Aspectos clínicos y moleculares de la miotonía congénita.

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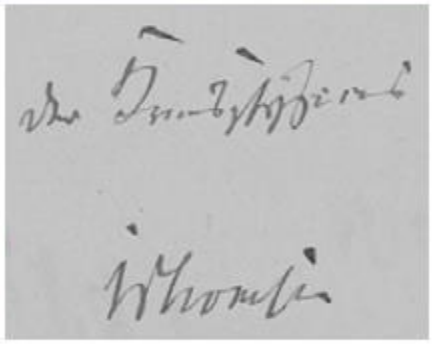
s Thomas Thomsen (Figure 1) was born in sholm in the Parish of Esgrus on the Angeln the Danish Duchy of Slesvig (from the mid- ed into Prussian Schleswig-Holstein). After tuition and later attending Slesvig's Cathedral dertook his university studies in Kiel, Berlin agen, and obtained his medical doctorate 1839. He returned to the Angeln Peninsula nedicine and was appointed Kreisphysikus sician) in Kappeln on the Schlei River in a et al. 1990), eventually being awarded the ical practitioner's title 'Sanitätsrat' (Member of Health) in 1885 (Nissen Family Collection, Kristina Wiberg[1]). It was from there in 1876 provoked into publishing an earlier-prepared n the muscle cramping and stiffness disease iself and his family, after spending much of aling it, because his youngest son was accused ig to avoid military service. It was entitled ämpfe in willkürlich beweglichen Muskeln ererbter psychischer Disposition (Ataxia [Tonic Cramps in Voluntary Muscles as a of a Hereditary Psychological Trait (Ataxia].



ure 1: Asmus Julius Thomas Thomsen (courtesy of Kristina Wiberg[1], from Nissen Family Collection) and his signature 'Dr Kreisphysikus, J Thomsen' n Thomsen's letter accepting his 1853 appointment as district physician in peln, courtesy of the Landesarchiv Schleswig-Holstein, Abt. 309 Nr. 27 973).

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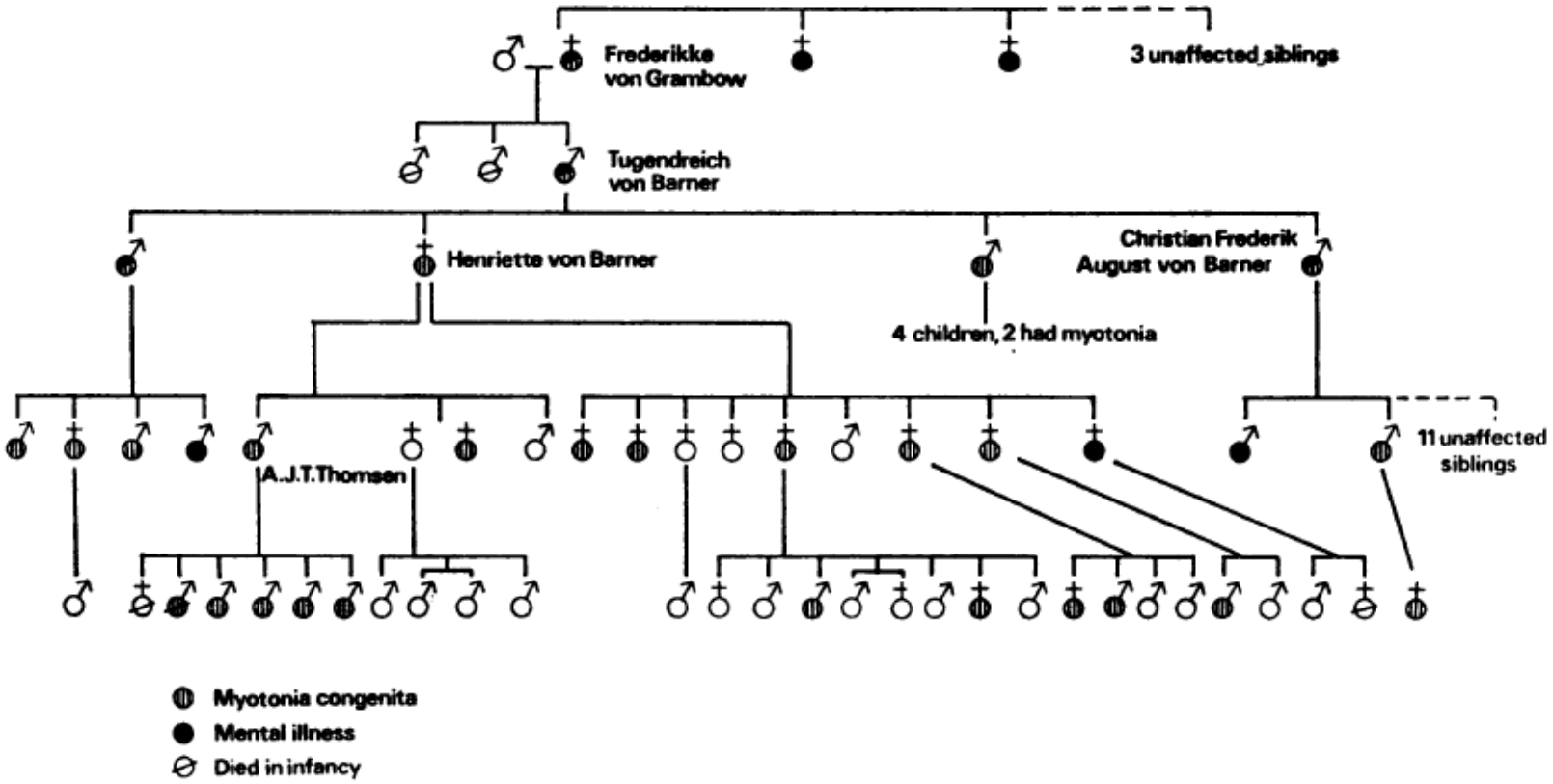

Frederikke von Grambow
3 unaffected siblings
Tugendreich von Barner
Henriette von Barner
Christian Frederik August von Barner
4 children, 2 had myotonia
A.J.T.Thomsen
11 unaffected siblings
Myotonia congenita
Mental illness
Died in infancy

***Miotonía*: Disminución de la relajación muscular con efectos indeseables**

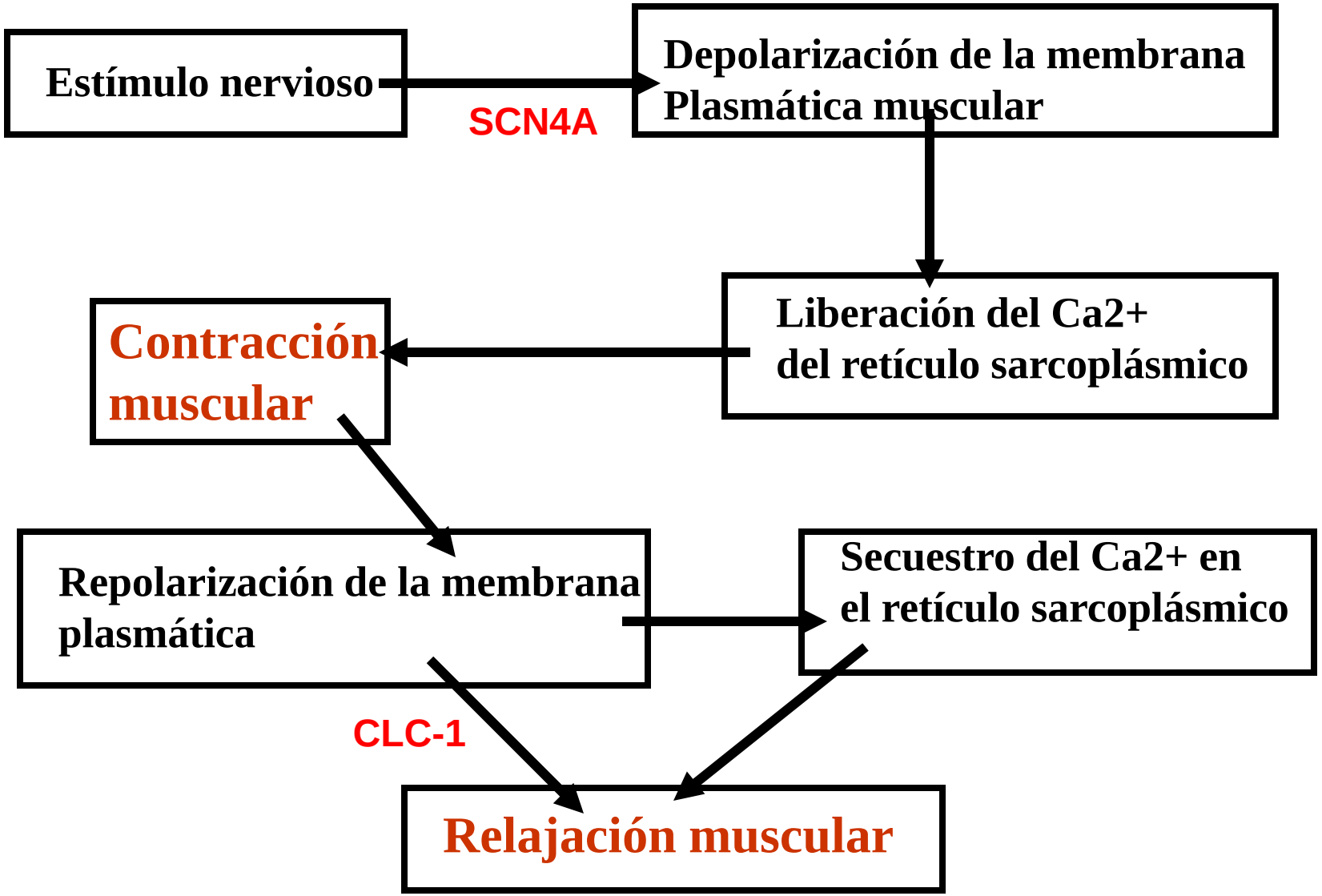
***Enfermedades que causan miotonia*:**

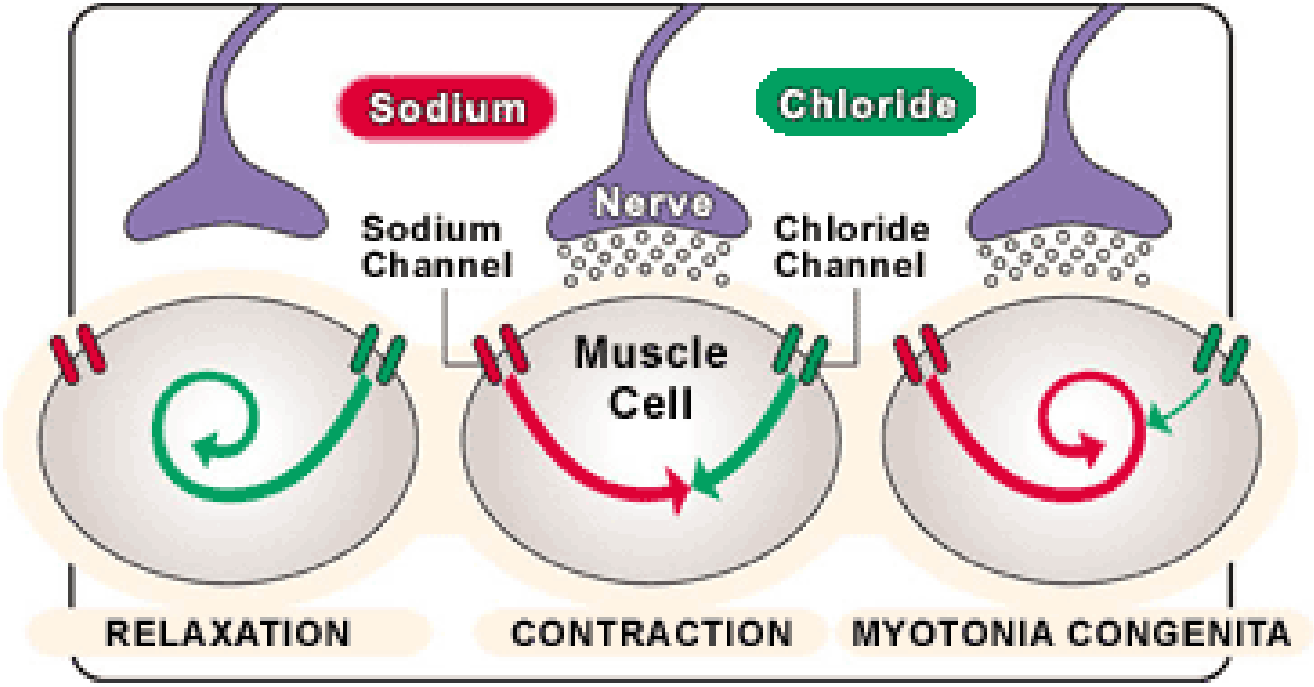
Miotonía congénita (gen *CLCN1*)

Distrofias miotónicas 1 y 2 (genes *DMPK* y *ZNF9*)

Paramiotonia congénita (gen *SCN4A*)

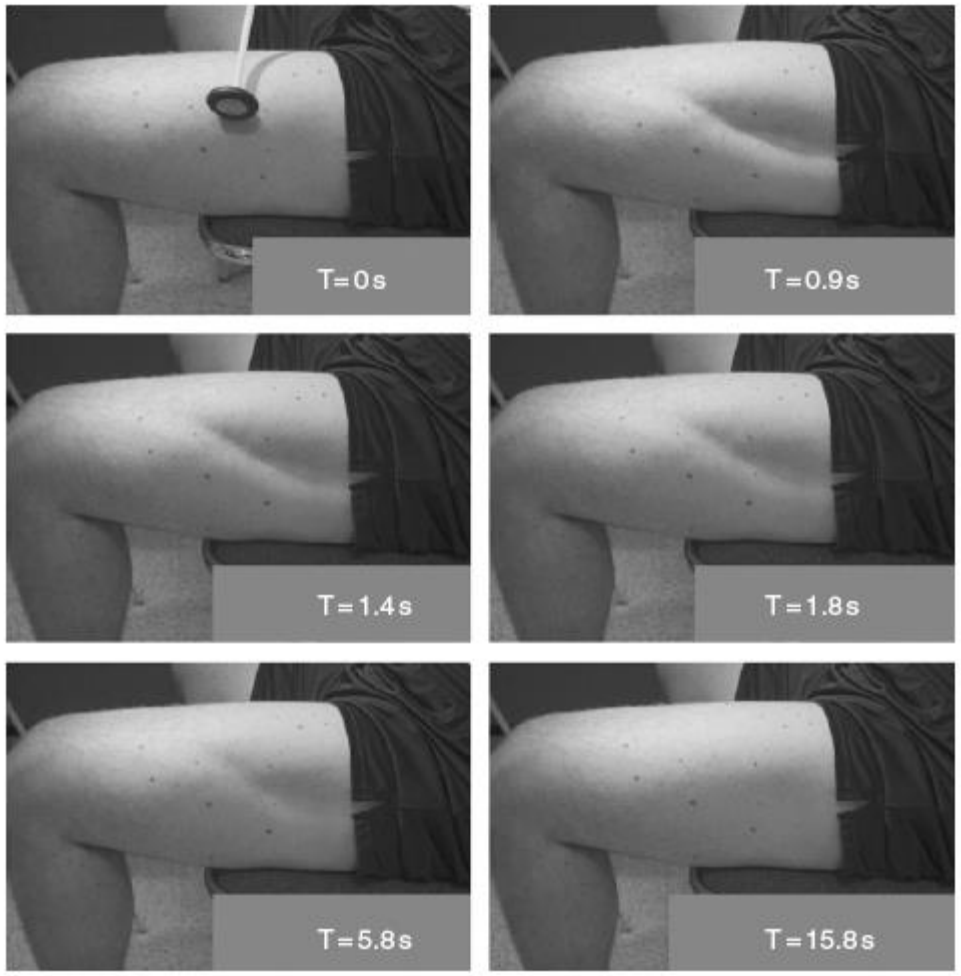
Parálisis periódica hiperpotasémica (gen *SCN4A*)


Estímulo nervioso
SCN4A
Depolarización de la membrana Plasmática muscular
Liberación del Ca2+ del retículo sarcoplásmico
Contracción muscular
Repolarización de la membrana plasmática
Secuestro del Ca2+ en el retículo sarcoplásmico
CLC-1
Relajación muscular


Sodium
Chloride
Nerve
Sodium Channel
Chloride Channel
Muscle Cell
RELAXATION
CONTRACTION
MYOTONIA CONGENITA

Miotonia congénita. Síntomas

- **Miotonia**
- **Afecta más a los músculos proximales de miembros inferiores**
- **Debut en los primeros años de vida**
- **Cansancio**
- **Dificultad para iniciar movimientos. Alivio después de unos minutos (fenómeno warm-up)**
- **Descargas miotónicas en el electromiograma**



Christoph Lossin and Alfred L. George, Jr. Advances in Genetics, Vol. 63, 2008

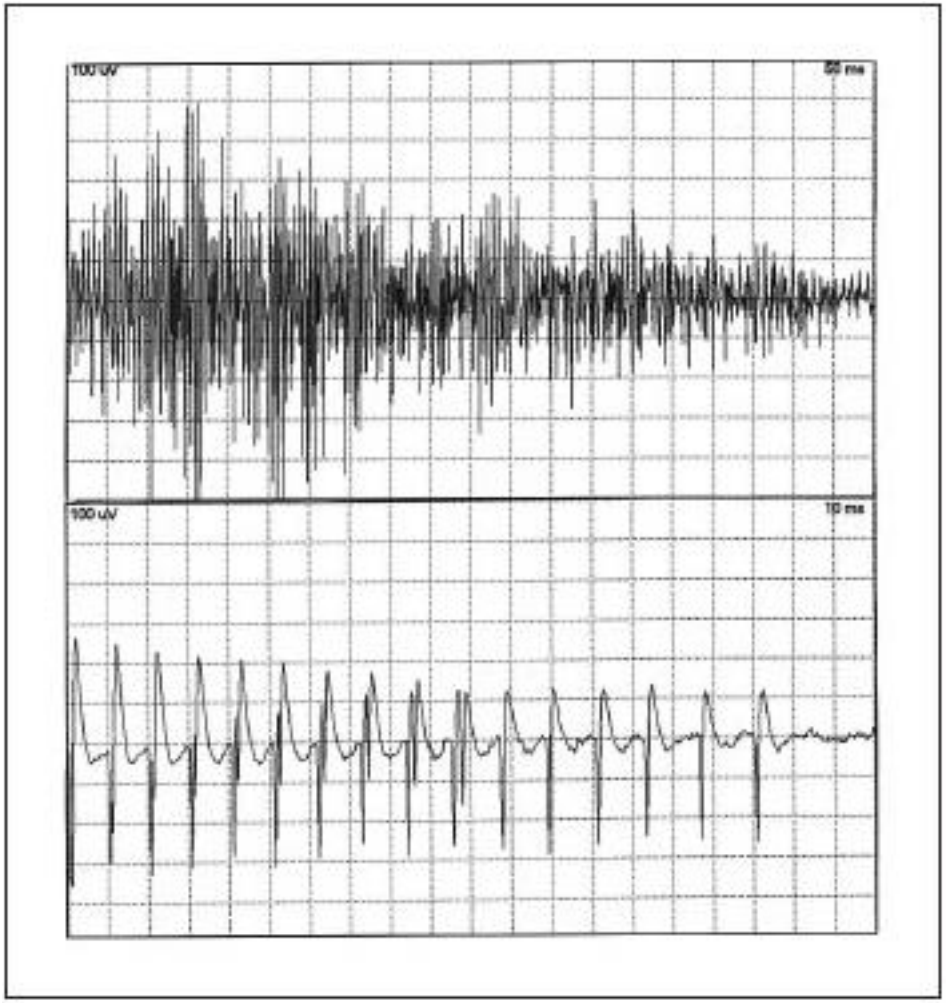
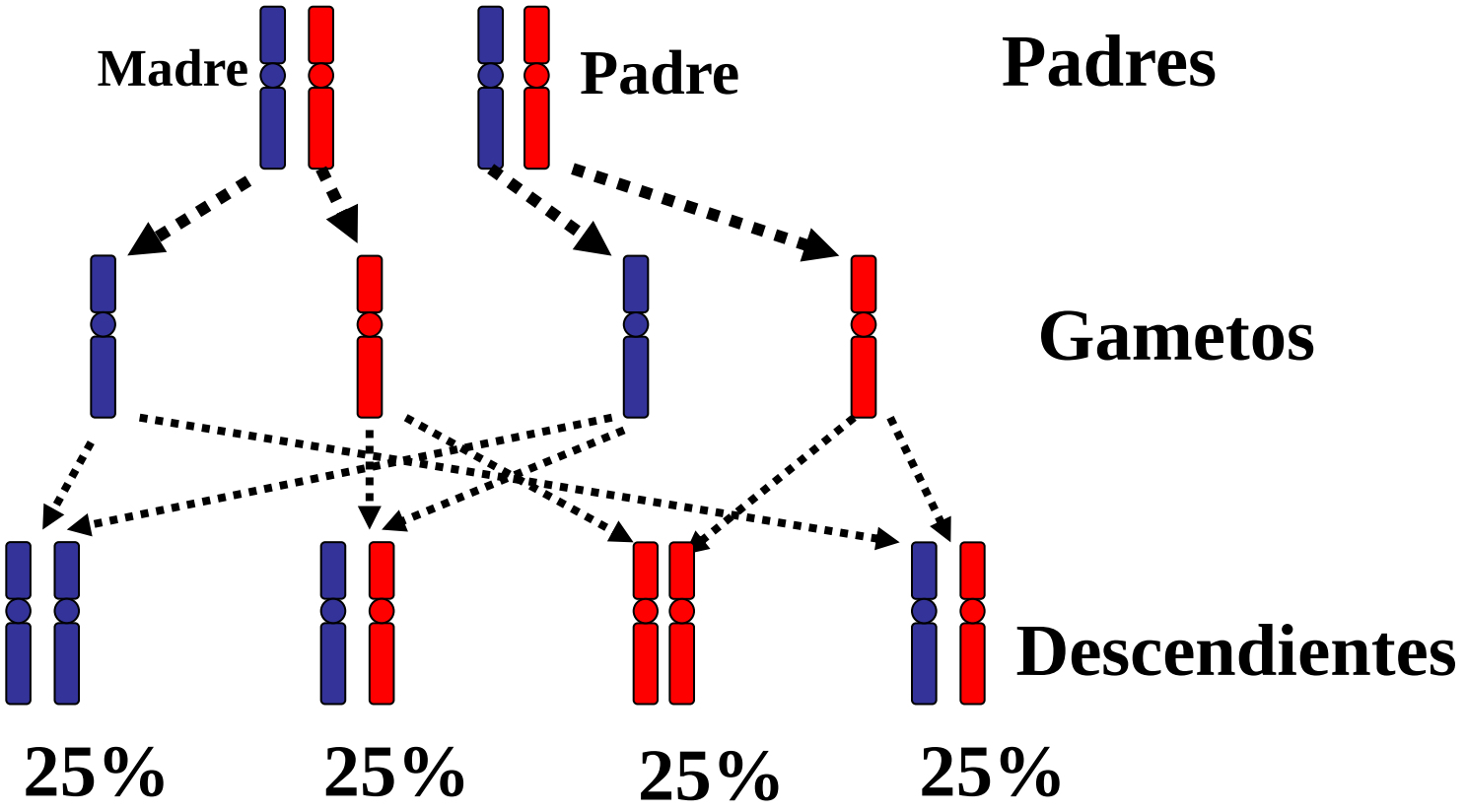


Figure. Myotonic potentials in the right deltoid muscle.

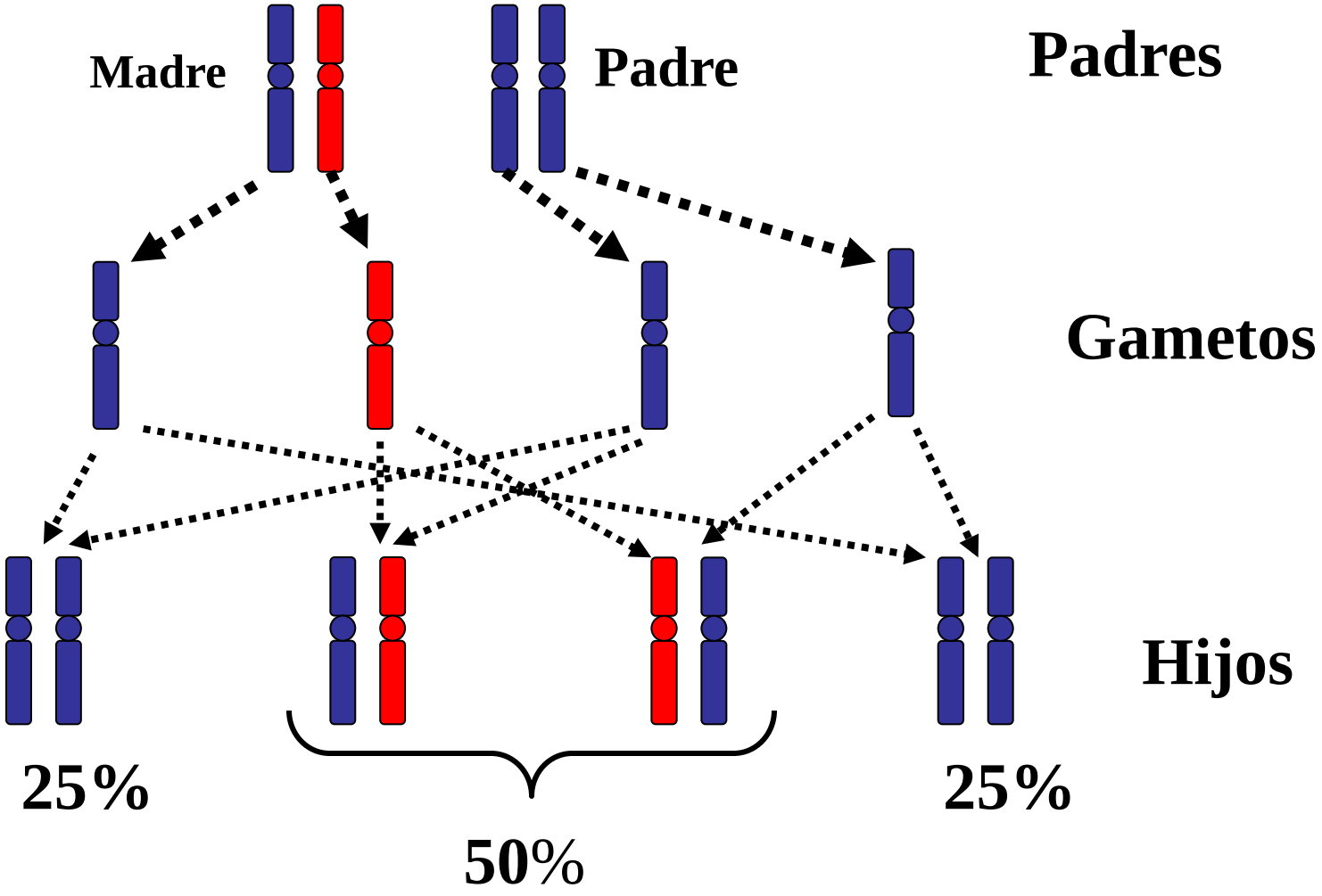
Genética molecular de la miotonia congénita

- Debida a mutaciones en el gen *CLCN1*
- Herencia autosómica dominante (Thompsen)
- Herencia autosómica recesiva (Becker)
- Está alterada la función del canal de iones cloruros Clc-1 del músculo (canal dependiente de voltaje)
- El potencial de membrana de la célula muscular está alterado causando miotonía
- Prevalencia: 1 en 20.000-40.000 individuos

Herencia mendeliana autosómica recesiva



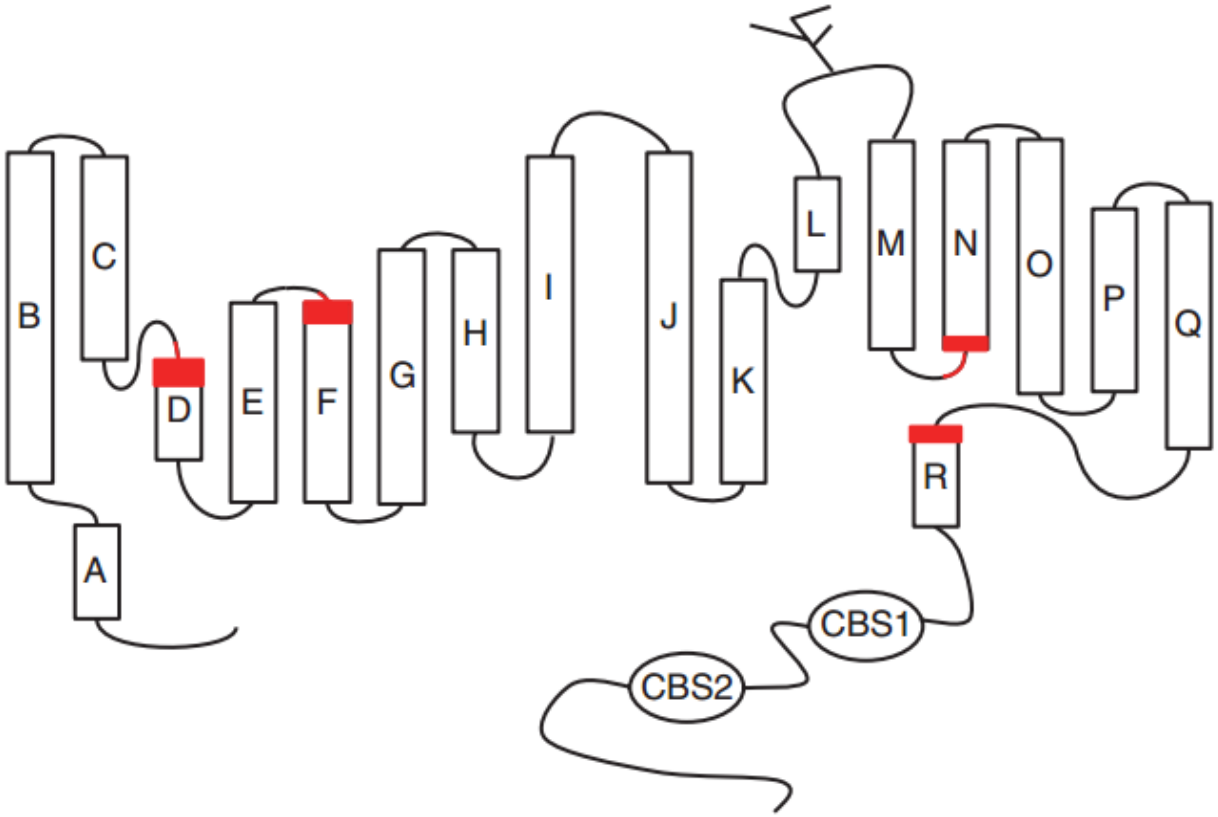
Herencia mendeliana autosómica dominante



Miotonia congénita (gen CLCN1)

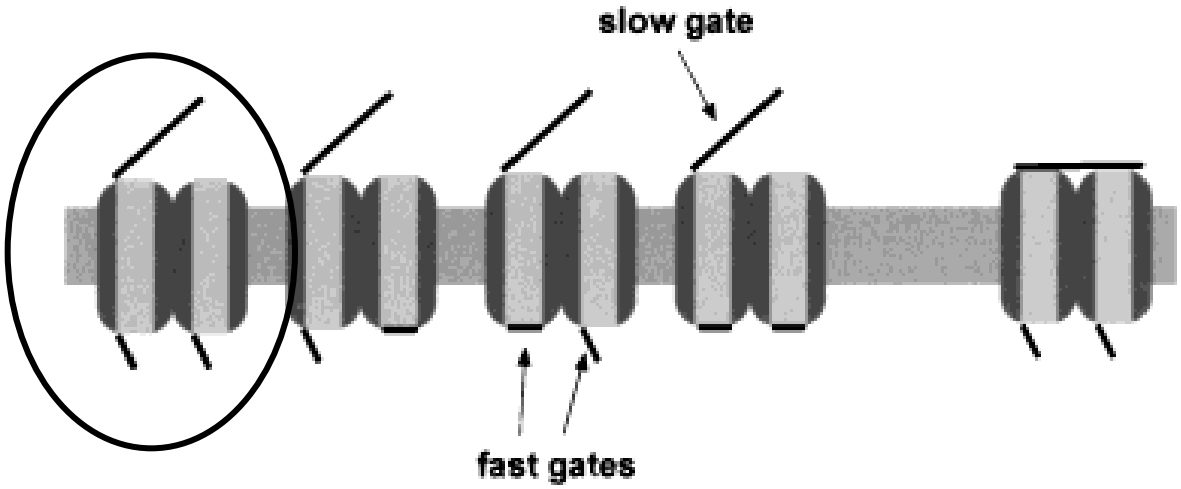
	Thomsen	Becker
Gravedad de los síntomas	0-3	3-5
	Miotonia leve-moderada	Miotonia moderada-grave
	Herencia dominante	Herencia recesiva

Tabla elaborada a partir de los datos de Fialho et al. Brain. 2007 Dec;130:3265-74

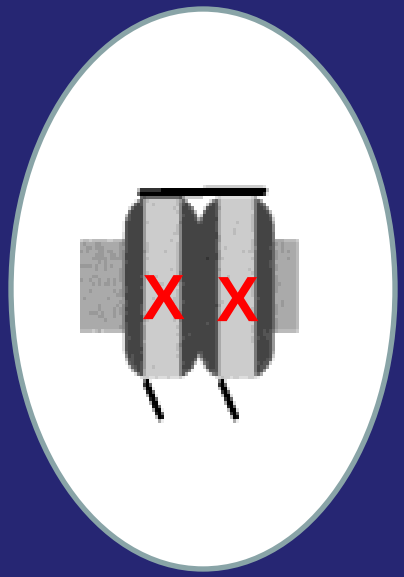


***Esquema del monómero del canal de iones cloruro* ClC-1**

Homodímeros del canal Clc-1



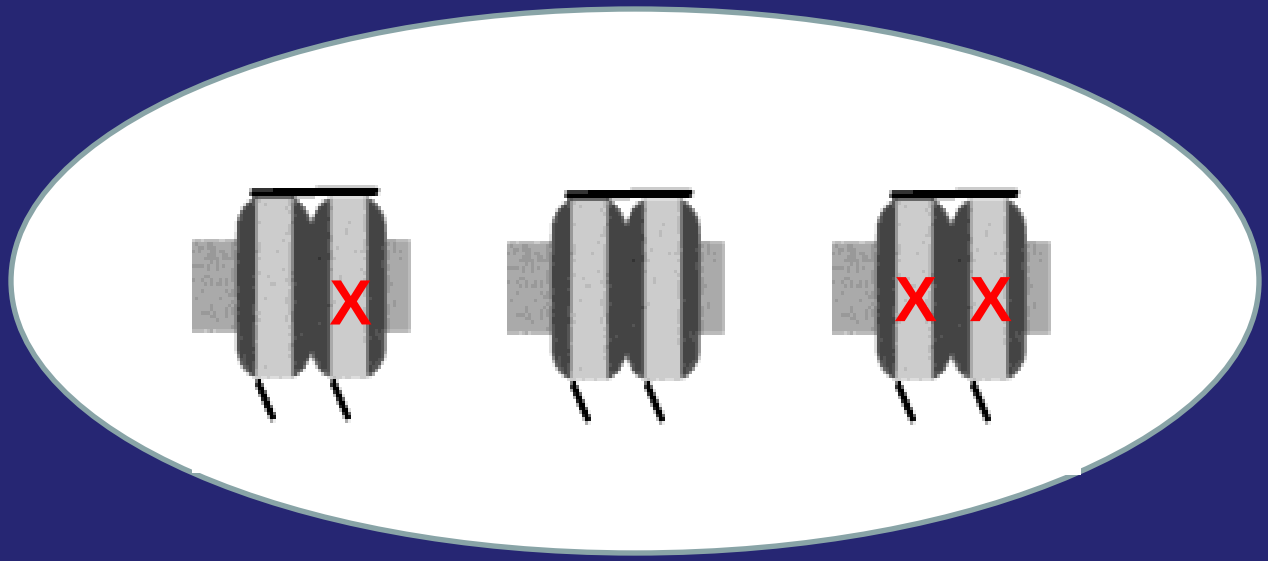
Actividad del canal ClC-1 en la herencia autosómica recesiva



0% ⟵ Actividad

Pacientes

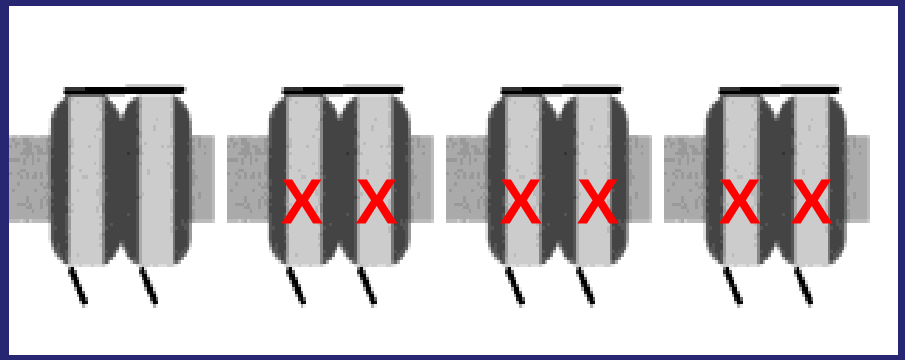
Actividad del canal ClC-1 en la herencia autosómica recesiva



Actividad ⟶ 50%

Portadores

Actividad del canal ClC-1 en la herencia autosómica dominante



N N	N M	M N	M M
25%	0%	0%	0%

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Table 1. *CLCN1* mutations (modified after Pusch[83]).

Nucleotide	Amino acid	Inheritance	References	Nucleotide	Amino acid	Inheritance	References
c.−3A > T	sd	R	95	1095-1096del	fs387X	R	75
202C > T	Q68X	R	119	1238T > G	F413C	R	55, 120
220C > T	Q74X	R	71	1244C > T	A415V	R	71
313C > T	R105C	R	75	1262insC	fs429X	R	75
382A > G	M128V	D	30, 46	1272C > G	I424M	?	20
394A > T	S132C	D?	115	1278–1281del	fs433X	R	50
407A > G	D136G	R	40, 50	1283T > C	F428S	D?	115
*449A > G	*Y150C	R	71, 114	1333C > T	Q445X	R	90
481T > G	F161V	R	81	1412C > T	S471F	D?	53
494T > G	V165G	R	75, 120	1437–1450del	fs503X	R	74
501C > G	F167L	R	45, 120	1438C > A	P480T	D	91
577G > A	E193K	D	30, 46	1439C > T	P480L	D	82, 99
577G > T	E193X	R	115	1443C > A	C481X	R	89
592C > G	L198V	D	94	1444G > A	G482R	D?	75, 53
598G > A	G200R	D	71, 114	1453A > G	M485V	R	75, 114
601insG	fs 258X	R	38	c.1471 + 1G > A	sd	R	75
652G > A	A218T	D?	32	1488G > T	R496S	R	68, 82
689G > A	G230E	D/R	41, 45, 75, 99	1495G > A	G499R	R	121
c.696 + 2T > A	fs231X; sd	R	20	1592C > T	A531V	D/R	80, 102
706G > C	V236L	R	58	1649C > T	T550M	D?	115
*782A > G	*Y261C	R	71, 114	1655A > G	Q552R	D	63, 82, 87
803C > T	T268M	D?	20	1667T > A	I556N	D	58, 81, 92
831insG	fs289X	R	77	1687G > A	V563I	R	89
NR	sa	R	81	1723C > T	P575S	R?	53
847C > T	L283F	D?	115	1931A > G	D644G	R?	53
854G > A	G285E	R	58	NR	Skip exon 17	R	28
857T > C	V286A	D?	58	1972C > T	Q658X	R	32
862C > T	F287S	R?	102	1976C > T	A659V	R	90
870C > G	I290M	D	56, 63, 82, 92	2005C > T	R669C	R?	32
871G > A	E291K	R	75, 82	2124C > G	F708L	D?	89
898C > T	R300X	R	45, 75	2149delG	E717X	R	81
920T > C	F307S	D?	8, 58, 30	2264delC	fs793X	R	89
929C > T	T310M	D	115	2284 + 5C > T	sd	R	102
937G > A	A313T	D	8, 81, 58	2419C > T	Q807X	R	27
950G > A	R317Q	D	38, 75, 82	c.2452 + 2T > A	sd	R	89
979G > A	V327I; sd	R	68	2512insCTCA	fs872X	D	32
986T > C	I329T	R	75, 120	2518–2519del	fs840X	R	30
1013G > A	R338Q	D?	45, 119, 120	2576Q > A	G859D	R	33
1063G > C	G355R	R	33	2680C > T	R894X	D/R	45, 75
1078G > A	A331T	R	102, 111	*2795C > T	*P932L	D	77, 94

D, dominant; NR, sequence change not reported; R, recessive; sa, splice acceptor mutation; sd, splice donor mutation.
**Pathogenicity debated.*

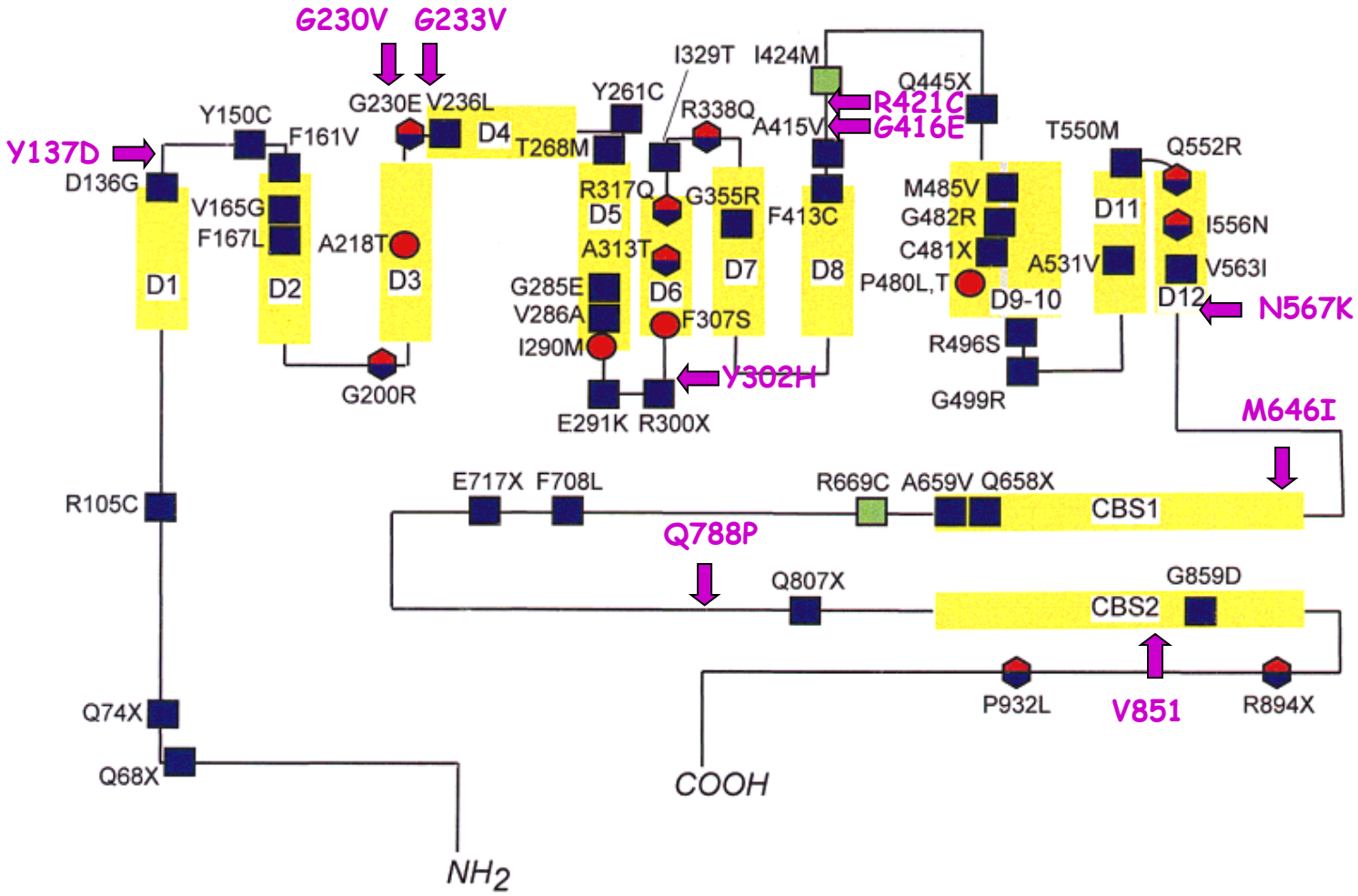
Colding-Jorgensen.E *Muscle Nerve* 32: 19–34, 2005

Table 1
Mutations found in the *CLCN1* gene in Spanish families with myotonia congenita.

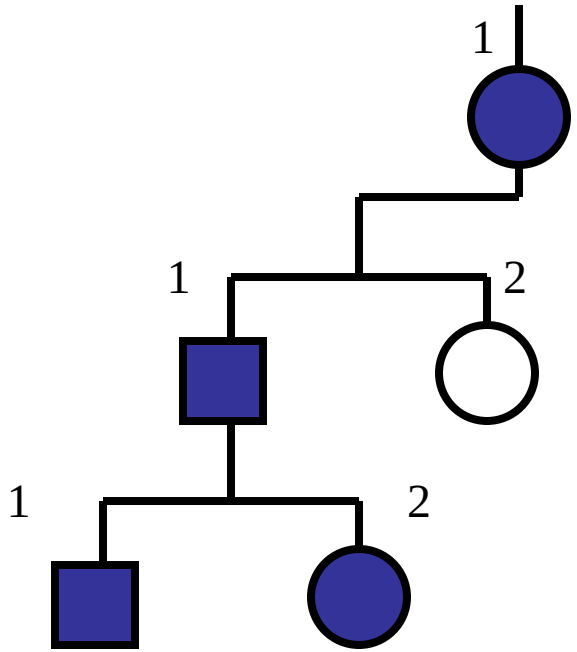
Family ID (n tested)	Genotype	Protein change	Exon/intron	Reference
A (8)	Mutation 1: c.904T>C	p.Tyr302His	e8	This study
	Mutation 2: c.180+3A>T	sd	il	[7]
B (3)	Mutation 1: c.698G>T	p.Gly233Val	e6	This study
	Mutation 2: c.1262insC	p.Pro420fs429X	e12	[3]
C (1)	Mutation 1: c.501C>G	p.Phe167Leu	e4	[6]
	Mutation 2: c.313C>T	p.Arg105Cys	e3	[3]
	Mutation 3: c.180+3A>T	sd	il	[7]
D (4)	Mutation 1: c.2363A>C	p.Gln788Pro	e19	This study
	Mutation 2: c.180+3A>T	sd	il	[7]
E (1)	Mutation 1: c.501C>G	p.Phe167Leu	e4	[6]
	Mutation 2: c.180+3A>T	sd	il	[7]
F (3)	Mutation 1: c.904T>C	p.Tyr302His	e8	This study
	Mutation 2: c.1247G>A	p.Gly416Glu	e11	This study
G (2)	Mutation 1: c.1938G>A	p.Met646Ile	e17	[5]
	Mutation 2: c.180+3A>T	sd	il	[7]
H (4)	Mutation 1: c.689G>T	p.Gly230Val	e5	This study
	Mutation 2: c.689G>T	p.Gly230Val		
I (3)	Mutation 1: c.180+3A>T	sd	il	[7]
J (2)	Mutation 1: c.2680C>T	p.Arg894Stop	e23	[6]
	Mutation 2: c.180+3A>T	sd	il	[7]
K (4)	Mutation 1: c.2680C>T	p.Arg894Stop	e23	[6]
	Mutation 2: c.1592C>T	p.Ala531Glu	e15	[4]
L (1)	Mutation 1: c.1453A>G	p.Met485Val	e13	[3]
	Mutation 2: c.1453A>G	p.Met485Val		
M (5)	Mutation 1: c.1488G>T	p.Arg496Ser	e14	[8]
	Mutation 2: c.1488G>T	p.Arg496Ser		
N (1)	Mutation 1: c.1261C>T	p.Arg421Cys	e12	This study
	Mutation 2: c.2680C>T	p.Arg894Stop	e23	[6]
O (3)	Mutation 1: c.409T>G	p.Tyr137Asp	e3	This study
	Mutation 2: c.1247G>A	p.Gly416Glu	e11	This study
P (7)	Mutation 1: c.180+3A>T	sd	il	[7]
	Mutation 2: c.180+3A>T			
Q (1)	Mutation 1: c.1453A>G	p.Met485Val	e13	[3]
	Mutation 2: c.1453A>G	p.Met485Val		
R (3)	Mutation 1: c.2284+5C>T	sd	i18	[15]
S (1)	Mutation 1: c.501C>G	p.Phe167Leu	e4	[6]
	Mutation 2: c.180+3A>T	sd	il	[7]
T (2)	Mutation 1: c.1701C>A	p.Asn567Lys	e15	This study
U (1)	Mutation 1: c.1488G>T	p.Arg496Ser	e14	[8]
	Mutation 2: c.1453A>G	p.Met485Val	e13	[3]
V (4)	Mutation 1: c.501C>G	p.Phe167Leu	e4	[6]
	Mutation 2: c.652G>A	p.Ala218Val	e5	This study
W (1)	Mutation 1: c.1261C>T	p.Arg421Cys	e12	This study
	Mutation 2: c.180+3A>T	sd	il	[7]
X (1)	Mutation 1: c.1453A>G	p.Met485Val	e13	[3]
	Mutation 2: c.2177delT	p.Pro726fs794Stop	e18	This study
Y (7)	Mutation 1: c.180+3A>T	sd	il	[7]
	Mutation 2: c.1167-10T>G	sa	il1	[5]
Z (1)	Mutation 1: c.1453A>G	p.Met485Val	e13	[3]
	Mutation 2: c.302-1G>A	sa	i2	[5]
AA (1)	Mutation 1: c.1453A>G	p.Met485Val sd	e13	[3]
	Mutation 2: c.180+3A>T	sd	il	[7]
AB (1)	Mutation 1: c.180+3A>T	sd	il	[7]
	Mutation 2: c.180+3A>T			
AC (1)	Mutation 1: c.2552G>A	p.Val851Met	e22	This study
	Mutation 2: c.2552G > A	p.Val851Met	e22	This study
AD (1)	Mutation 1: c.180+3A>T	sd	il	[7]
AE (1)	Mutation 1: c.1471+1G>A	sd	il3	[3]
	Mutation 2: c.180+3A>T	sd	il	[7]
AF (3)	Mutation 1: c.696+1G>T	sd	i5	This study
	Mutation 2: c.180+3A>T	sd	il	[7]
	Mutation 3: c.809G>A	p.Gly270Asp	7	This study

sd, Splice-site donor mutation; sa, splice-site acceptor mutation.

Nuevas mutaciones identificadas en pacientes estudiados en la Unidad de Genética Molecular



Mutaciones dominantes de elevada penetrancia

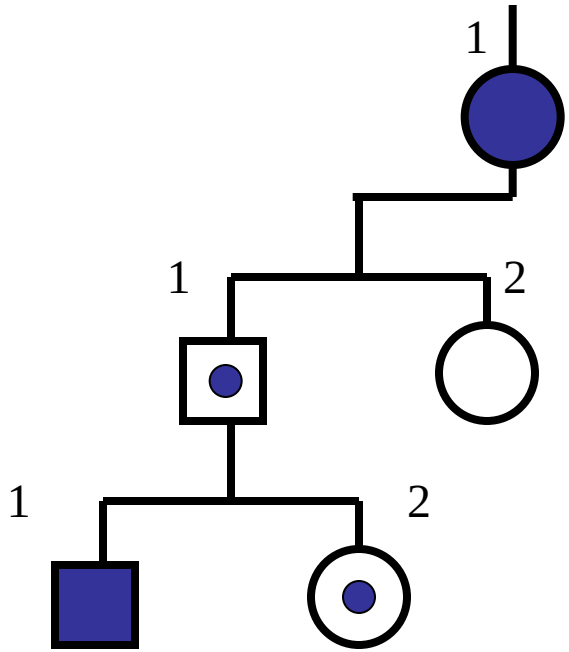


Ejemplos

R338Q
M128V
E193K
Etc.

Según datos revisados por Colding-Jorgensen.E *Muscle Nerve* 32: 19–34, 2005

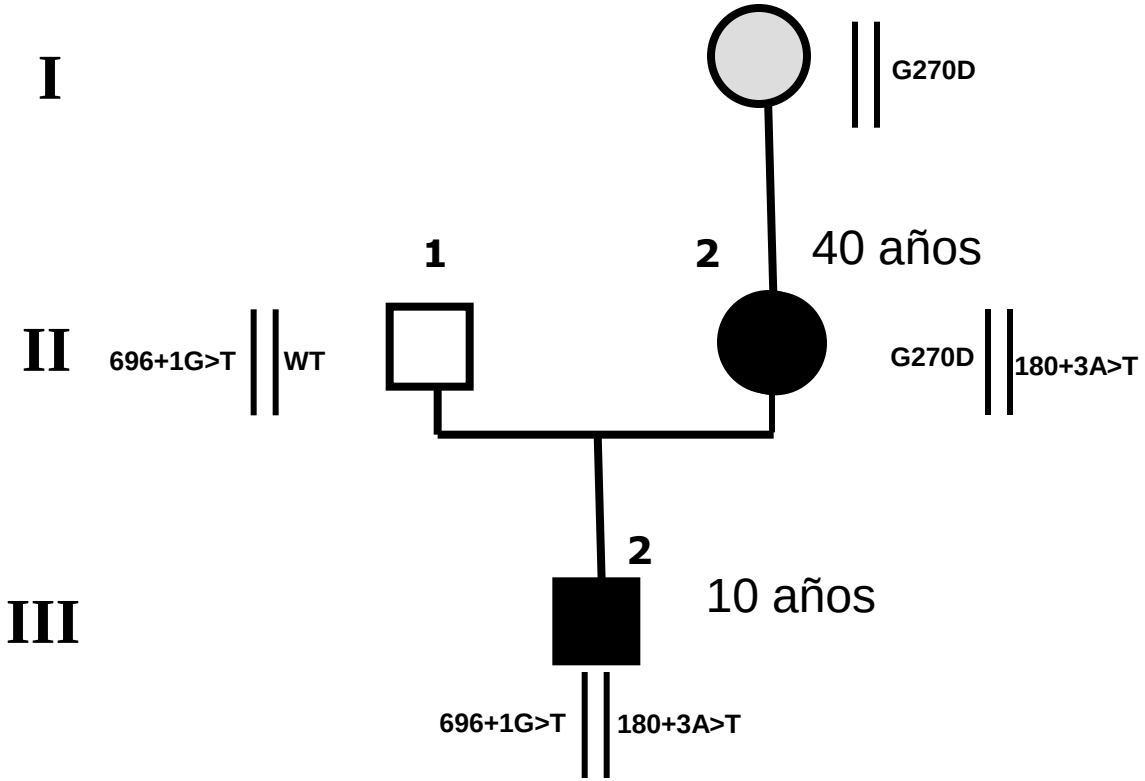
Mutaciones dominantes de penetrancia reducida

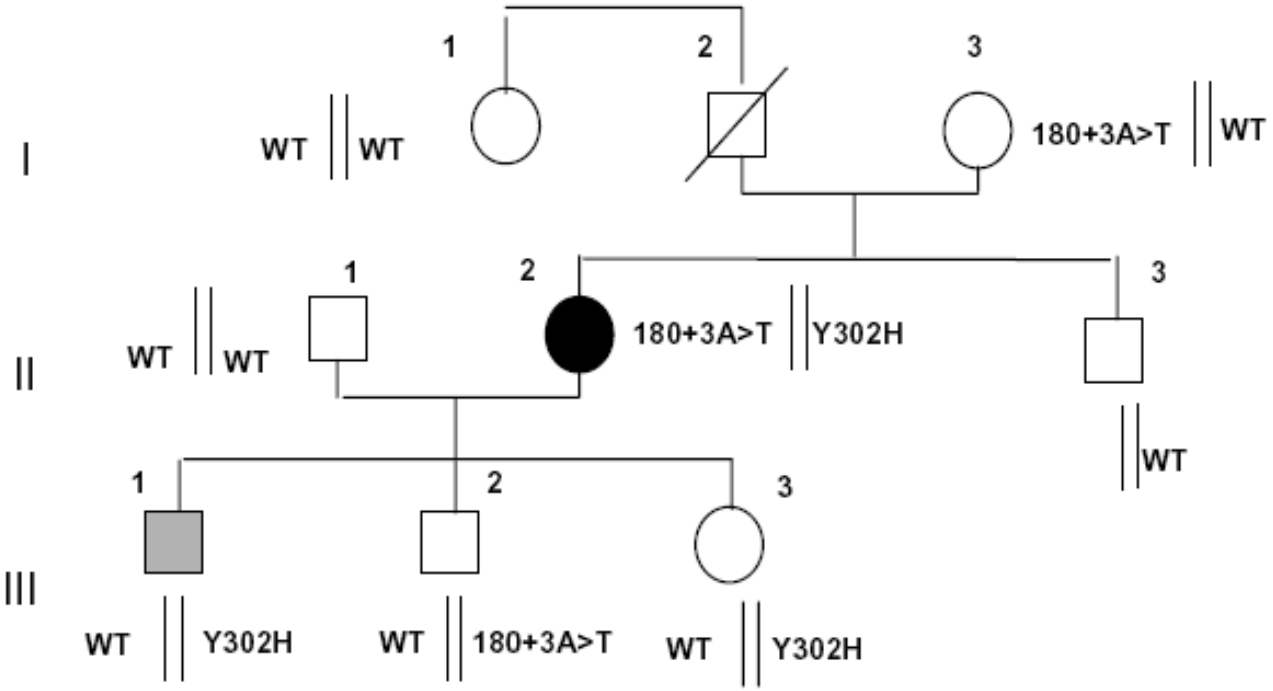


Ejemplos

A313T
P480T
I556N
L198V
Etc.

Según datos revisados por Colding-Jorgensen.E *Muscle Nerve* 32: 19–34, 2005


I
G270D
1
2
40 años
II
696+1G>T
WT
G270D
180+3A>T
2
III
10 años
696+1G>T
180+3A>T



Family A

Clínica de la paciente de la familia A

- Mujer de 35 años
- Retraso en empezar a andar (18-20 meses de edad)
- Miotonía
- Complexión fornida. Baja talla
- Descargas miotónicas en el electromiograma
- CPK elevada

Evolución mutación CLCN1 Tyr302His (exón 8)

GVLFSIEVTSTYFAVRNYWRGFFAATFSAFVFRVLA *Homo sapiens*

GVLFSIEVTSTYFAVRNYWRGFFAATFSAFVFRVLA *Mus musculus*

GVLFSIEVTSTYFAVRNYWRGFFAATFSAFVFRVLA *Rattus norvegicus*

GVLFSIEVTSTFFAVRNYWRGFFSATFSAFIFRVLA *Cavia porcellus*

GVLFSIEVTSTFFAVRNYWRGFFAATFSAFIFRVLA *Oryctolagus cuniculus*

GVLFSIEVTCSHFGVRSYWRQFLGGAFSAFIFRVLS *Torpedo marmorata*

GVLFSIEVTCSHFGVRSYWRGFLGGAFSAFIFRVLS *Torpedo californica*

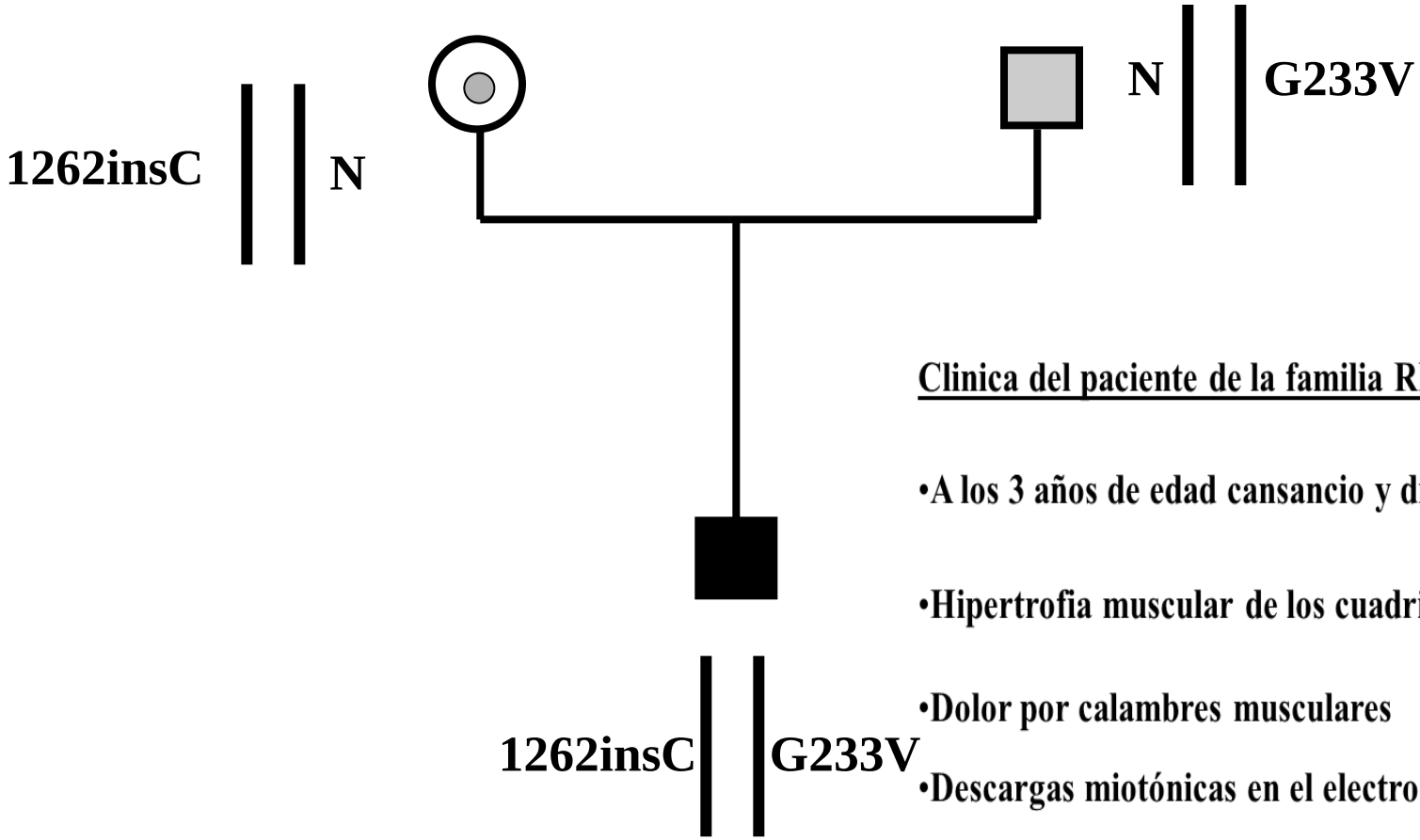
GVLFSVEVMSSHFAIRNYWRGFFAATCGAFVFRLLA *Xenopus laevis*

GVLFSIEVTTTYFAVRNYWRGFFAAVCGATVFRLLA *Drosophila melanogaster*

GVLFSIEVTTTYFAVRNYWRGFFAAVCGATVFRLLA *Anopheles gambiae*

GVLFSIEVTSVYFAVRNYWRGFFAATCSATLFRILA *Caenorhabditis elegans*

Familia RL
Enfermedad de Becker
Miotonía congénita AR

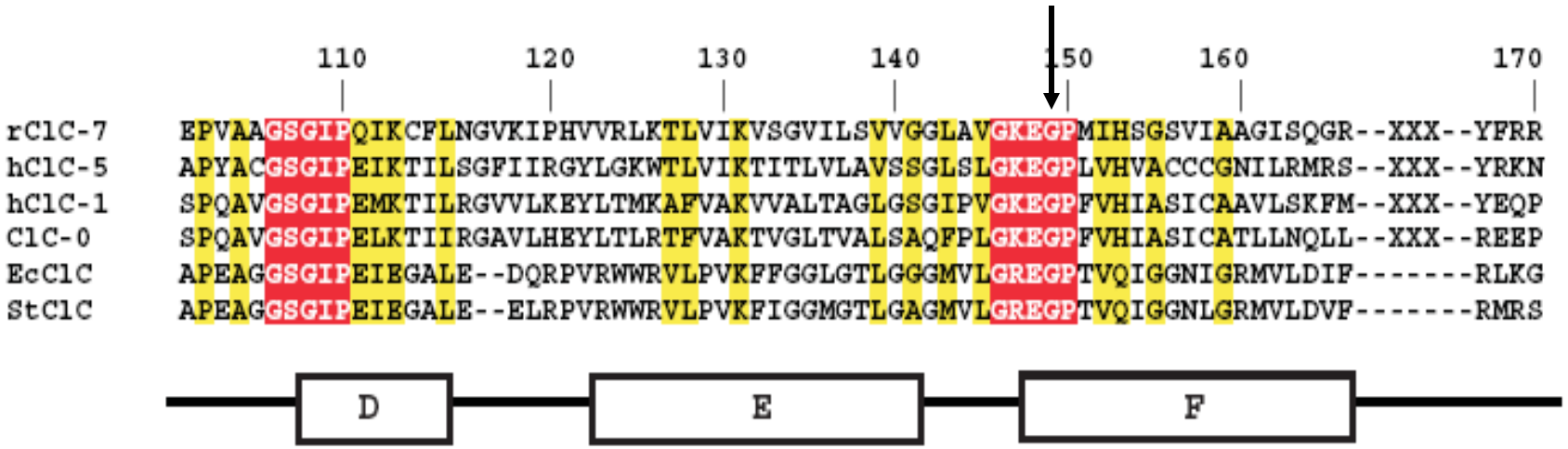


Clinica del paciente de la familia RL

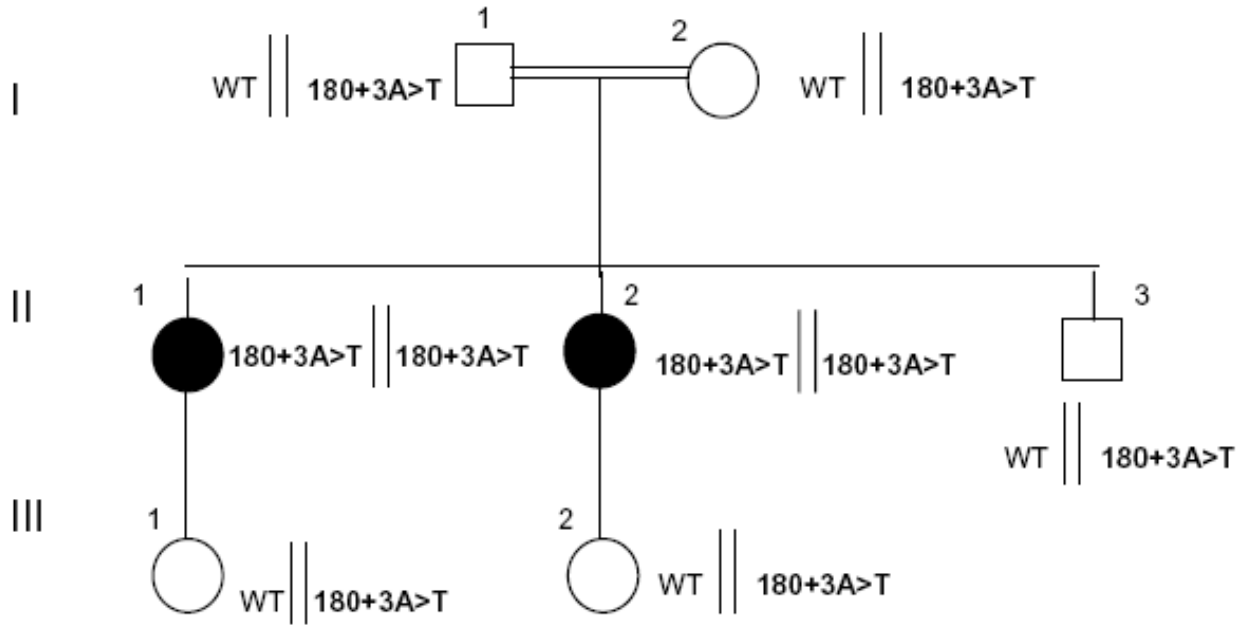
- A los 3 años de edad cansancio y dificultad para la marcha
- Hipertrofia muscular de los cuadriceps y gemelos
- Dolor por calambres musculares
- Descargas miotónicas en el electromiograma

Evolución mutación CLCN1 Gly233Val

VALTAGLGSGIPVGKEGPFVHIASICAAV	*Homo sapiens*
VALTAGLGSGIPVGKEGPFVHIASICAAV	*Mus musculus*
VALTAGLGSGIPVGKEGPFVHIASICAAV	*Rattus norvegicus*
VALTAGLGSGIPVGKEGPFVHIASICAAV	*Canis familiaris*
LTAGLGSGIPVGKEGPFVHIASICA	*Cavia porcellus*
VALTAGLGSGIPVGKEGPFVHIASICA	*Torpedo marmorata*
VGLTVALSAGFPLGKEGPFVHIASICA	*Torpedo californica*
LTAGLGSGIPVGKEGPFVHIASI	*Drosophila melanogaster*
STLTAGLGSGIPVGKEGPFVHIASI	*Anopheles gambiae*
LTAGLGSGIPVGKEGPFVHIASI	*Caenorhabditis elegans*
GSGIPVGKEGPFVHI	*Leishmania*
VGKEGPFVHIA	*Schizosaccharomyces pombe*



Dutzler R et al. 2002. NATURE |VOL 415 | 17 JANUARY , p. 287-94


I
1
2
WT
180+3A>T
WT
180+3A>T
II
1
2
3
180+3A>T
180+3A>T
180+3A>T
180+3A>T
WT
180+3A>T
III
1
2
WT
180+3A>T
WT
180+3A>T

Family Q

NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/)

SNP Pos	rs ID	Alleles	EA Allele #	AA Allele #	All Allele #	Avg. Sample Read Depth	Genes	mRNA Accession #	GVS Function	Amino Acid	Protein Pos.	cDNA Pos.	Filter Status
7:143013285	rs34904831	T/C	T=488/C=6530	T=39/C=3699	T=527/C=10229	27	CLCN1	NM_000083.2	utr-5	none	NA	NA	PASS
7:143013293	unknown	A/G	A=1/G=7019	A=1/G=3737	A=2/G=10756	34	CLCN1	NM_000083.2	utr-5	none	NA	NA	PASS
7:143013295	unknown	T/G	T=0/G=7020	T=1/G=3737	T=1/G=10757	37	CLCN1	NM_000083.2	utr-5	none	NA	NA	PASS
7:143013329	rs150304865	A/G	A=2/G=7018	A=0/G=3738	A=2/G=10756	76	CLCN1	NM_000083.2	coding-synonymous	none	8/989	24	PASS
7:143013331	rs115379077	A/G	A=0/G=7020	A=71/G=3667	A=71/G=10687	79	CLCN1	NM_000083.2	missense	HIS,ARG	9/989	26	PASS
7:143013342	rs143025648	A/C	A=1/C=7019	A=0/C=3738	A=1/C=10757	91	CLCN1	NM_000083.2	missense	LYS,GLN	13/989	37	PASS
7:143013391	rs146160029	C/A	C=27/A=6993	C=1/A=3737	C=28/A=10730	131	CLCN1	NM_000083.2	missense	PRO,HIS	29/989	86	PASS
7:143013404	rs138922145	T/C	T=1/C=7019	T=0/C=3738	T=1/C=10757	123	CLCN1	NM_000083.2	coding-synonymous	none	33/989	99	PASS
7:143013438	unknown	G/A	G=0/A=7020	G=2/A=3736	G=2/A=10756	77	CLCN1	NM_000083.2	missense	GLY,ARG	45/989	133	PASS
7:143013488	unknown	T/A	T=4/A=6998	T=0/A=3732	T=4/A=10730	57	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143013528	unknown	A/G	A=0/G=7002	A=4/G=3730	A=4/G=10732	35	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143013530	unknown	A/C	A=0/C=7002	A=1/C=3733	A=1/C=10735	34	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143016799	rs145150180	G/T	G=1/T=7019	G=0/T=3738	G=1/T=10757	93	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143016804	unknown	C/T	C=3/T=7017	C=0/T=3738	C=3/T=10755	100	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143016805	unknown	C/A	C=10/A=7010	C=0/A=3738	C=10/A=10748	103	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143016862	unknown	T/C	T=1/C=7019	T=0/C=3738	T=1/C=10757	178	CLCN1	NM_000083.2	coding-synonymous	none	65/989	195	PASS
7:143016908	rs149407148	G/A	G=0/A=7020	G=1/A=3737	G=1/A=10757	204	CLCN1	NM_000083.2	missense	GLU,LYS	81/989	241	PASS
7:143016928	rs6962852	T/C	T=2277/C=4743	T=2125/C=1613	T=4402/C=6356	209	CLCN1	NM_000083.2	coding-synonymous	none	87/989	261	PASS
7:143016995	rs6948526	A/T	A=662/T=6358	A=1131/T=2607	A=1793/T=8965	112	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143017714	unknown	C/G	C=0/G=7020	C=2/G=3736	C=2/G=10756	37	CLCN1	NM_000083.2	intron	none	NA	NA	SVM
7:143017720	rs112059687	C/T	C=0/T=7020	C=87/T=3651	C=87/T=10671	43	CLCN1	NM_000083.2	intron	none	NA	NA	PASS
7:143017753	rs113839156	T/C	T=0/C=7020	T=84/C=3654	T=84/C=10674	85	CLCN1	NM_000083.2	intron	none	NA	NA	PASS

SNP Pos	rs ID	Alleles	EA Allele #	AA Allele #	All Allele #	Avg. Sample Read	Gene
7:143013488	unknown	T/A	T=4/A=6998	T=0/A=3732	T=4/A=10730	57	*CLCN1*

De 32 familias españolas con miotonia congénita:

16 eran portadoras de la mutación c.180+3A>T (50 %)

6 eran portadoras de la mutación M485V (19%)

4 eran portadoras de la mutación F167L (12%)

3 eran portadoras de la mutación R894X (9%)

2 eran portadoras de la mutación R496S (6%)

Miotonía congénita. Resumen

- **Miotonía**
- **Debut en los primeros años de vida**
- **Fenómeno *warm-up***
- **Debida a mutaciones en el gen *CLCN1***
- **Dos formas de herencia: Herencia autosómica dominante (Thompsen) y herencia autosómica recesiva (Becker)**
- **El espectro de mutaciones en España es diferente del norteeuropeo y norteamericano**