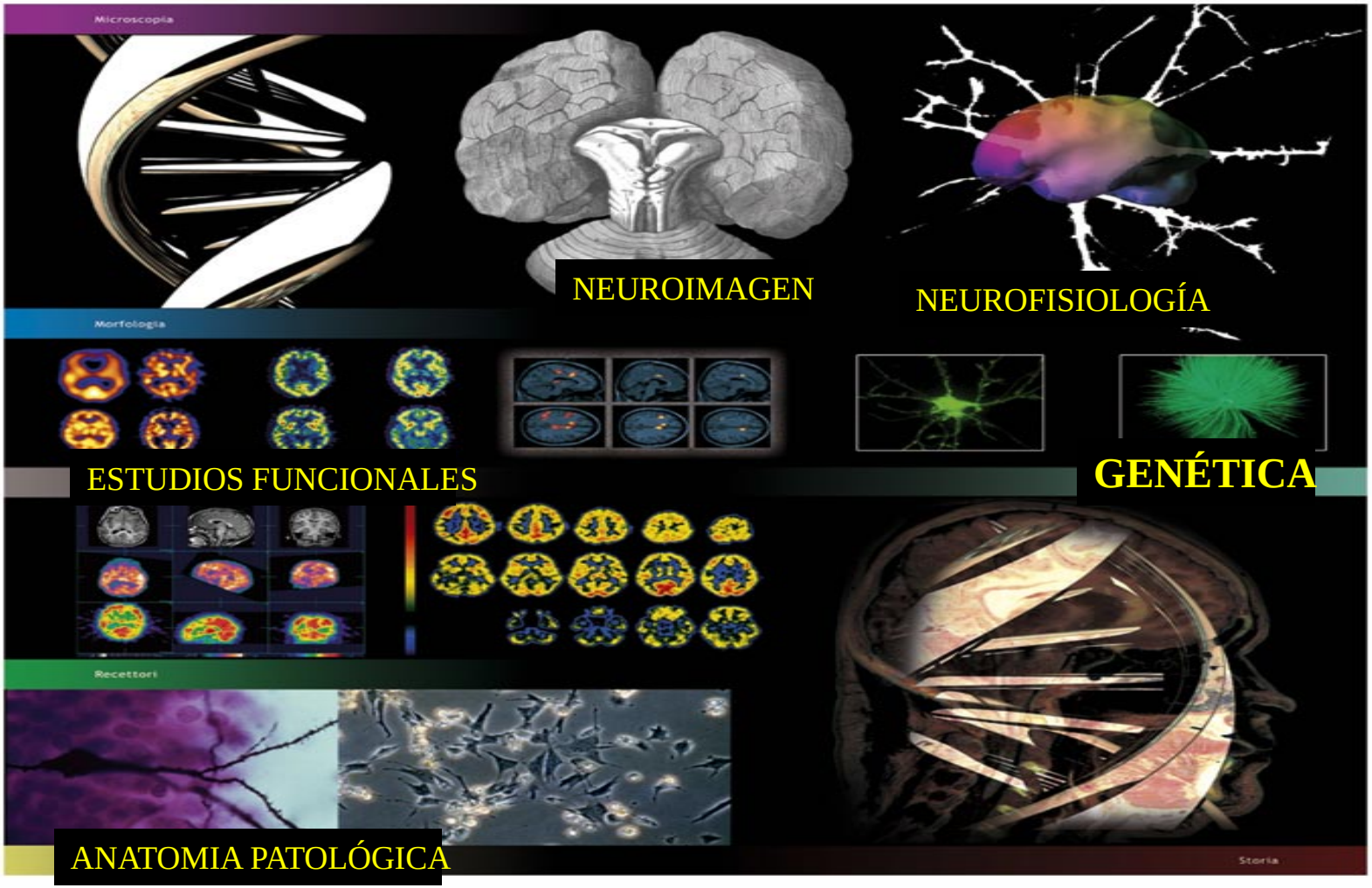
Diagnóstico genético y enfermedad neuromuscular

Dra. Victoria Alvarez. Unidad de Genética.

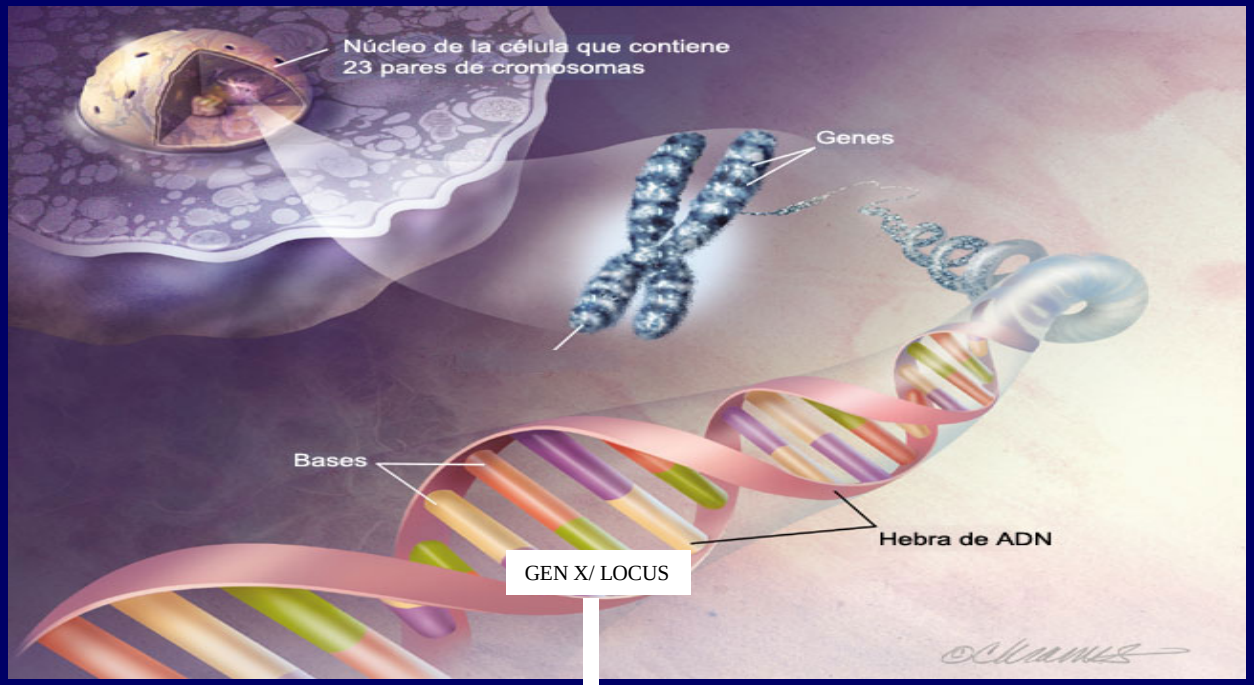
Laboratorio de Medicina. Hospital Central de Asturias

ENFERMEDAD NEUROLÓGICA



DIAGNÓSTICOS MÁS PRECISOS Y FIABLES

NEUROGENÉTICA : TESTS DIAGNÓSTICOS



GEN X/ LOCUS

ANÁLISIS MOLECULAR DIRECTO (FIABILIDAD 100%)/INDIRECTO (PROBABILIDAD)

IDENTIFICACIÓN DE LA MUTACIÓN /LIGAMIENTO POSITIVO

DESCARTAR O CONFIRMAR DIAGNÓSTICO

TEST GENÉTICOS

- **DIAGNÓSTICOS**

  Identificación de mutación responsable de la patología

  - **Diagnóstico genético confirmativo**
  - **Diagnóstico presintomático**
  - **Diagnóstico prenatal**

- **PRONÓSTICOS (susceptibilidad/cribado)**

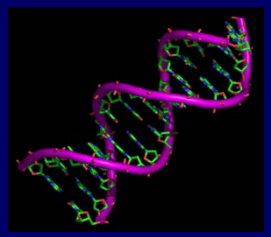
  - **Factores de riesgo asociado a susceptibilidad**
    - **uso clínico limitado**
    - **investigación**
  - **Farmacogenéticos**

Análisis genético-molecular

Células nucleadas

- leucocitos sangre periférica,
- amniócitos y vellosidad coriónica
- bloques de parafina

ADN



Análisis molecular

- Amplificación mediante PCR
- PCR a tiempo real (genotipación)
- Secuenciación automática
- Análisis de fragmentos
  - marcadores microsatelites; MLPA
- Digestión con endonucleasas
- Arrays

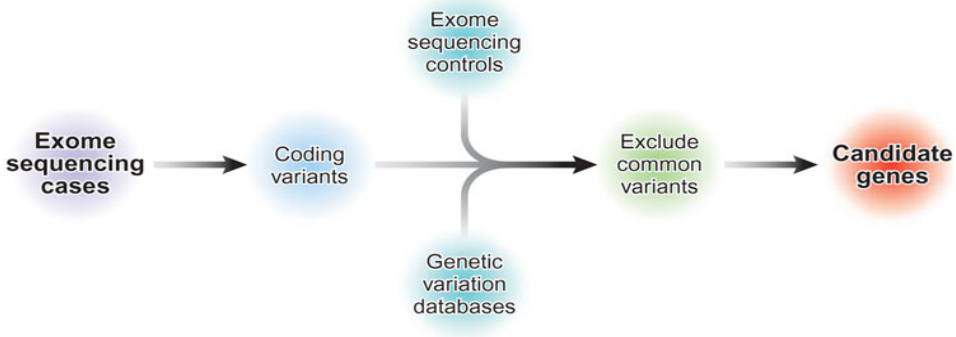
Presencia mutación

Ausencia de mutación

Secuenciación de nueva generacion (NGS)

- Identificación de nuevos genes
- Nuevas vías fisiológicas

Secuenciación exómica



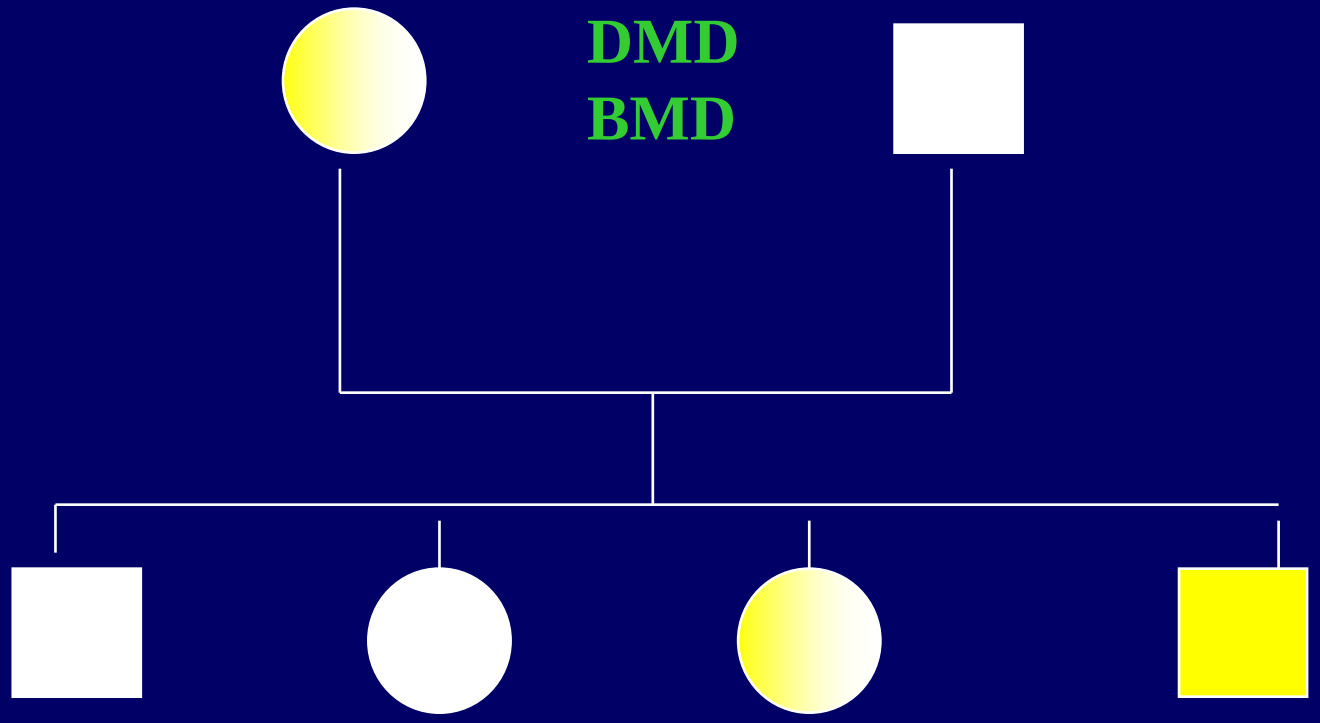
Leslie G Biesecker1 Journal name:Nature GeneticsVolume:42,Pages:13–14Year published:2010

Table 2. Muscle disease gene discovery by NGS.

Disease	OMIM	Inheritance	Strategy	Gene	Locus	Reference
Early-onset myopathy, areflexia, respiratory distress, and dysphagia (EMARDD)	614399	AR	Haplotype analysis + Targeted NGS	MEGF10	5q23.2	Logan et al. (17)
Centronuclear myopathy-4 (CNM4)	614807	AD	Linkage + Exome	CCDC78	16p13.3	Majczenko et al. (18)
Limb-girdle muscular dystrophy type 1E (LGMD1E)	603511	AD	Exome + Functional analysis in Zebrafish	DNAJB6	7q36.3	Harms et al. (19); Sarparanta et al. (20)
Hereditary myopathy with early respiratory failure (HMERF)	603689	AD	Linkage + Exome	TTN	2q31.2	Pfeffer et al. (21)
Facioscapulohumeral muscular dystrophy type 2 (FSHD2)	158901	Digenic	Exome	SMCHD1	18p11.32	Lemmers et al. (24)
Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A7 (MDDGA7)	614643	AR	On-Cell complementation assay + Homozygosity mapping + Targeted NGS	ISPD	7p21.2	Cirak et al. (25); Willer et al. (26)

HERENCIA LIGADA AL CROMOSOMA X

Madre Portadora obligada **Padre sano**

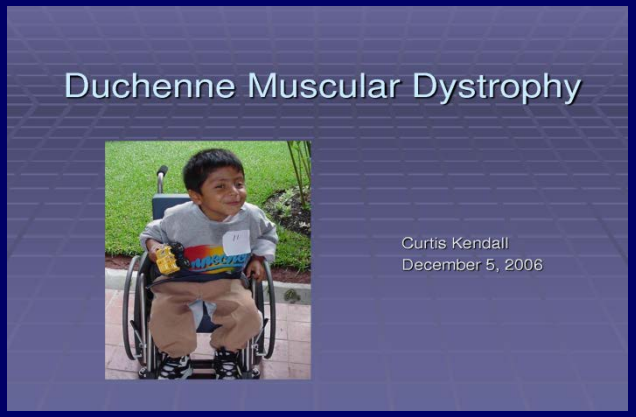


Hijo sano 25%

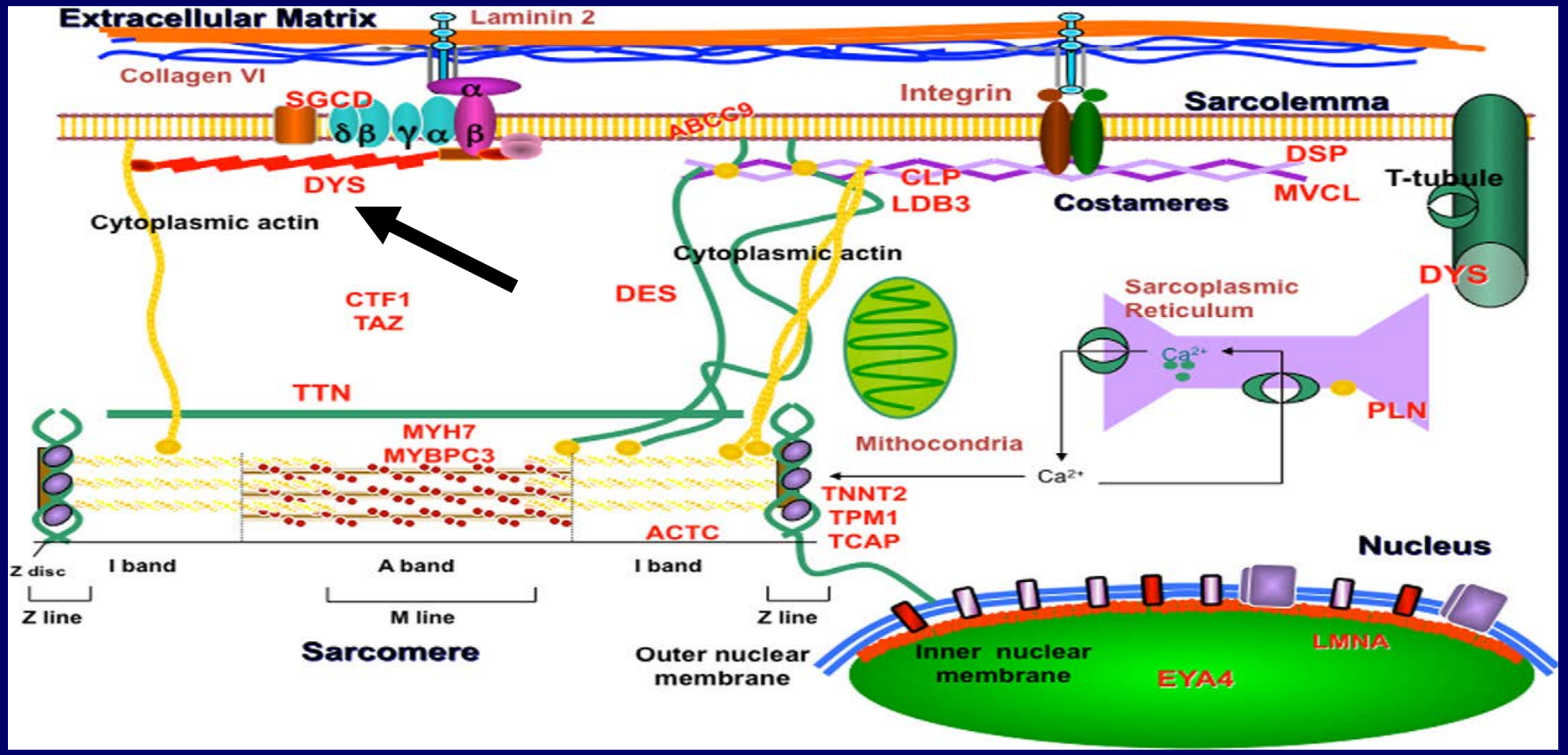
Hija sana 25%

Hija portadora 25%

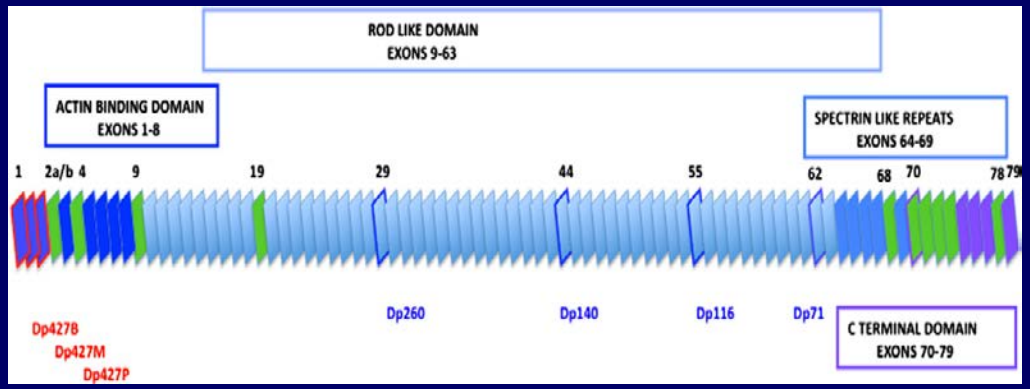
Hijo enfermo 25%


Duchenne Muscular Dystrophy
Curtis Kendall
December 5, 2006

BECKER


Extracellular Matrix
Laminin 2
Collagen VI
SGCD
α
δ β γ α β
Integrin
Sarcolemma
ABCC9
DSP
CLP
LDB3
MVCL
Costameres
T-tubule
DYS
Cytoplasmic actin
CTF1
TAZ
DES
Cytoplasmic actin
Sarcoplasmic
Reticulum
Ca2+
PLN
TTN
MYH7
MYBPC3
Mithocondria
Ca2+
TNNT2
TPM1
TCAP
ACTC
Nucleus
Z disc
I band
A band
I band
Z line
M line
Z line
Sarcomere
Outer nuclear
membrane
Inner nuclear
membrane
LMNA
EYA4

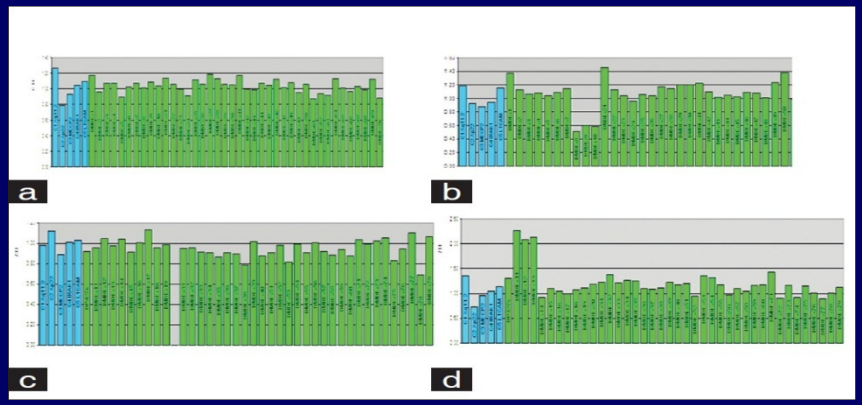
Gen de la distrofina – Xp21

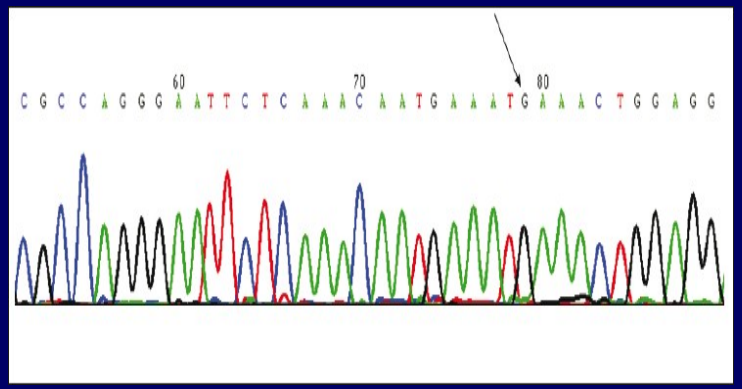


Distrofía Duchenne-
ausencia de distrofína
Distrofía Becker
distrofína funcional

Análisis genético

75% mutaciones deleciones/duplicaciones (ex3-7; ex44-53)
20% mutaciones puntuales

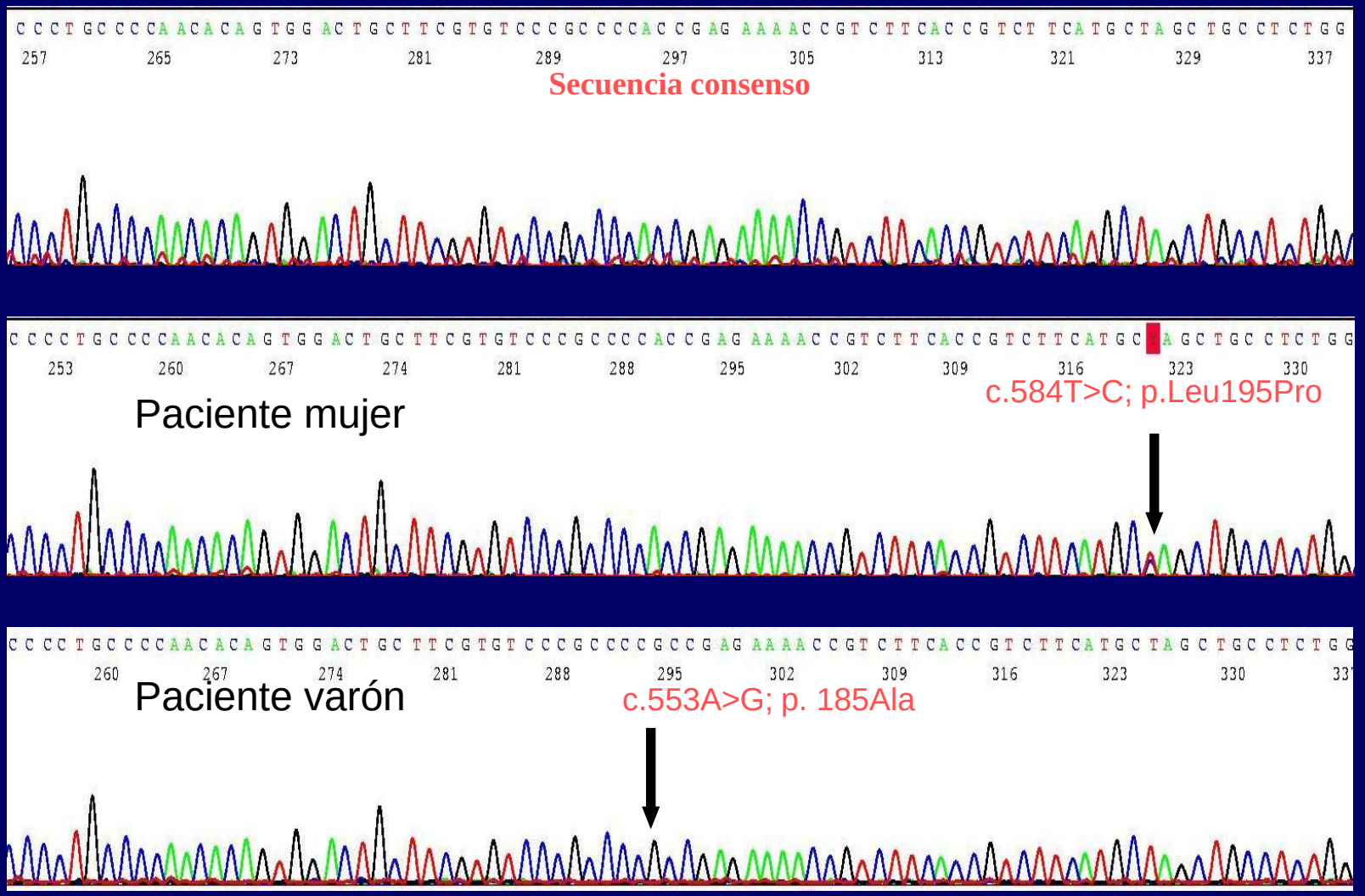




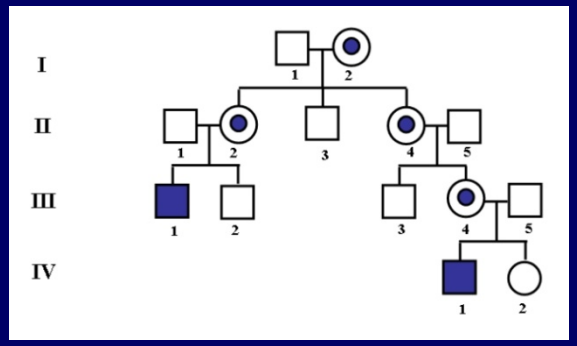
Confirmación diagnóstico clínico, detección de portadoras,
Terapías individualizadas dependiendo del tipo de mutación (exón skipping)

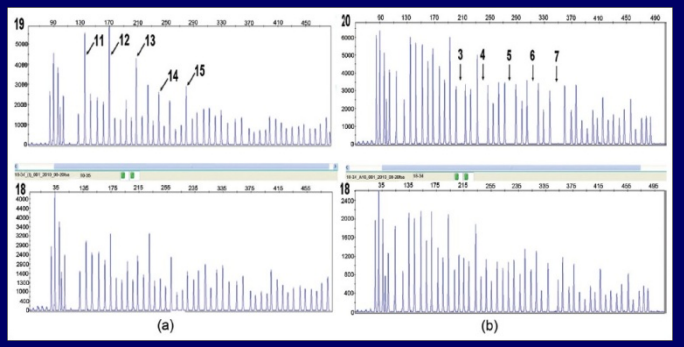
CMT 1X ; GEN *GJB1*

Neuropatía con fenotipo intermedio/mixto ligada al X



Asesoramiento genético



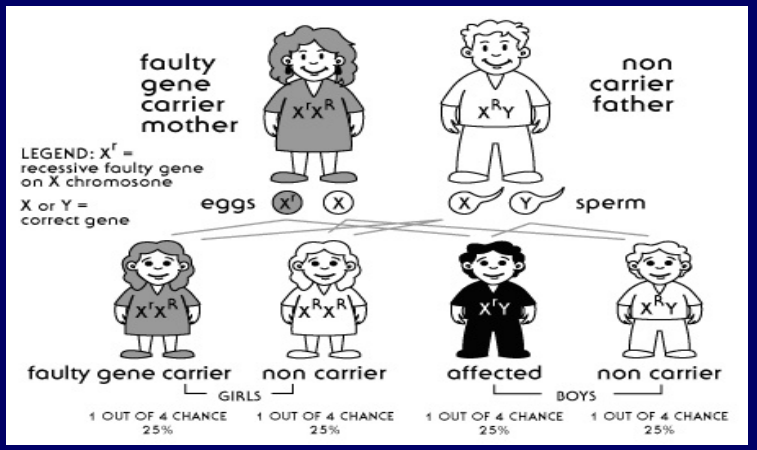


DMD

- ❑ varones no sobreviven más alla de los 20 años
- ❑ hembras portadoras riesgo del 50% para la descendencia

BMD

- ❑ varones alcanzan edad reproductiva
  - ❑ ningún hijo varón afectado
  - ❑ riesgo hembras de ser portadoras 50%



Planificación de descendencia- Diagnóstico genético Prenatal

EJHG Open

European Journal of Human Genetics (2013) 21, 21–26
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www.nature.com/ejhg

ARTICLE

An urgent need for a change in policy revealed by a study on prenatal testing for Duchenne muscular dystrophy

Apollonia TJM Helderman-van den Enden*,[1,4], Kamlesh Madan[1], Martijn H Breuning[1], Annemieke H van der Hout[2], Egbert Bakker[1], Christine EM de Die-Smulders[3] and Hendrika B Ginjaar[1]

Prenatal diagnosis for Duchenne muscular dystrophy (DMD) was introduced in the Netherlands in 1984. We have investigated the impact of 26 years (1984–2009) of prenatal testing. Of the 635 prenatal diagnoses, 51% were males; nearly half (46%) of these were affected or had an increased risk of DMD. As a result 145 male fetuses were aborted and 174 unaffected boys were born. The vast majority (78%) of females, now 16 years or older, who were identified prenatally have not been tested for carrier status. Their average risk of being a carrier is 28%. We compared the incidences of DMD in the periods 1961–1974 and 1993–2002. The incidence of DMD did not decline but the percentage of first affected boys increased from 62 to 88%. We conclude that a high proportion of families with *de novo* mutations in the *DMD* gene cannot make use of prenatal diagnosis, partly because the older affected boys are not diagnosed before the age of five. Current policy, widely accepted in the genetic community, dictates that female fetuses are not tested for carrier status. These females remain untested as adults and risk having affected offspring as well as progressive cardiac disease. We see an urgent need for a change in policy to improve the chances of prevention of DMD. The first step would be to introduce neonatal screening of males. The next is to test females for carrier status if requested, prenatally if fetal DNA is available or postnatally even before adulthood.

European Journal of Human Genetics (2013) 21, 21–26; doi:10.1038/ejhg.2012.101; published online 6 June 2012

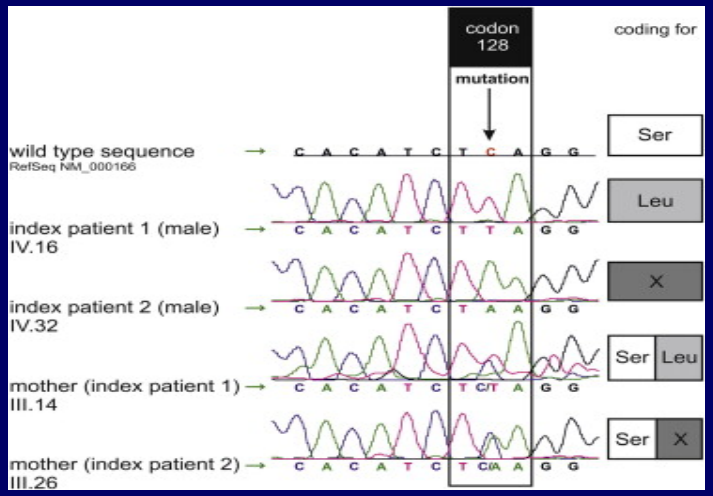
Muchas mutaciones de novo (56%). No beneficios de prenatal

Cribado neonatal en varones

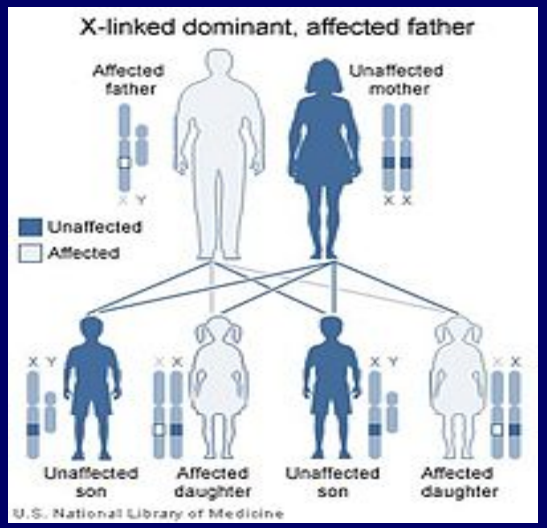
- **identificación precoz de casos/terapías**
- **utilidad de diagnóstico prenatal**

En mujeres determinar si son o no portadoras (patología cardiaca)

Asesoramiento genético



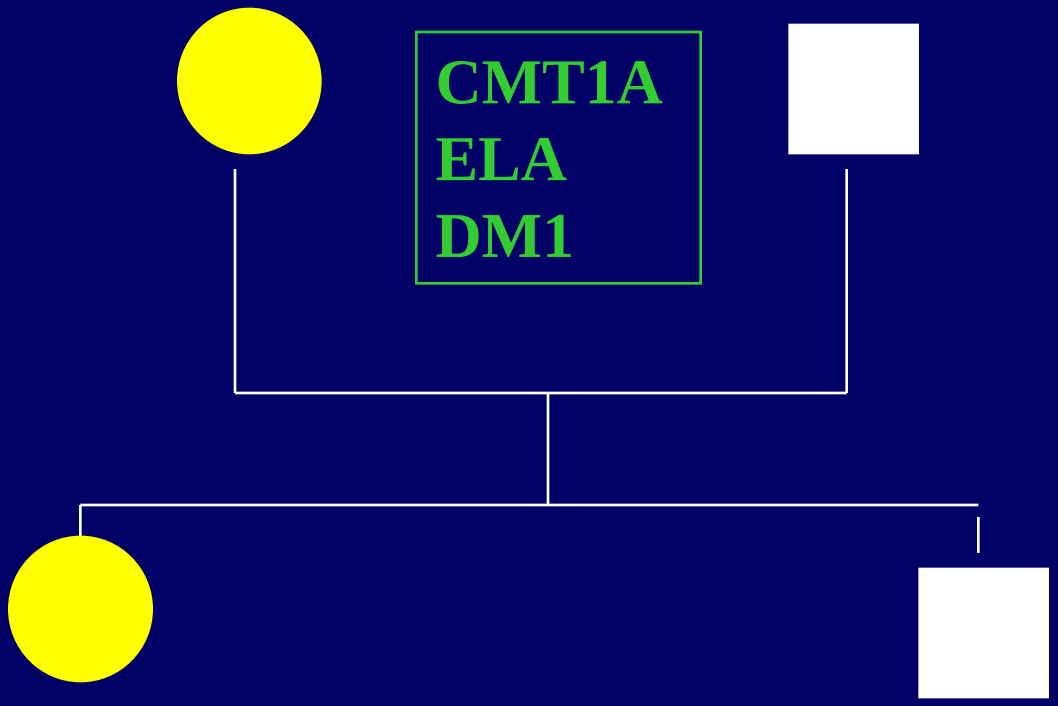
- **CMTX- paciente mujer**
  - **Hijos e hijas 50% riesgo de ser portadora**
- **CMT- paciente varón**
  - **Todas sus hijas portadoras**
  - **Ningún hijo varón portador**



Planificación de descendencia- Diagnóstico genético Prenatal ?????

HERENCIA AUTOSÓMICA DOMINANTE

Madre Enferma **Padre sano**



Hijo enfermo
50%

Hijo sano
50%

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Table 1 Classification of Charcot–Marie–Tooth disease

Type	Gene/locus	Specific phenotype
Autosomal dominant CMT1 (AD CMT1)		
CMT 1A	Dup 17p (PMP22)	Classic CMT1
	PMP22 (point mutation)	Classic CMT1/DSN/CHN/HNPP
CMT 1B	MPZ	CMT1/DSN/CHN/intermediate/CMT2
CMT 1C	LITAF	Classic CMT1
CMT 1D	EGR2	Classic CMT1/DSN/CHN
CMT 1	NEFL	CMT2 but can have slow MCVs in CMT1 range +/− early onset severe disease
Hereditary neuropathy with liability to pressure palsies (HNPP)		
HNPP	Del 17p (PMP-22)	Typical HNPP
	PMP-22 (point mutation)	Typical HNPP
X linked CMT1 (CMT 1X)		
CMT 1X	GJB1	Intermediate +/− patchy MCVs/male MCVs < female MCVs
Autosomal recessive demyelinating (CMT4)		
CMT4A	GDAP1	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
CMT4B1	MTMR2	Severe CMT1/facial/bulbar/focally folded myelin
CMT4B2	MTMR13	Severe CMT1/glaucoma/focally folded myelin
CMT4C	KIAA1985 (SH3TC2)	Severe CMT1/scoliosis/cytoplasmic expansions
CMT4D (HMSNL)	NDRG1	Severe CMT1/gypsy/deafness/tongue atrophy
CMT4E	EGR2	Classic CMT1/DSN/CHN
CMT4F	PRX	CMT1/more sensory/focally folded myelin
CMT4H	FGD4	CMT1
CMT4J	FIG4	CMT1
CCFDN	CTDP1	CMT1/gypsy/cataracts/dysmorphic features
HMSN Russe	10q22–q23	CMT1
CMT1	PMP22 (point mutation)	Classic CMT1/DSN/CHN/HNPP
CMT1	MPZ	CMT1/DSN/CHN/intermediate/CMT2
Autosomal dominant CMT2 (AD CMT 2)		
CMT2A	KIF1Bβ	Classic CMT2
CMT2A	MFN 2	CMT2/usually severe/optic atrophy
CMT2B	RAB7	CMT2 with predominant sensory involvement and sensory complications
CMT2C	12q23–q24	CMT2 with vocal cord and respiratory involvement
CMT2D	GARS	CMT2 with predominant hand wasting/weakness or dHMN-V
CMT2E	NEFL	CMT2 but can have slow MCVs in CMT1 range +/− early onset severe disease
CMT2F	HSP27 (HSPB1)	Classic CMT2 or dHMN-II
CMT2G	12q12–q13.3	Classic CMT2
CMT2L	HSP22 (HSPB8)	Classic CMT2 or dHMN-II
CMT2	MPZ	CMT1/DSN/CHN/intermediate/CMT2
CMT2 (HMSNP)	3q13.1	CMT2 with proximal involvement
Autosomal recessive CMT 2 (also called CMT4)		
AR CMT2A	LMNA	CMT2 proximal involvement and rapid progression described/also causes muscular dystrophy/cardiomyopathy/lipodystrophy
AR CMT2B	19q13.1–13.3	Typical CMT2
AR CMT2	GDAP1	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
Dominant intermediate CMT (DI-CMT)		
DI-CMTA	10q24.1–25.1	Typical CMT
DI-CMTB	DNM2	Typical CMT
DI-CMTC	YARS	Typical CMT
Hereditary neuralgic amyotrophy (HNA)		
HNA	SEPT9	Recurrent neuralgic amyotrophy

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Table 2 Classification of the hereditary sensory and autonomic neuropathies

Type	Inheritance	Gene/locus	Specific phenotype
HSAN I	AD	SPTLC1	Mainly sensory, sensory complications, motor involvement variable, males may be more severe
CMT2B	AD	RAB7	Sensorimotor, sensory complications, no pain
HSAN 1B	AD	3p22–p24	Sensory, cough, gastro-oesophageal reflux
HSAN II	AR	HSN2	Severe sensory complications, mutilations, onset first 2 decades
HSAN III	AR	IKBKAP	Familial dysautonomia or Riley-Day syndrome, prominent autonomic, absence fungiform papillae of the tongue
HSAN IV	AR	NTRK1	Congenital insensitivity to pain with anhydrosis(CIPA), severe sensory, anhydrosis, mental retardation, unmyelinated fibres mainly affected
HSAN V	AR	NTRK1	Congenital insensitivity to pain with mild anhydrosis, no mental retardation, small myelinated fibres mainly affected
HSAN V	AR	NGFB	Congenital insensitivity to pain, minimal autonomic, no mental retardation, mainly unmyelinated fibres affected
Channelopathy associated insensitivity to pain	AR	SCN9A	Congenital insensitivity to pain

AD, autosomal dominant; AR, autosomal recessive; CMT, Charcot–Marie–Tooth; HSN2, hereditary sensory neuropathy type II gene; IKBKAP, Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein; NGFB, nerve growth factor beta polypeptide; NTRK1, neurotrophic tyrosine kinase receptor type 1; SCN9A, sodium channel, voltage gated, type IX, alpha subunit; RAB7, RAB7, member RAS oncogene family; SPLTC1, serine palmitoyltransferase, long chain base subunit-1.

Table 3 Classification of the distal hereditary motor neuropathies

Type	Inheritance	Gene/locus	Specific phenotype
HMN I	AD	Unknown	Juvenile onset dHMN
HMN II	AD	HSP27(HSPB1)	Adult onset typical dHMN/CMT2F
HMN II	AD	HSP22(HSPB8)	Adult onset typical dHMN/CMT2L
HMN III	AR	11q13	Early onset, slowly progressive
HMN IV	AR	11q13	Juvenile onset, diaphragmatic involvement
HMN V	AD	GARS	Upper limb onset, slowly progressive/CMT2D
HMN V	AD	BSCL2	Upper limb onset, +/−spasticity lower limbs/Silver syndrome
HMN VI	AR	IGHMBP2	Spinal muscle atrophy with respiratory distress (SMARD1), infantile onset respiratory distress
HMN VIIA	AD	2q14	Adult onset, vocal cord paralysis
HMN VIIB	AD	DCTN1	Adult onset/vocal cord paralysis/facial weakness
HMN/ALS4	AD	SETX	Early onset, pyramidal signs
HMN-J	AR	9p21.1–p12	Juvenile onset, pyramidal features, Jerash
Congenital distal SMA	AD	12q23–12q24	Antenatal onset, arthrogryposis

AD, autosomal dominant; AR, autosomal recessive; BSCL2, Berardinelli-Seip congenital lipodystrophy 2 (Seipin); CMT, Charcot–Marie–Tooth; dHMN, distal hereditary motor neuropathy; DCTN1, dynactin1; HSP22, heat shock 22 kDa protein 8; HSP27, heat shock 27 kDa protein 1; GARS, glycyl tRNA synthetase; IGHMBP2, immunoglobulin mu binding protein 2; SETX, sentaxin; SMA, spinal muscular atrophy.

J Neurol Neurosurg Psychiatry 2009;**80**:1304–1314. doi:10.1136/jnnp.2008.158295

NEUROPATIAS HEREDITARIAS

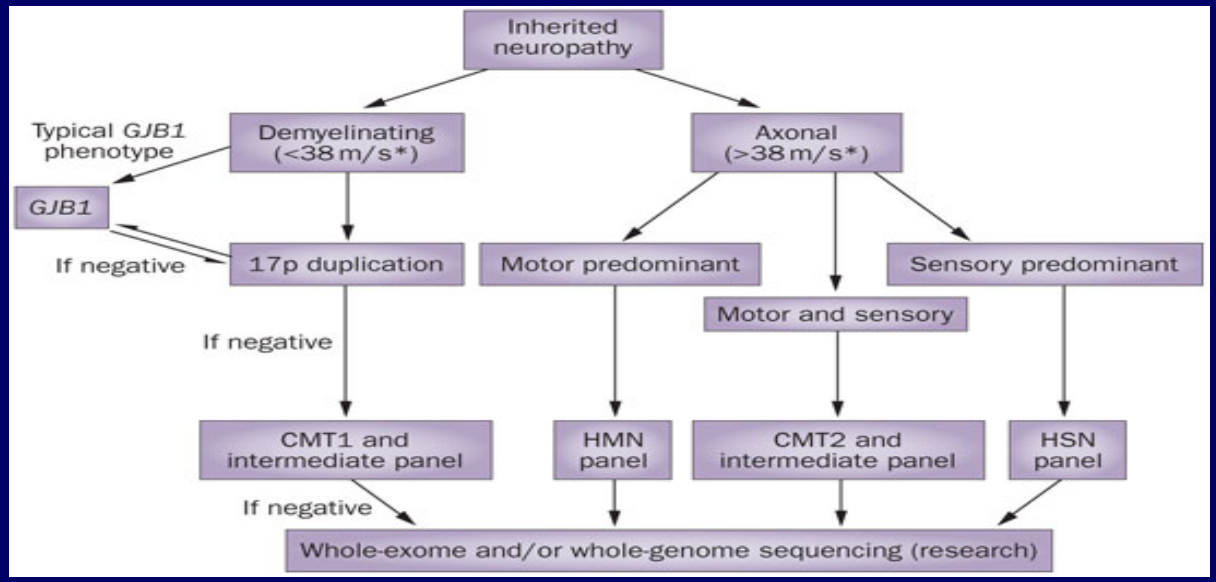
- Heterogeneidad clínica y genética; clasificación criterios clínicos y genéticos
- Neuropatía pura
  - Enfermedad de Charcot Marie Tooth
  - Neuropatía Hereditaria por susceptibilidad a la parálisis por presión
  - Neuropatías Hereditarias sensoriales y autonómicas
  - Neuropatías Hereditarias Distales
- Desórdenes multisistémicos
  - Enfermedades mitocondríales.
  - Neuropatías asociadas con ataxias hereditarias
- Más de 30 genes identificados
  - 10 de ellos son utilizados en diagnóstico rutinario
- Diagnóstico clínico-genético
  - examen clínico
  - estudios neurofisiológicos
  - árbol genealógico
  - estudios moleculares
- Nuevos tratamientos- terapia génica

ENFERMEDAD DE CHARCOT MARIE TOOTH

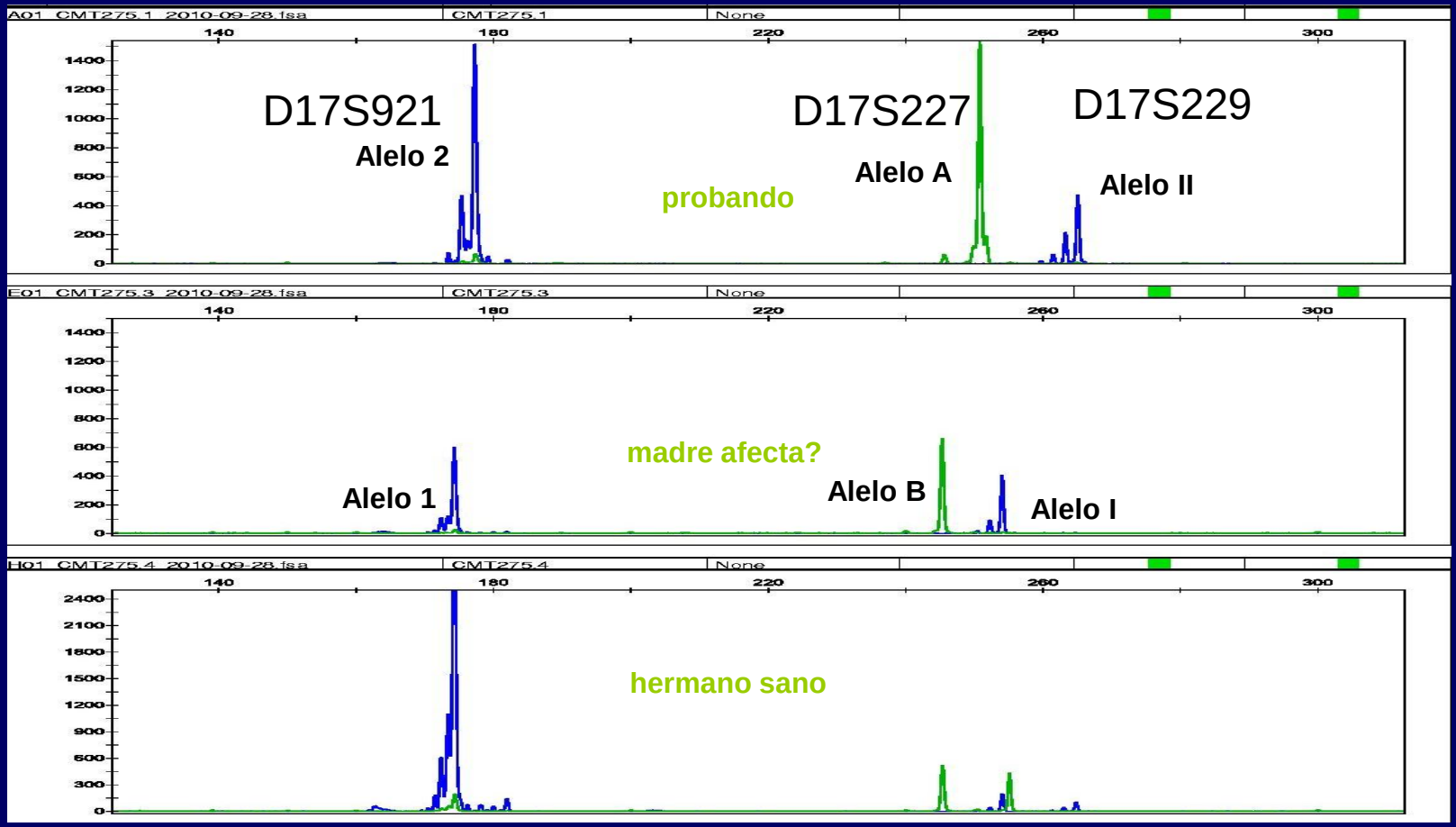
Patrón de herencia /velocidad de conducción nerviosa y gen o locus implicado 28casos /100.000 habitantes en España

Desmielinizante;Axonal ;Intermedia

- **Mismo fenotipo causado por mutaciones en diferentes genes**
  - **CMT1 AD–genes MPZ (CMT1B) , PMP22 (CMT1A); LITAF (CMT1C)**
- **Mutaciones en el mismo gen pueden causar diferentes fenotipos**
  - **MPZ(CMT1B) – CMT1/DSN/CHN/CMT2**
  - **GDAP (CMT4A) - CMT1 (AR)/CMT2 (AD)**
- **Formas dominantes y ligadas al X aprox 90% de CMT; poblaciones endogámicas AR CMT puede alcanzar un 40%.**

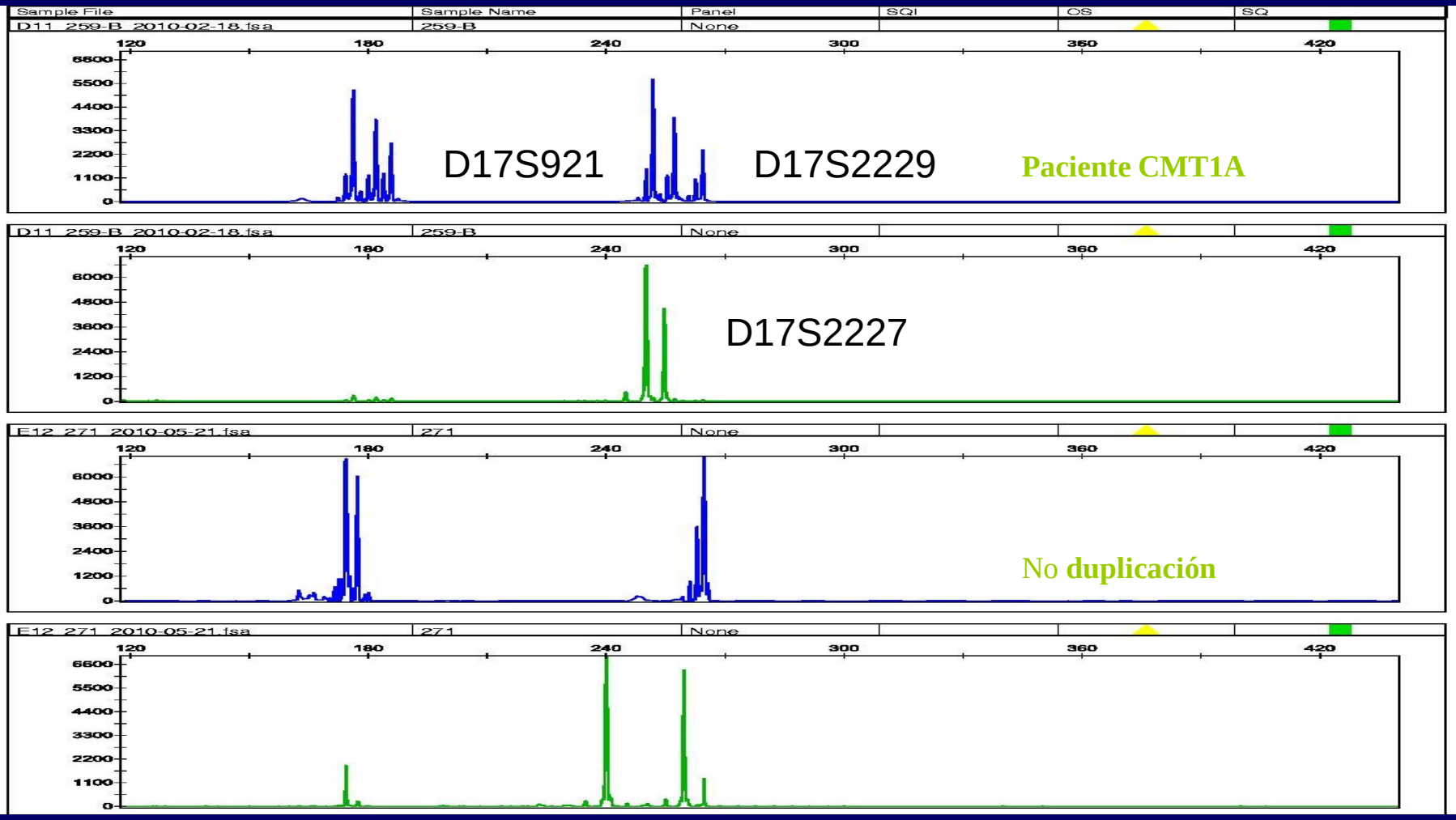


HNPP POR DELECIÓN 17P (PMP22) . Análisis con marcadores microsatélites



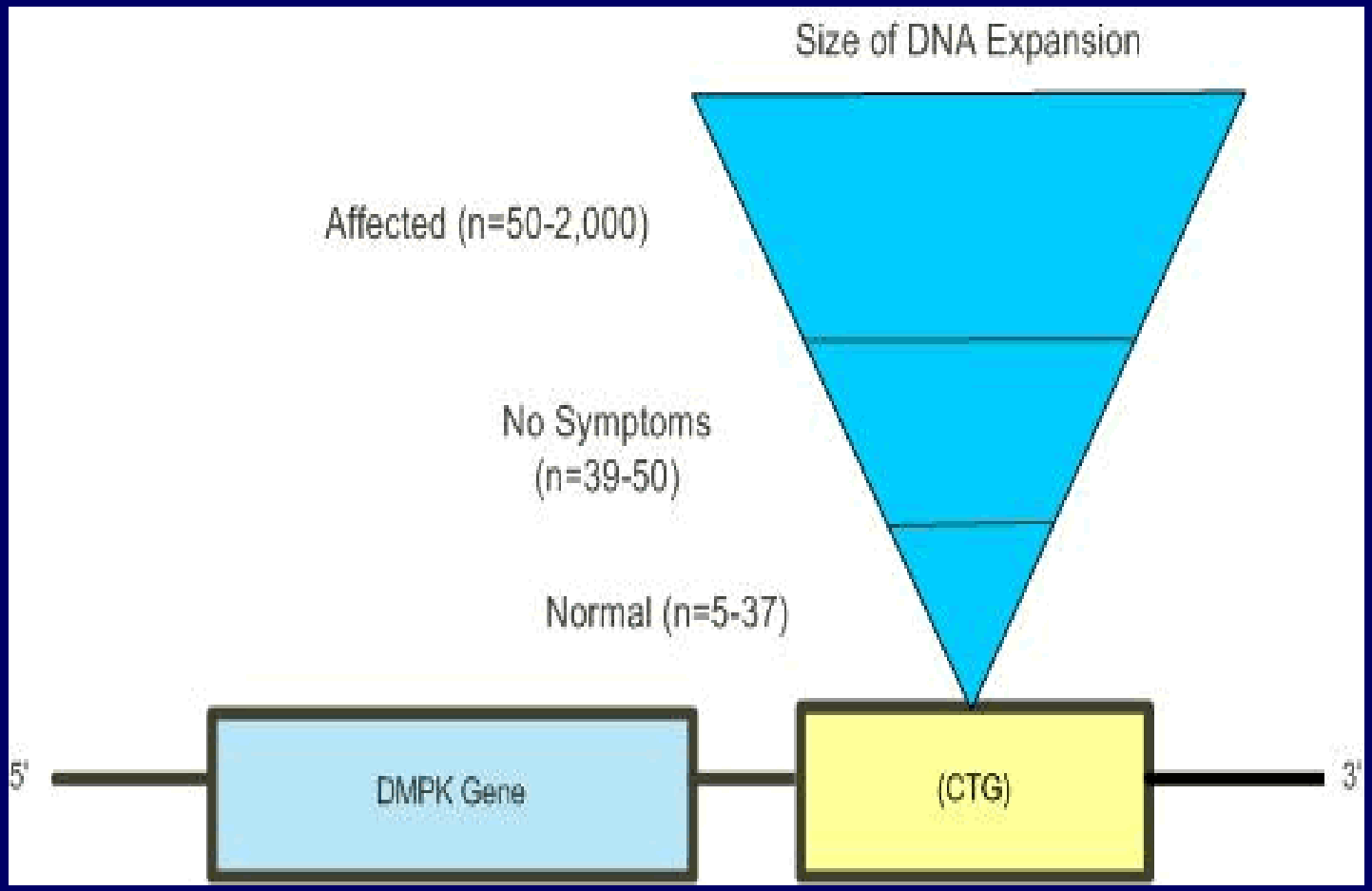
Herencia dominante. Riesgo de transmisión a la descendencia 50%.

CMT1A POR DUPLICACIÓN 17P (PMP22) . Análisis con marcadores microsatélites



Herencia dominante. Riesgo de transmisión a la descendencia 50%.

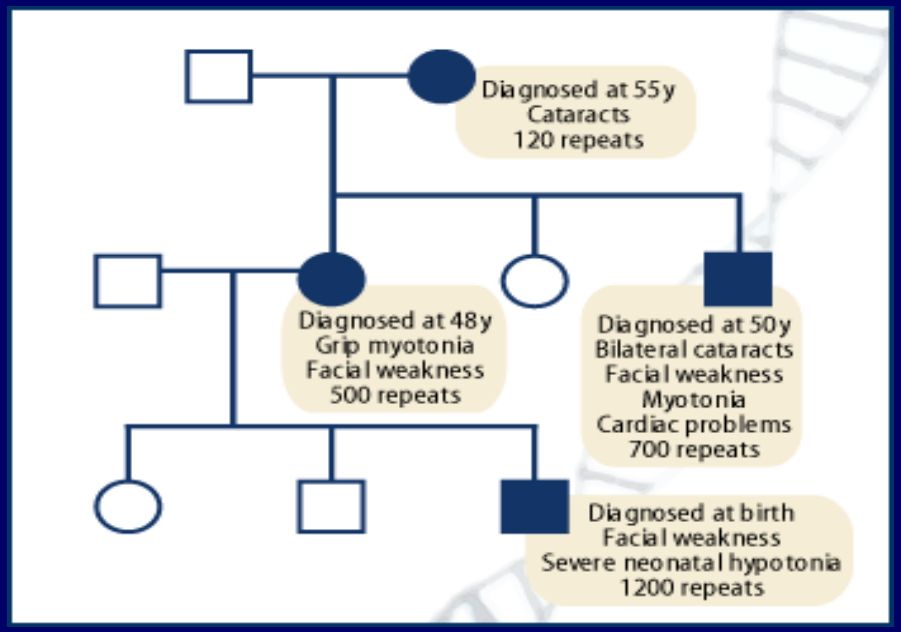
DISTROFÍA MIOTÓNICA

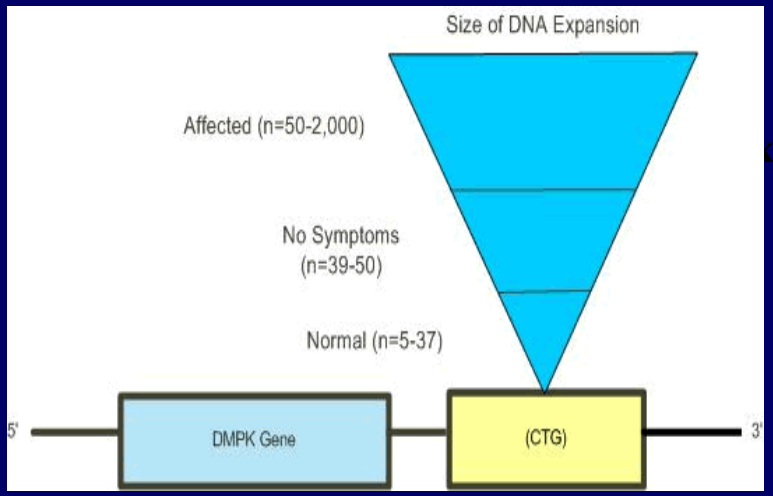


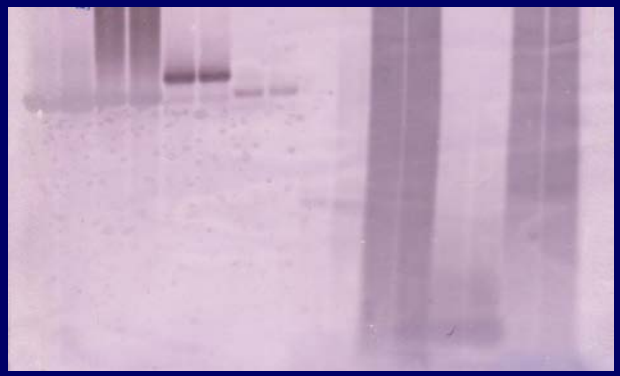
Expansión CTG; autosómico dominante; formas congénitas transmisión materna

DISTROFÍA MIOTÓNICA

Variabilidad fenotípica- tamaño triplete CTG







Esclerosis lateral amiotrófica

Formas esporádicas y formas familiares (10%)
Patrón dominante y recesivo (formas juveniles)

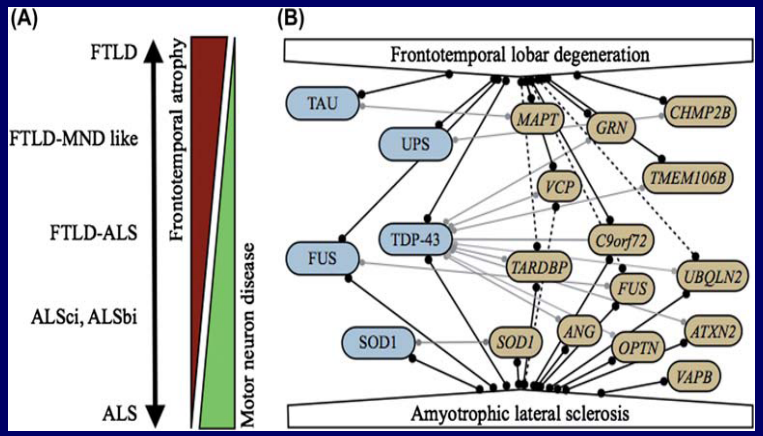
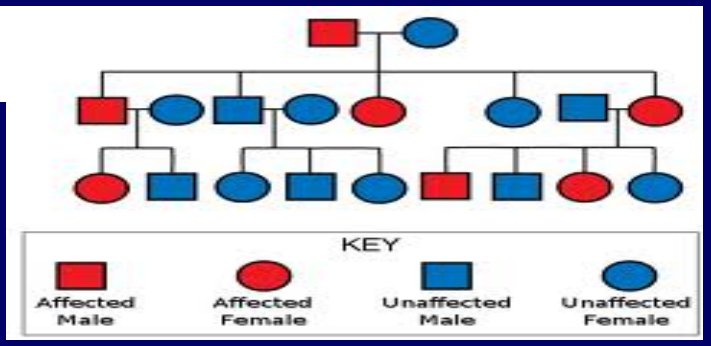


Table 1 The genetics Of fALS

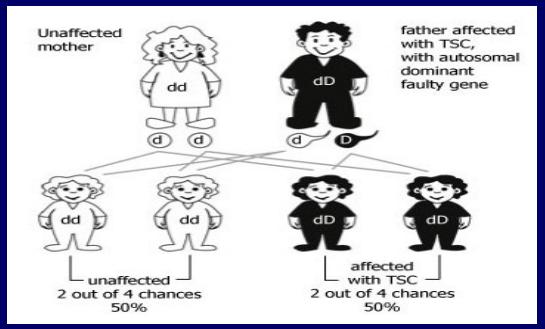
Genetic subtype	Chromosomal locus	Gene	Protein	Onset	Inheritance	Clinical feature	Other diseases caused by the gene
ALS1	21q22.1	SOD1	Cu/Zn SOD-1	Adult	AD/AR	Typical ALS	NA
ALS2	2q33-2q35	Alsin	Alsin	Juv	AR	Slowly progressive, predominantly UMN signs like limb, & facial spasticity	PLS IAHSP
ALS3	18q21	Unknown	Unknown	Adu	AD	Typical ALS with limb onset especially lower limb	NA
ALS4	9q34	SETX	Senataxin	Juv	AD	Slowly progressive, distal hereditary motor neuropathy with pyramidal signs	SCAR 1 and AOA2
ALS5	15q15-21	SPG 11	Spatacsin	Juv	AR	Slowly progressive	HSP
ALS6	16p11.2	FUS	Fused in Sarcoma	Juv/Adu	AD/AR	Typical ALS	NA
ALS8	20q13.3	VAPB	VAPB	Adu	AD	Typical and atypical ALS	SMA
ALS9	14q11.2	ANG	Angiogenin	Adu	AD	Typical ALS, FTD and Parkinsonism	NA
ALS10	1p36.2	TARDBP	DNA-binding protein	Adu	AD	Typical ALS	NA
ALS11	6q21	FIG 4	Phospholnositide-Sphosphatease	Adu	AD	Rapid progressive with prominent corticospinal tract signs	CMT 4 J
ALS12	10p13	OPTN	Optineurin	Adu	AD/AR	Slowly progressive with limb onset and predominant UMN signs	Primary Open Angle Glaucoma
ALS14	9p13.3	VCP	VCP	Adu	AD	Adult onset, with or without FTD	IBMPFD
ALS15/ ALSX	Xp11	UBQLN2	Ubiquilin 2	Adu/Juv	XD	UMN signs proceeding LMN signs	NA
ALS16	9p13.2-21.3	SIGMAR1	SIGMAR1	Juv	AR	Juvenile onset typical ALS	FTD
ALS-FTD1	9q21-22	unknown	unknown	Adu	AD	ALS with FTD	FTD
ALS-FTD2	9p21	C9ORF72	C9ORF72	Adu	AD	ALS with FTD	FTD
NA	2p13	DCTN1	Dynactin	Adu	AD	Distal hereditary motor neuropathy with vocal paresis	NA
Other rare-occurring ALS genes							
ALS3	18q21	Unknown	Unknown	Adu	AD	Typical ALS with limb onset especially lower limb	NA
ALS7	20pter-p13	Unknown	Unknown	Adu	AD/AR	Typical ALS	NA
NA	12q22-23	DAO	DAO	Adu	AD	Typical ALS	NA

Up to date, more than 20-ALS genes have been identified in fALS. These genetic mutations represent different molecular pathways of motor neuron degeneration. Abbreviations for Table 1: *PLS* Primary Lateral Sclerosis, *IAHSP* Infantile onset ascending hereditary spastic paralysis, *SCAR 1* Autosomal Recessive Spino-cerebellar ataxia, *AOA2* Ataxia Ocular Apraxia 2, *HSP* Hereditary spastic paraplegia, *VAPB* Vesicle associated membrane protein associated protein B, *SMA* Spinal Muscular Atrophy, *CMT 4 J* Charcot-Marie Tooth disease type 4 J, *VCP* Valosin Containing Protein, *IBMPFD* Inclusion body myopathy with Pagets disease and fronto temporal dementia, *SIGMAR1* Sigma Non Opiod Intracellular Receptor, *C9ORF72* Chromosome 9 open reading frame 72, *PD* Parkinson disease, *DAO* D-Amino Acid Oxidase, *FTD* Frontal-temporal dementia, *AD* Autosomal dominant, *AR* Autosomal recessive.

CONSEJO GENÉTICO

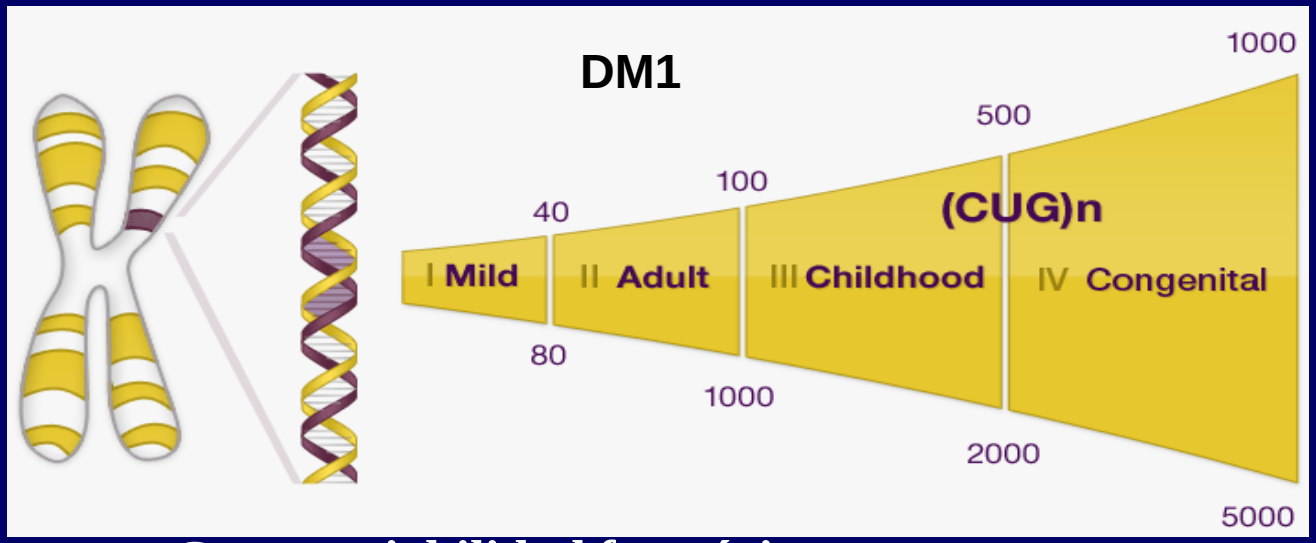


- ✓ **modo de herencia: estimación de riesgo**
  - ✓ **AD riesgo para la descendencia 50%**

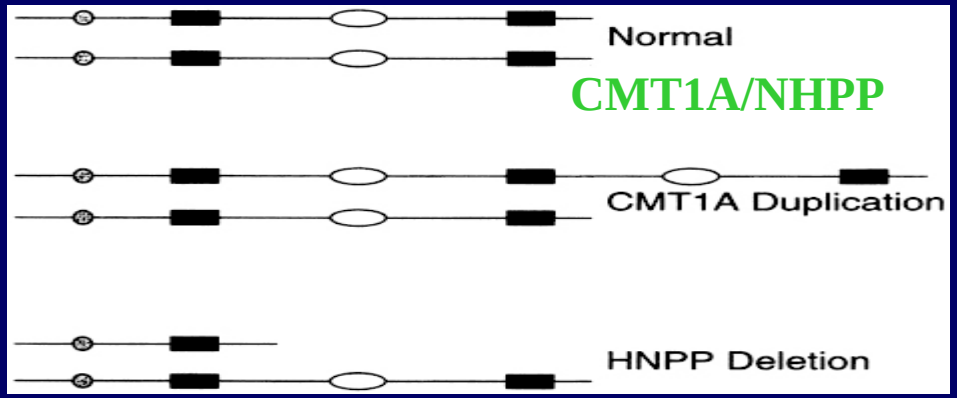


- ✓**determinar grado de penetrancia**
  - ✓ **penetrancia dependiente de la edad**
  - ✓ **penetrancia incompleta**
- ✓**diagnóstico presintomático y prenatal**
  - ✓**Test genético no predice edad de inicio ni forma de presentación clínica**

CONSEJO GENÉTICO



Gran variabilidad fenotípica
Formas congénitas transmisión vía materna



Valoración comité ética/ Pocos pacientes demandan prenatal

DIAGNÓSTICO PRESINTOMÁTICO EN ENFERMEDADES NEURODEGENERATIVAS

Patologías crónicas, progresivas, de curso irreversible y sin tratamiento. NO MENORES DE EDAD.

Imposible predecir con exactitud como y cuando empezará la enfermedad

Planificación de descendencia; eliminar la ansiedad por incertidumbre

Protocolo de consejo genético y psicológico

Impact of Presymptomatic Genetic Testing for Hereditary Ataxia and Neuromuscular Disorders. **Corrine O. Smith, MS; Hillary P. Lipe, ARNP; Thomas D. Bird, MD. Arch Neurol. 2004;61:875-880.**

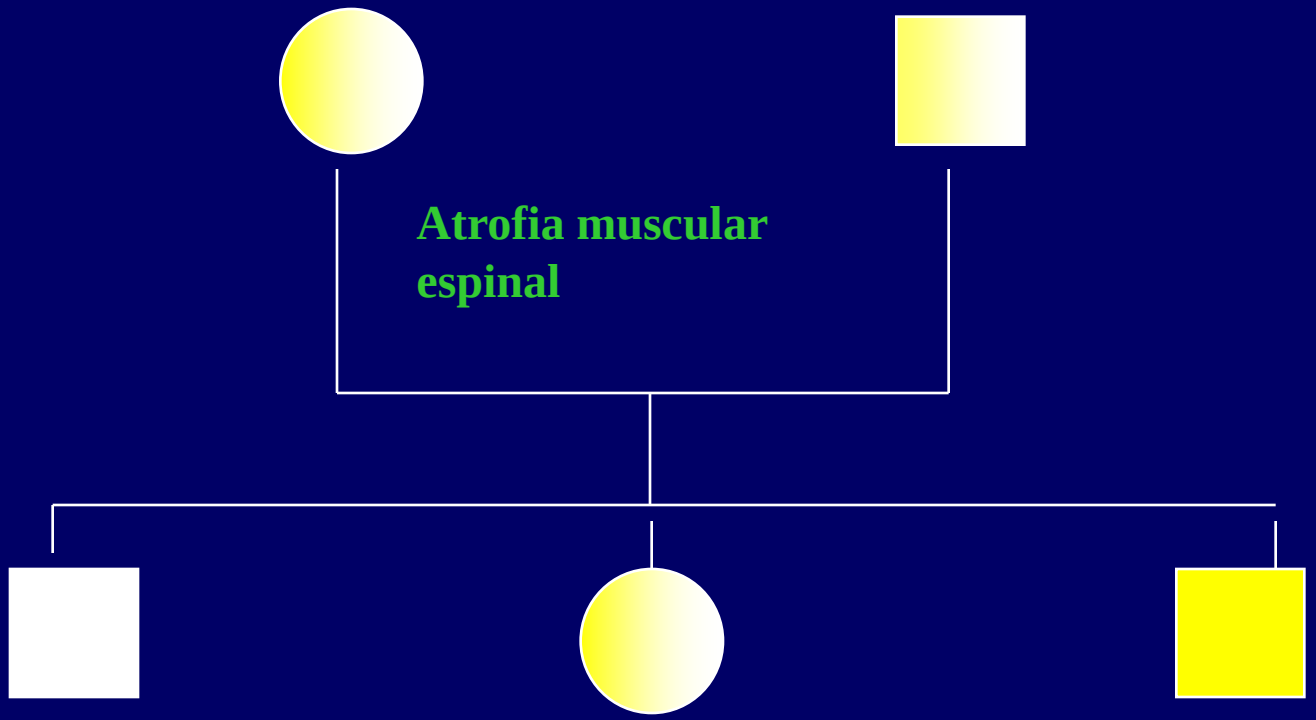
Patients: Fifty subjects at risk for autosomal dominant forms of spinocerebellar ataxia (n = 11), muscular dystrophy (n = 28), and hereditary neuropathy (n = 12).

Results: Thirty-nine subjects (78%) completed 6 months to 5 years of posttest follow-up. Common reasons for pursuing genetic testing were to provide an explanation for symptoms, emotional relief, and information for future planning. Thirty-four (68%) had positive and 16 (32%) had negative genetic results. In those with a positive result, 26 (76%) had nonspecific signs or symptoms of the relevant disorder. Forty-two participants (84%) felt genetic testing was beneficial. Groups with positive and negative test results coped well with results. However, 13 subjects (10 with positive and 3 with negative results) reported elevated anxiety levels, and 3 (1 with positive and 2 with negative results) expressed feelings of depression during the follow-up period. The test result was not predictive of anxiety or depression.

Conclusions :Most individuals find neurogenetic testing to be beneficial, regardless of the result. Anxiety or depression may persist in some persons with positive or negative test results. Testing can have a demonstrable impact on family planning and interpersonal relationships. Further studies are needed to assess the long-term impact of such testing.

HERENCIA AUTOSÓMICA RECESIVA

Madre Portadora asintomática **Padre portador asintomático**



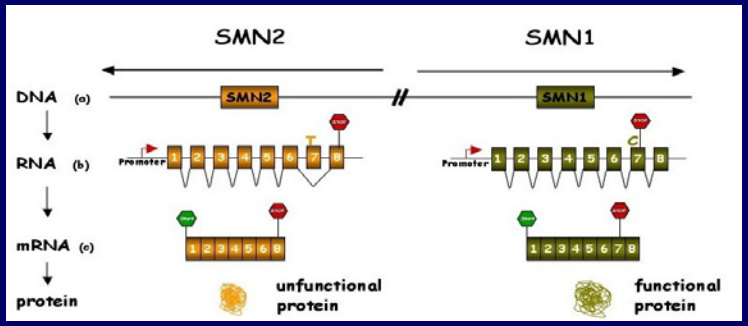
Hijo/a sano 25% **Portadora/portador asintomático 50%** **Hijo/a enfermo 25%**

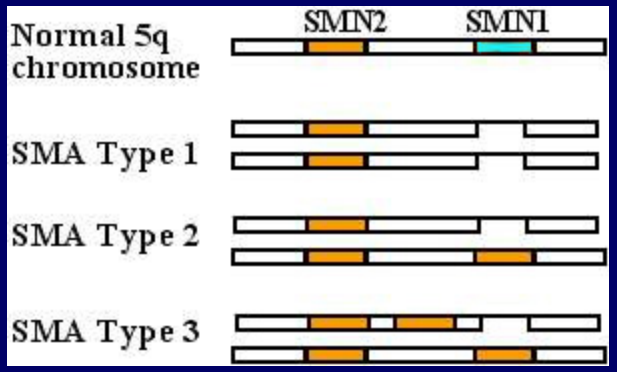
Atrofia muscular espinal

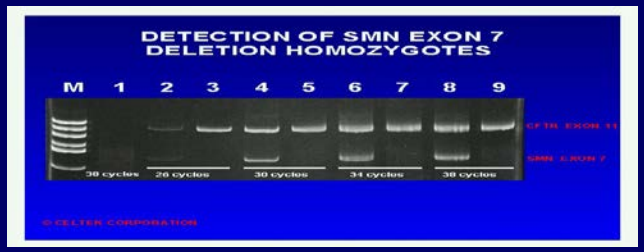
- segunda enfermedad recesiva en frecuencia; 1/10.000 y 1/50 individuos en la población son portadores

- 4 subformas: tipo I, tipo II, tipo III,

- Gen SMN1 .- 95% de los pacientes son portadores homocigotos de una deleción en el exón 7 del gen. 3-4% son heterocigotos compuestos

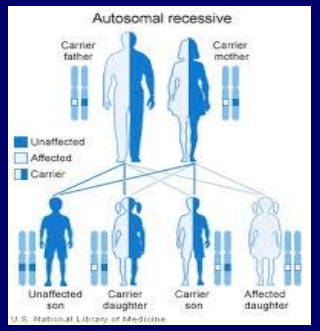


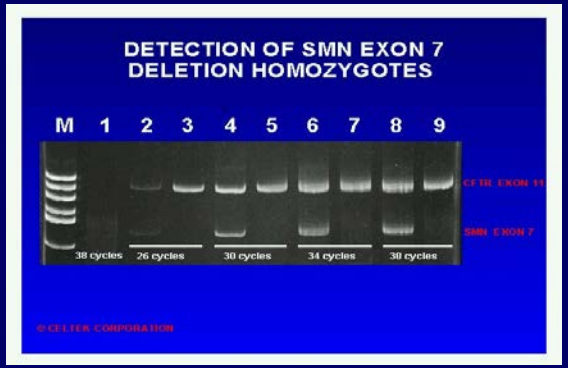




CONSEJO GENÉTICO

- 25% riesgo tener hijos afectados
- Detección de portadores
- Cribado poblacional? 1/50 portadores

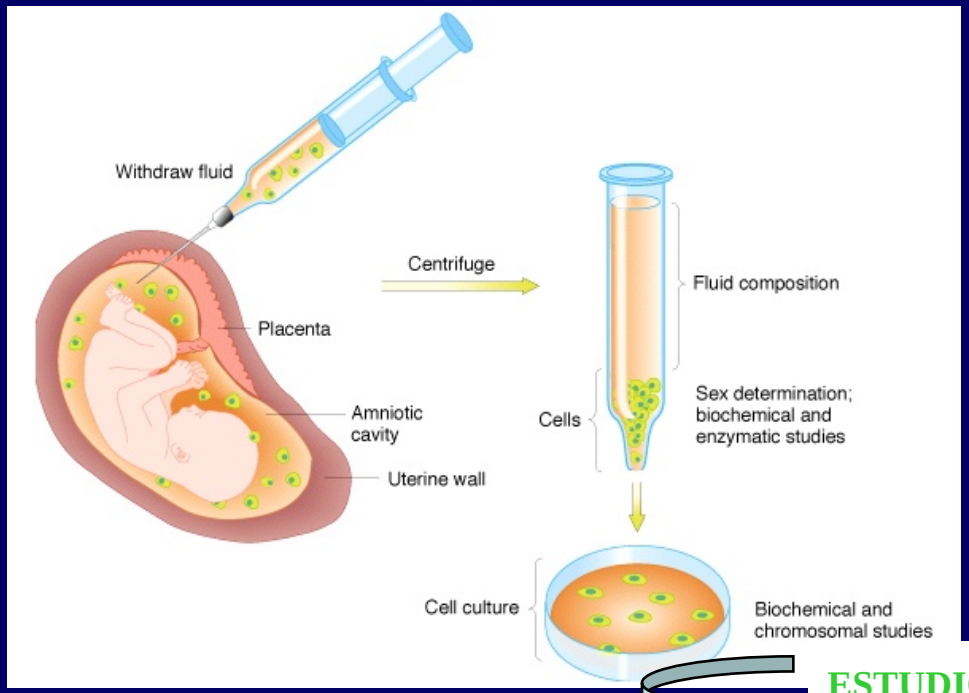




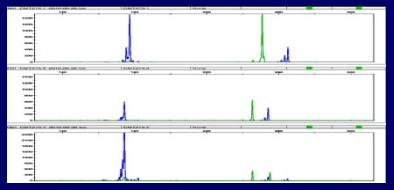
Riesgo en hijos portadores

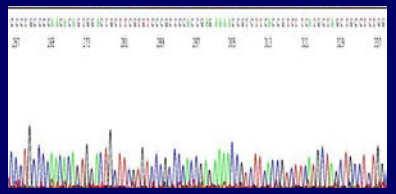
DIAGNÓSTICO GENÉTICO PRENATAL

Mutación caracterizada
Posibilidad de estudios directos/indirectos



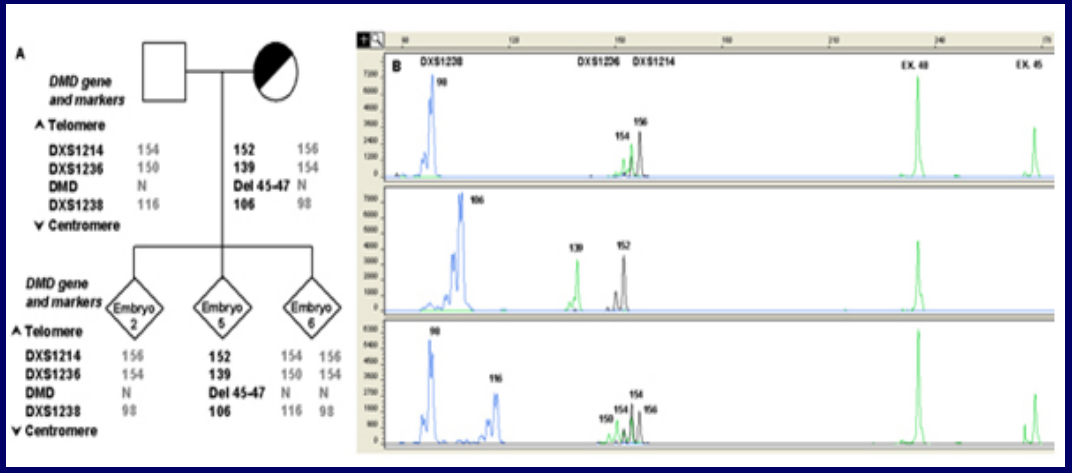
ESTUDIOS MOLECULARES

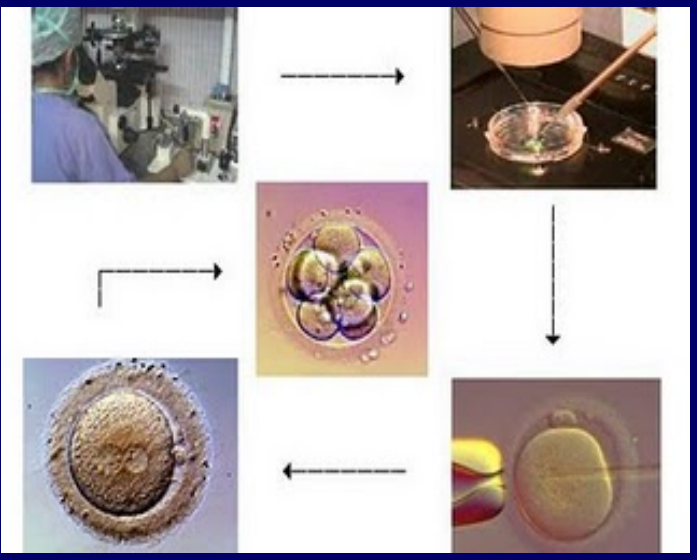




Diagnóstico genético preimplantacional

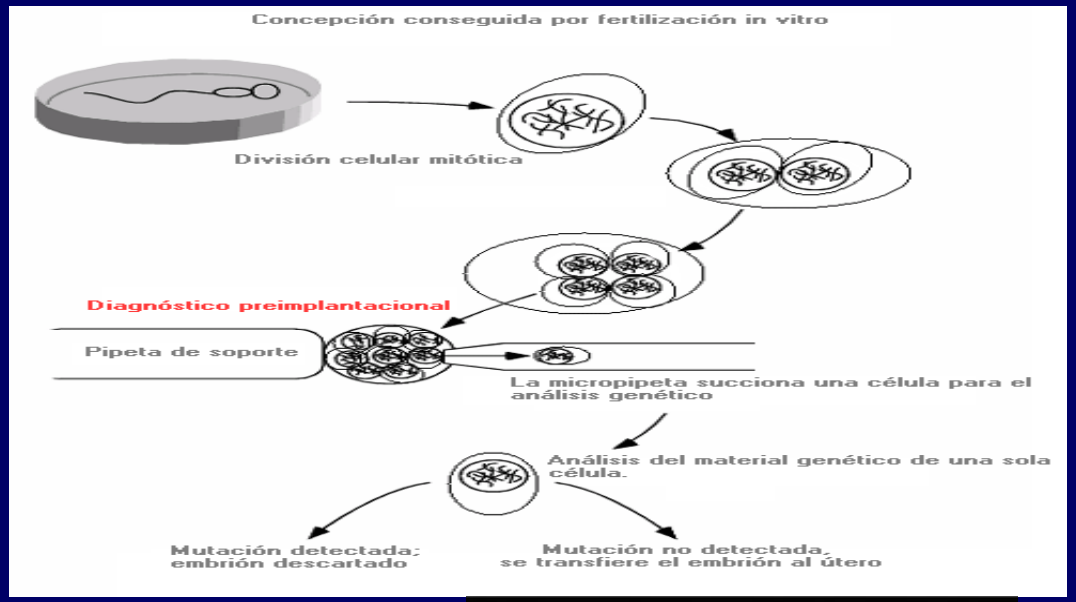
test genético en embriones para detectar la presencia de alteraciones patogénicas (enfermedades hereditarias) y/o embriones compatibles para trasplante de progenitores hematopoyéticos

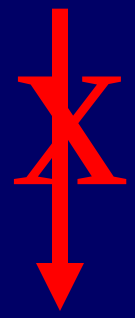




DIAGNOSTICO PREIMPLANTACIONAL-

Selección de embriones no portadores de la mutación





DIAGNÓSTICO GENÉTICO PREIMPLANTACIONAL Y ENFERMEDAD NEUROMUSCULAR

- ✓ técnica utilizada por primera vez 1990 (amplificación específica del cromosoma Y)
- ✓ biopsia+ análisis genético de célula única
- ✓ enfermedades ligadas al sexo
  - •determinación del sexo de los embriones (FISH)
- ✓Aplicaciones
  - • enfermedades monogénicas (hereditarias)
    - autosómico recesivo
      - atrofia muscular espinal
    - autosómico dominante
      - neuropatías,
    - ligadas al sexo:
      - distrofía muscular de Duchenne
- ✓ equipo multidisciplinar : unidad de reproducción asistida+ unidad de genética médica

- **Formación del personal**
  - **biopsia-embriólogo clínico**
  - **Técnicas moleculares (FISH, PCR)- citogenetistas y/o genetistas moleculares**

- **Definir criterios de inclusión y exclusión de pacientes en ciclos de DGP**
  - **normas reguladoras locales**

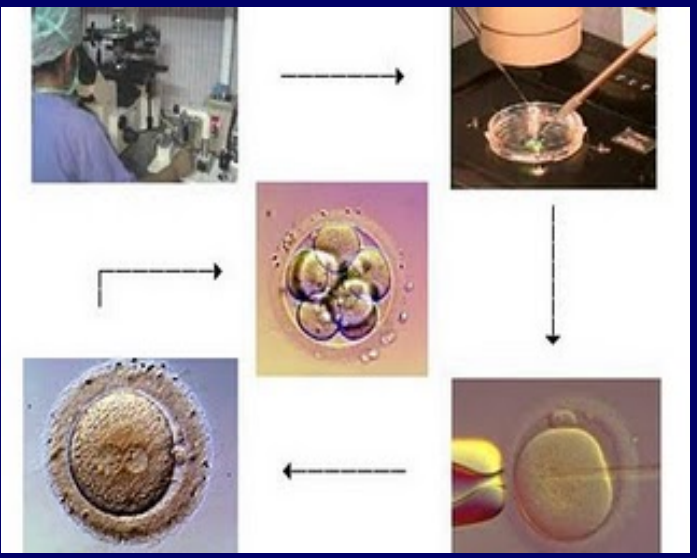
- **Ofrecer un adecuado asesoramiento genético a la pareja**

- **Amplia información acerca del proceso de DGP**
  - **% de diagnósticos erroneos (sensibilidad/especificidad)**

- **Acreditación del laboratorio**
  - **sistema de calidad**

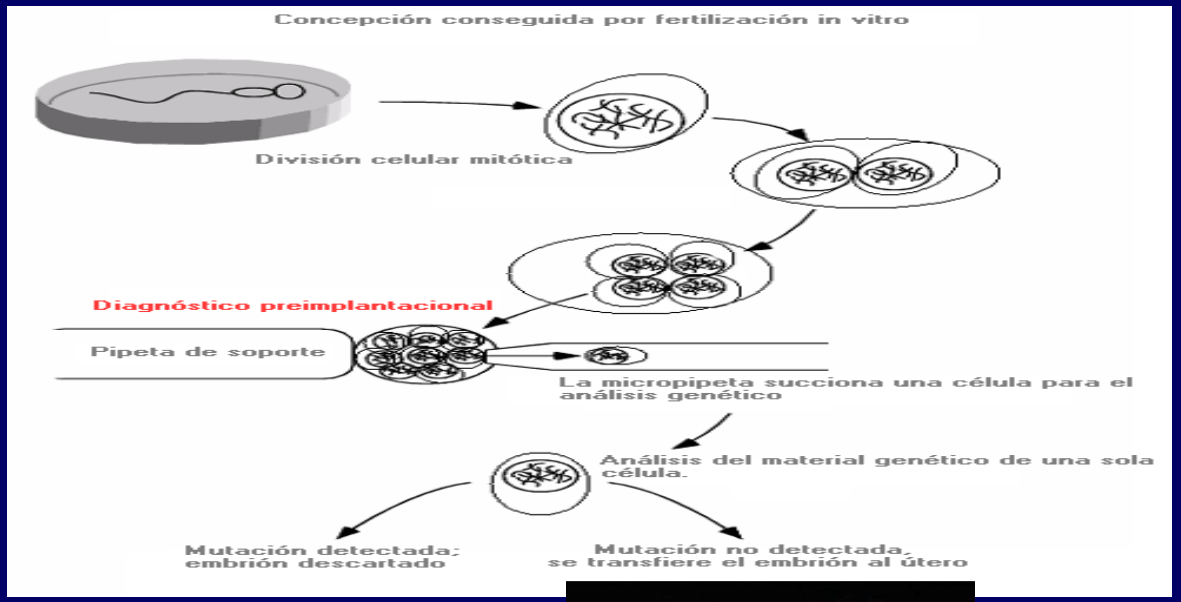
Tasa de errores 4-8%

- **error humano**
- **allele drop out**
- **contaminación y mosaicismo**



DIAGNOSTICO PREIMPLANTACIONAL

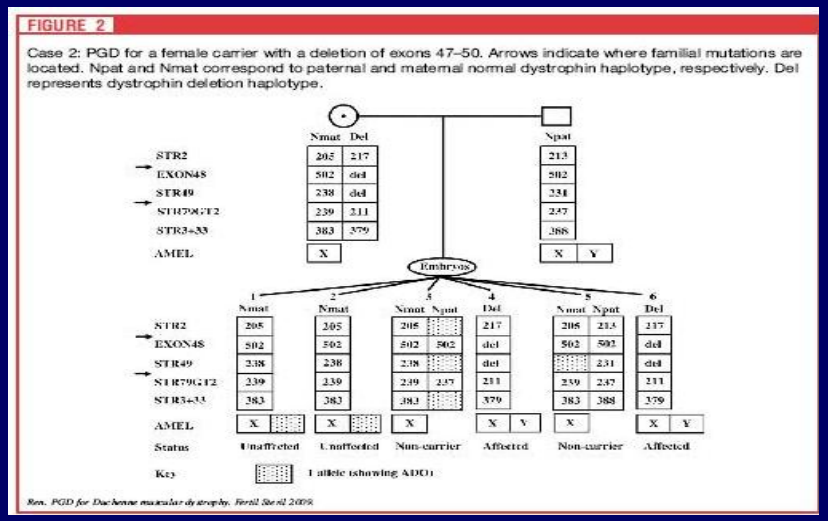
Selección de embriones no portadores de la mutación



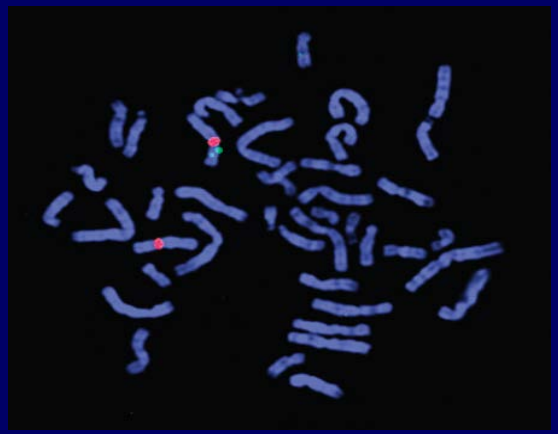
Preimplantation genetic diagnosis for Charcot-Marie-Tooth disease type 1A. Mol Hum Reprod. 2003 Jul;9(7):429-35. De Vos A, Sermon K, De Rijcke M, Goossens V, Henderix P, Van Ranst N, Platteau P, Lissens W, Devroey P, Van Steirteghem A, Liebaers I.

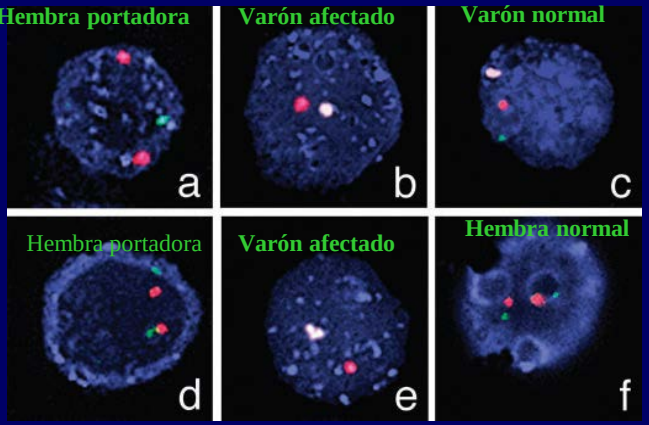
Centre for Reproductive Medicine, University Hospital, Dutch-speaking Brussels Free University, Brussels, Belgium.

DGP Y DISTROFIA MUSCULAR DE DUCHENNE



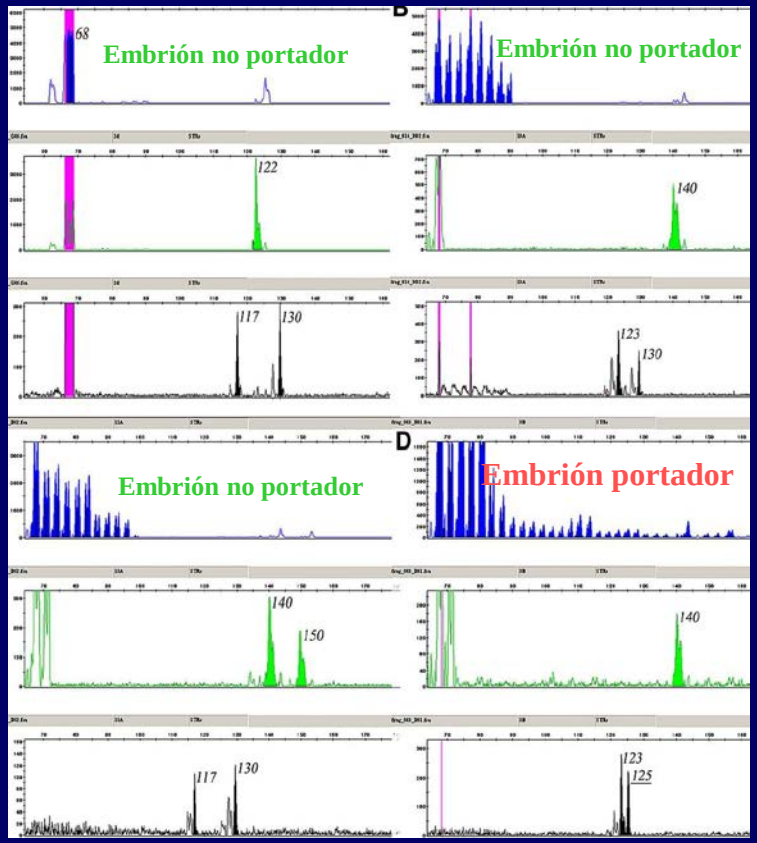
Hospital Virgen del Rocio 2006





Fish específico deleción exón 45

DGP Y DISTROFÍA MIOTÓNICA TIPO 1



European Journal of Human Genetics (2009) 17, 1403–1410
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www.nature.com/ejhg

ARTICLE

Preimplantation genetic diagnosis for myotonic dystrophy type 1: upon request to child

Marjan De Rademaeker[1], Willem Verpoest[2], Martine De Rycke[1,3], Sara Seneca[1], Karen Sermon[1,3], Sonja Desmyttere[1], Maryse Bonduelle[1,3], Josianne Van der Elst[2,3], Paul Devroey[2,3] and Inge Liebaers [1,3]

[1]*Centre for Medical Genetics, Universitair Ziekenhuis Brussel, Brussels, Belgium;* [2]*Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium;* [3]*Department of Embryology and Genetics, Vrije Universiteit Brussels, Belgium*

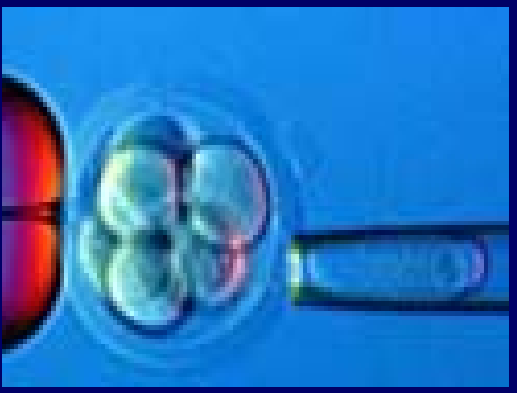
Preimplantation genetic diagnosis (PGD) is an alternative to prenatal diagnosis for patients at risk of transmitting an inherited disease such as myotonic dystrophy type 1(DM1) to their offspring. In this paper, the clinical application of preimplantation diagnosis for DM1 upon request to children born is described in a large cohort of risk couples. PGD could be offered to all 78 couples opting for PGD regardless of the triplet repeat size. The incidence of major complications was minimalised following a careful assessment in affected DM1 females anticipating possible cardiological, obstetrical and anaesthetical problems. A live-birth delivery rate per cycle with oocyte retrieval of 20% was the outcome. Forty-eight of the 49 children born are in good health and have normal psychomotor development.
European Journal of Human Genetics (2009) 17, 1403–1410; doi:10.1038/ejhg.2009.56; published online 15 April 2009

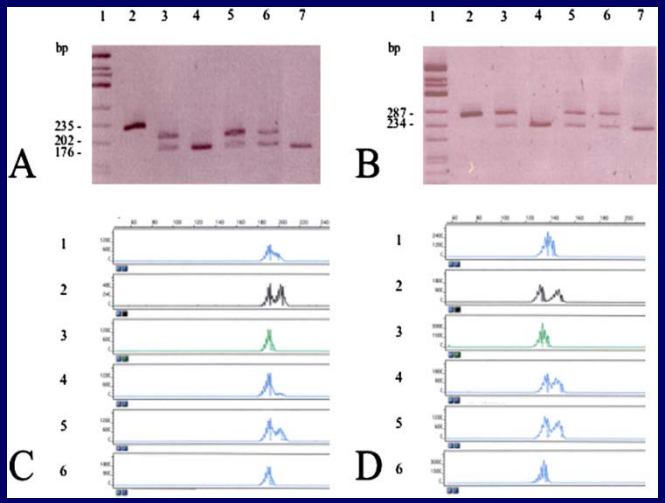
Keywords: preimplantation genetic diagnosis; myotonic dystrophy; counselling; child

Nace en Valencia una niña libre de distrofia miotónica de Steinert

El equipo de Reproducción Humana Asistida del Hospital la Fe de Valencia ha conseguido el nacimiento a finales del pasado mes de enero de una niña libre de la enfermedad degenerativa de distrofia miotónica de Steinert gracias a la aplicación de la técnica de estudio molecular por PCR (Reacción en cadena de la polimerasa) para enfermedades monogénicas, según ha informado la responsable de este tratamiento, la doctora Ana Monzó.16-04-2011

DGP y Atrofia muscular espinal





Xavier y María, afecta de SMN

actualidad

Distrofia facio escapulo humeral

Martes, 30.3.2010, 18:20 h

< anterior | siguiente >

Un DGP permite el nacimiento del primer bebé en España libre de una distrofia muscular

diagnóstico genético preimplantacional, Reprogenetics, Quirón

No hay ningún voto

El Hospital Quirón de Barcelona ha conseguido el nacimiento del primer bebé en España libre de una distrofia muscular que afecta a cara, hombros y brazos, mediante la técnica del diagnóstico genético preimplantacional (DGP). La niña está sana de esta patología y además no es portadora de la enfermedad.

DGP: Regulación en España

Ley14/2006. Art 26.c de Reproducción Asistida Humana .

- **Hay dos casos en los que no hace falta pedir permiso de la Comisión Nacional del RA, tan solo comunicar la realización a la autoridad sanitaria competente (Comunidad Autónoma) :**

- Detección de enfermedades graves hereditarias, de aparición precoz y sin cura.

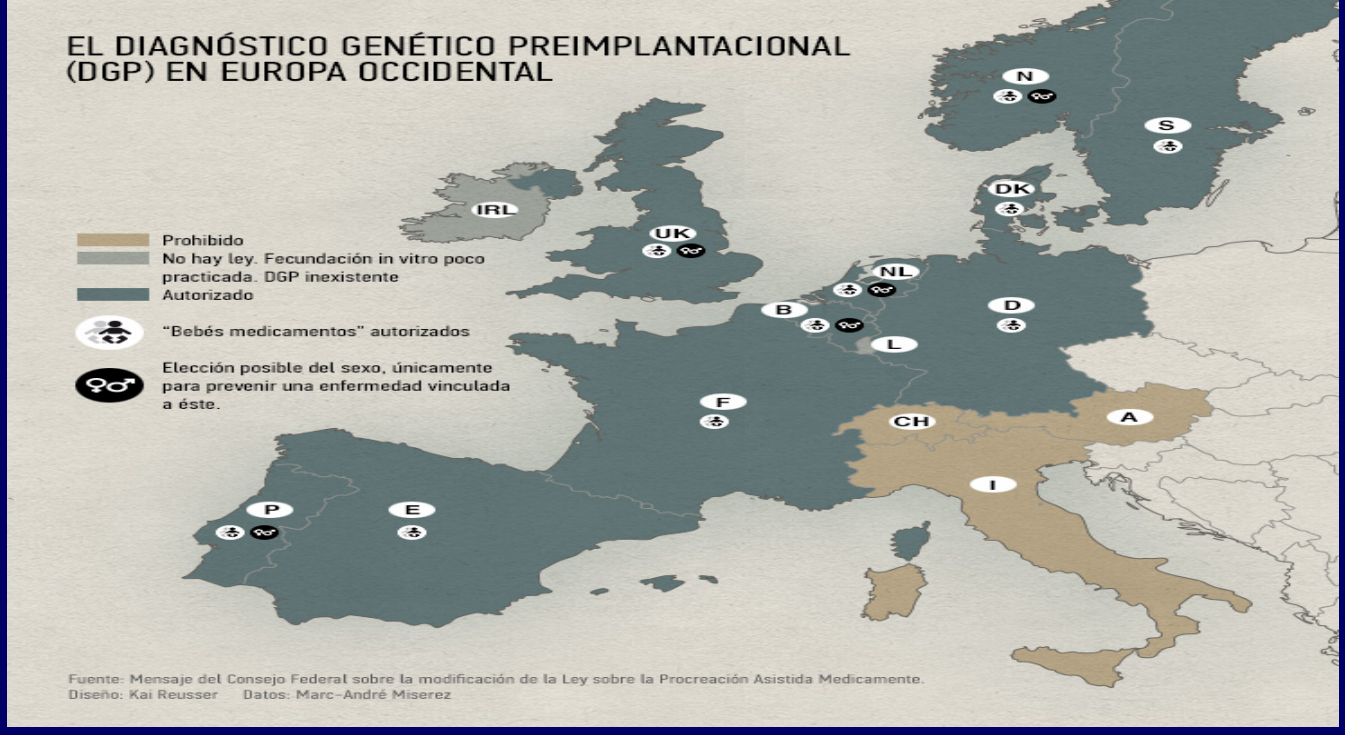
- Detección de alteraciones que comprometan la vida del embrión: cromosomopatías.

- **Son infracciones graves: La selección de sexo o manipulación genética con fines no terapéuticos o terapéuticos no autorizados.**

Convención Derechos Humanos y Biomedicina. Art 14

(Consejo de Europa)

La utilización de técnicas de reproducción asistida no pueden llevarse a cabo para elegir el sexo del niño, salvo de que se trate de evitar una enfermedad grave ligada al sexo.

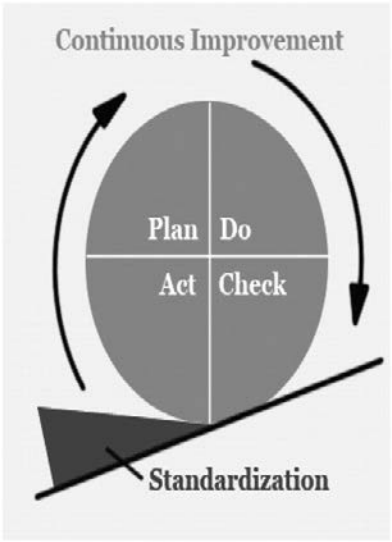


DE LOS 15 PAÍSES DE EUROPA OCCIDENTAL, 12 PERMITEN EL DGP, ALGUNOS DESDE HACE VEINTE AÑOS COMO ESPAÑA, REINO UNIDO Y FRANCIA. ALEMANIA FUE LA ÚLTIMA EN DAR EL PASO Y APENAS DESDE 2011 AUTORIZA EL DIAGNÓSTICO SOBRE LOS EMBRIONES.EN ITALIA, DE MANERA CONTRARIA, EL DGP ERA UNA PRÁCTICA COMÚN HASTA LA INTRODUCCIÓN DE UNA MODIFICACIÓN LEGISLATIVA EN 2004, QUE PROHÍBE LA PRÁCTICA Y QUE VALIÓ AL PAÍS UNA CONDENA DE LA CORTE EUROPEA DE DERECHOS HUMANOS.

ADEMÁS DEL DGP, NUEVE PAÍSES PERMITEN EL TIPAJE HLA (ANTÍGENOS LEUCOCITARIOS HUMANOS), UNA TÉCNICA QUE PERMITE SELECCIONAR UN EMBRIÓN INMUNOCOMPATIBLE CON UN HERMANO O HERMANA AFECTADO (A) POR UNA ENFERMEDAD GRAVE. EL NUEVO SER PUEDE CONVERTIRSE EN DONADOR DE CÉLULAS MADRE PARA AYUDAR A SU HERMANO (A).

EN CINCO PAÍSES, LA LEY MENCIONA ESPECÍFICAMENTE EL DGP COMO MÉTODO PARA ELEGIR EL SEXO DEL BEBÉ, PERO SOLAMENTE PARA EVITAR UNA ENFERMEDAD RELACIONADA CON ESTE ÚLTIMO. A PESAR DE ESA RESTRICCIÓN, UN ESTUDIO CITADO EN EL MENSAJE DEL CONSEJO FEDERAL (GOBIERNO), EN APOYO DEL CAMBIO EN LA LEGISLACIÓN SUIZA, ESTIMA QUE EN EUROPA "EL DGP SE REALIZA EN EL 2% DE LOS CASOS CON EL FIN DE ELEGIR EL SEXO, SIN RELACIÓN CON UNA ENFERMEDAD". EN ESTADOS UNIDOS, DONDE LA PRÁCTICA ES MUCHO MÁS LIBERAL, ESTA PROPORCIÓN ALCANZARÍA EL 10%.

The 'Deming' or 'PDCA' cycle is a rolling circle of four compartments; Plan, Do, Check and Act.



Harper J et al. Hum. Reprod. 2010;25:1051-1065

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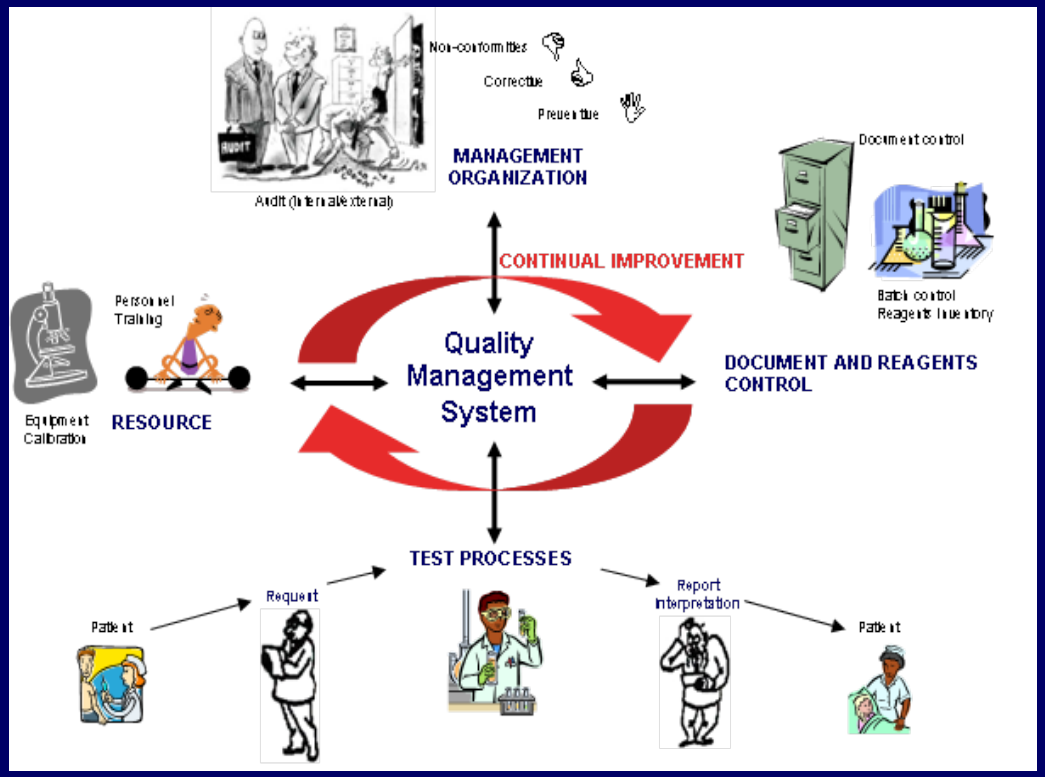

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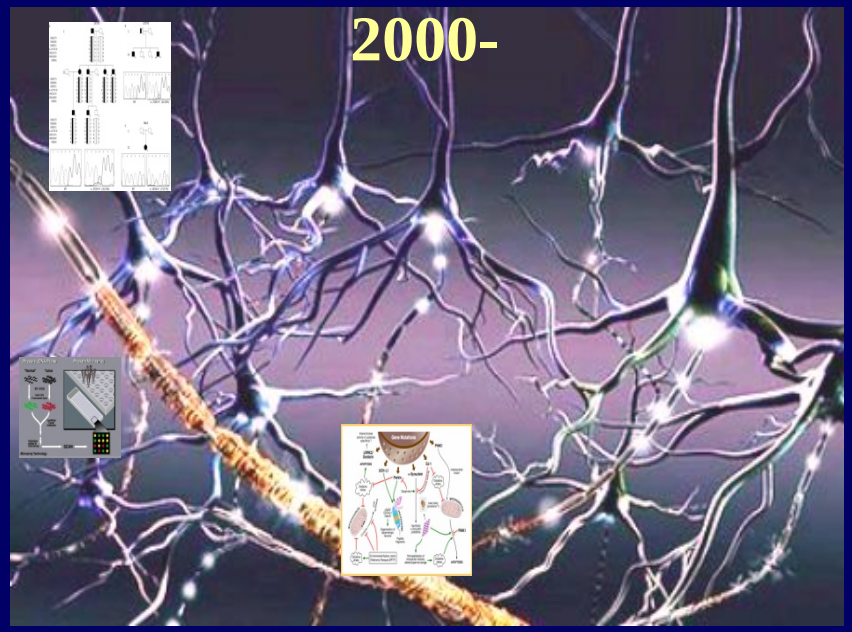
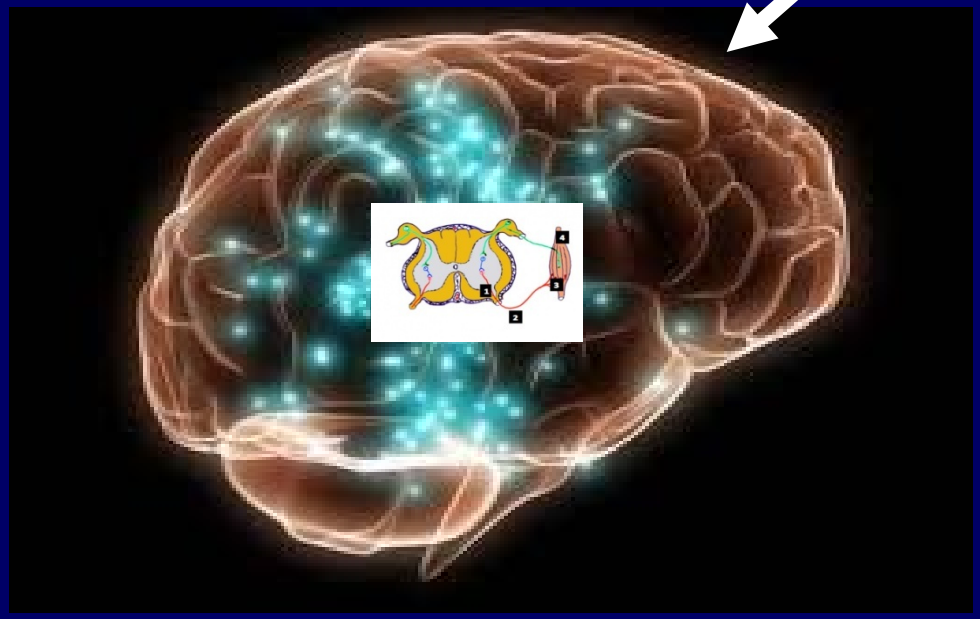
THE HUMAN GENOME PROJECT
EXPLORING OUR
MOLECULAR SELVES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