ESPECIAL  
DISPLASIA ESQUELÉTICA**

**ADULTOS**

**“FORMAS SUAVIZADAS”  
TALLA BAJA O CERCANA A LA NORMAL  
PROBLEMAS OSTEO-ARTICULARES  
ASPECTO FÍSICO O FACIAL ESPECIAL  
PATOLOGÍA RESPIRATORIA CRÓNICA  
PATOLOGÍA CARDIOVASCULAR (HTA)**

# The NEW ENGLAND JOURNAL of MEDICINE



## Mutations in the Lysosomal Enzyme–Targeting Pathway and Persistent Stuttering

Changsoo Kang, Ph.D., Sheikh Riazuddin, Ph.D., Jennifer Mundorff, M.A., Donna Krasnewich, M.D., Ph.D., Penelope Friedman, M.D., James C. Mullikin, Ph.D., and Dennis Drayna, Ph.D.

### ABSTRACT

#### BACKGROUND

Stuttering is a disorder of unknown cause characterized by repetitions, prolongations, and interruptions in the flow of speech. Genetic factors have been implicated in this disorder, and previous studies of stuttering have identified linkage to markers on chromosome 12.

#### METHODS

We analyzed the chromosome 12q23.3 genomic region in consanguineous Pakistani families, some members of which had nonsyndromic stuttering and in unrelated case and control subjects from Pakistan and North America.

#### RESULTS

We identified a missense mutation in the *N*-acetylglucosamine-1-phosphate transferase gene (*GNPTAB*), which encodes the alpha and beta catalytic subunits of GlcNAc-phosphotransferase (*GNPT* [NC\_2.7.8.15]), that was associated with stuttering in a large, consanguineous Pakistani family. This mutation occurred in the affected members of approximately 10% of Pakistani families studied, but it occurred only once in 192 chromosomes from unaffected, unrelated Pakistani control subjects and was not observed in 552 chromosomes from unaffected, unrelated North American control subjects. This and three other mutations in *GNPTAB* occurred in unrelated subjects with stuttering but not in control subjects. We also identified three mutations in the *GNPTG* gene, which encodes the gamma subunit of *GNPT*, in affected subjects of Asian and European descent but not in control subjects. Furthermore, we identified three mutations in the *NAGPA* gene, which encodes the so-called uncovering enzyme, in other affected subjects but not in control subjects. These genes encode enzymes that generate the mannose-6-phosphate signal, which directs a diverse group of hydrolases to the lysosome. Deficits in this system are associated with the mucolipidoses, rare lysosomal storage disorders that are most commonly associated with bone, connective tissue, and neurologic symptoms.

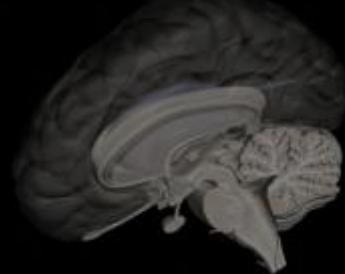
#### CONCLUSIONS

Susceptibility to nonsyndromic stuttering is associated with variations in genes governing lysosomal metabolism.

From the National Institute on Deafness and Other Communication Disorders (C.K., D.D.), the National Human Genome Research Institute (NHGRI) (D.K.), the Clinical Center (P.F.), and the Genome Technology Branch, NHGRI (J.C.M.), National Institutes of Health — all in Bethesda, MD; the Center of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan (S.R.); and Hollins Communications Research Institute, Roanoke, VA (J.M.). Address reprint requests to Dr. Drayna at 5 Research Ct., Rm. 2B-46, Rockville, MD 20850, or at drayna@nidcd.nih.gov.

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# **ENFOQUE DIAGNÓSTICO DISCAPACIDAD CRÓNICA EN PACIENTES CON CUADROS NEUROGENÉTICOS CON FOCO EN DISPLASIAS ESQUELÉTICAS Y MUCOPOLISACARIDOSIS**

**DR. PATRICIO GUERRA  
NEURÓLOGO INFANTIL Y ADOLESCENTES  
MAGÍSTER NEUROCIENCIAS**

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