La genetica e la clinica: un imprescindibile connubio nella diagnosi delle malattie muscolari complesse il punto di vista del clinico

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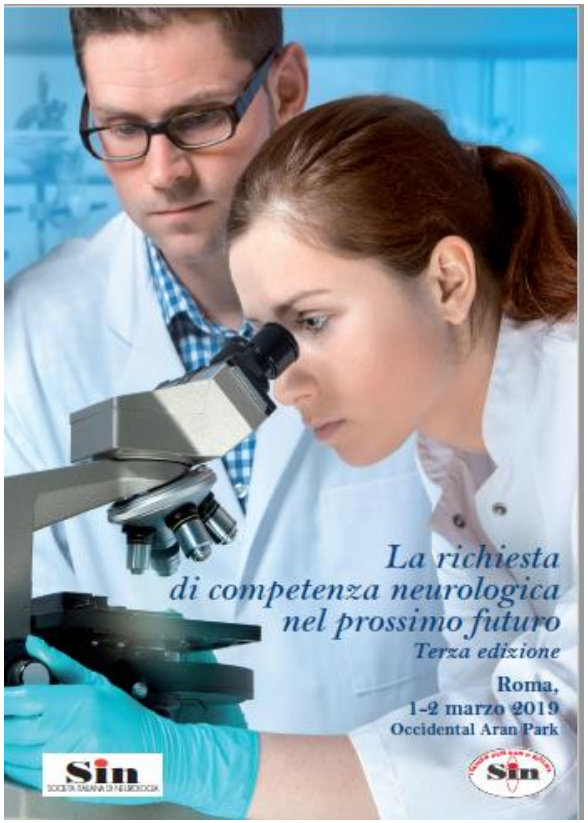


Le Miopatie sono Malattie Rare

- Nella Unione Europea una malattia è considerata rara se colpisce un numero di pazienti con una prevalenza di 5/10.000
- esistono 7000-8000 malattie rare e >50% sono malattie neurologiche
- in Europa ci sono 24-36 milioni di persone con malattia rara su circa 500 milioni di abitanti

in Italia

- le malattie rare interessano circa 2 milioni di persone e < 1 milione ha una patologia neurologica rara

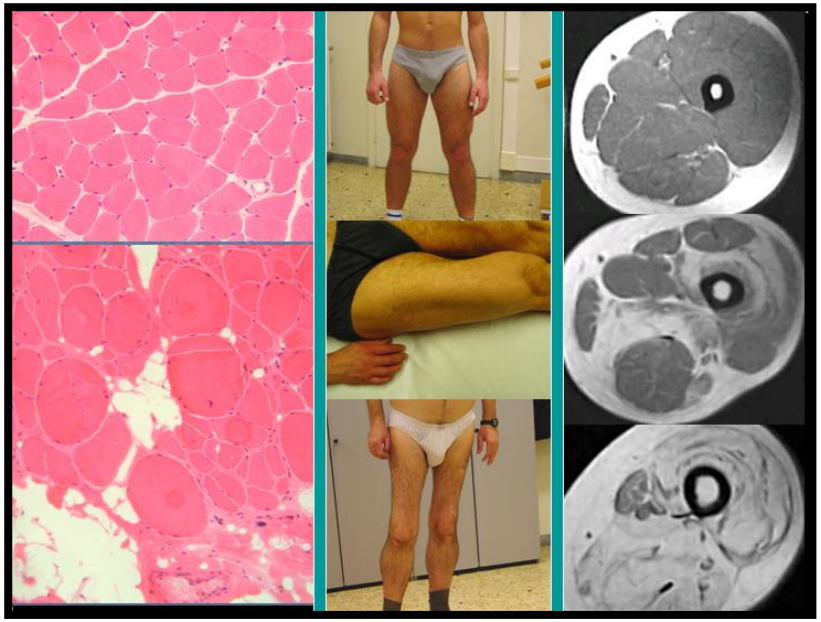
Le miopatie

Miopatie infiammatorie

Miopatie distrofiche e/o degenerative

Miopatie metaboliche

Miopatie -> diagnosi



- La diagnosi di una miopatia si fa combinando le caratteristiche cliniche, le evidenze che vengono dalla biopsia muscolare e gli aspetti di RM - > tali elementi orientano l'indagine genetica o indirizzano la cura
- L'analisi genetica è in genere l'ultimo step dell'iter diagnostico; in alcuni casi in cui la clinica consente una forte ipotesi diagnostica si effettua come primo step -> analisi di singoli geni: es. Duchenne, Distrofia Miotoniche, FSH…

Miopatie -> diagnosi

La relativa accessibilità delle tecnologie di NGS *next sequencing* rende potenzialmente più semplice la definizione genetica delle malattie neuromuscolari.

Con le nuove tecnologie di NGS è possibile effettuare un'indagine genetica estesa senza dover necessariamente ipotizzare un gene responsabile *a priori*.

Problematiche

a) Mancata individuazione delle <espansioni di triplette>

b) Identificazione di varianti non correlate al fenotipo

c) Non completa copertura dei geni

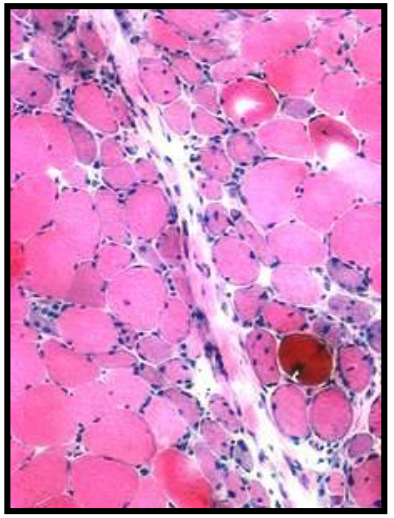
d) Numero elevato di varianti non riportate

Biopsia muscolare

- Riveste ancora un ruolo centrale nell'iter diagnostico nell'adulto
- L'esame della biopsia muscolare consente

1. analisi morfologica convenzionale
2. analisi istoenzimatica per informazioni inerenti la struttura e il funzionamento metabolico
3. analisi morfometrica per dimensione e distribuzione per tipo delle fibre
4. analisi immunopatologica per lo studio delle cellule infiammatorie
5. analisi immunoistochimica per lo studio delle proteine muscolari coinvolte nelle varie patologie
6. analisi molecolare per i livelli di espressione delle varie proteine
7. dosaggi biochimici (nel sospetto di una miopatia metabolica),
8. estrazione e analisi del DNA mitocondriale (non di routine)
9. analisi ultrastrutturale (non di routine)

Miopatie infiammatorie



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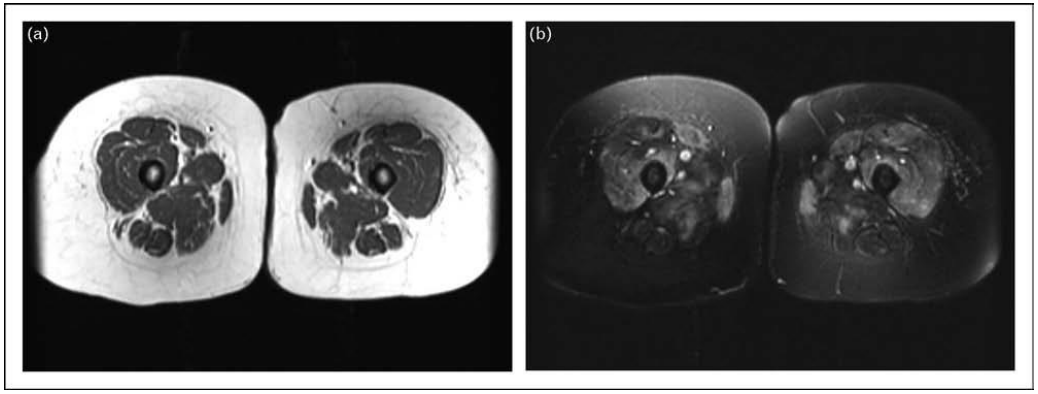
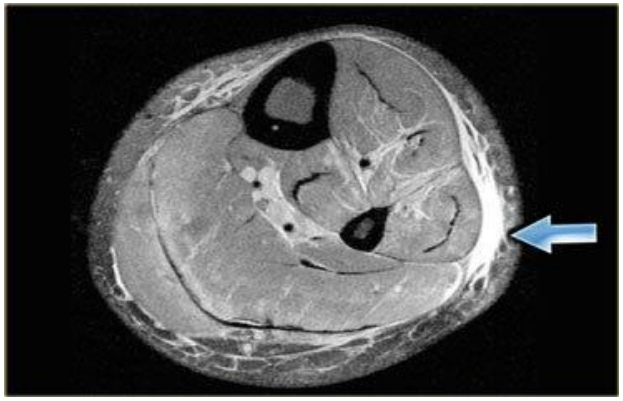
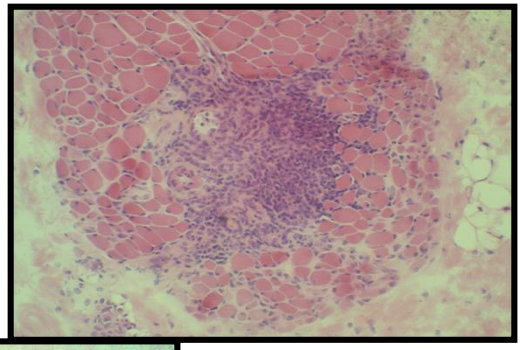
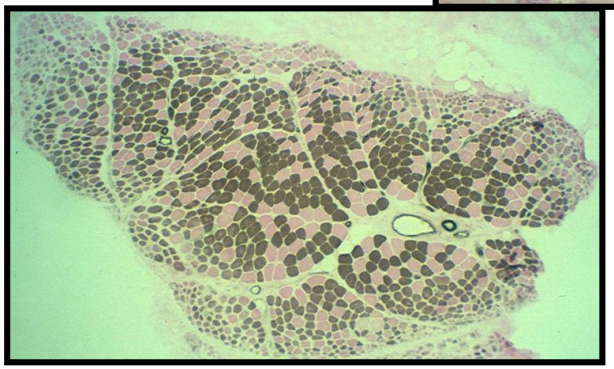
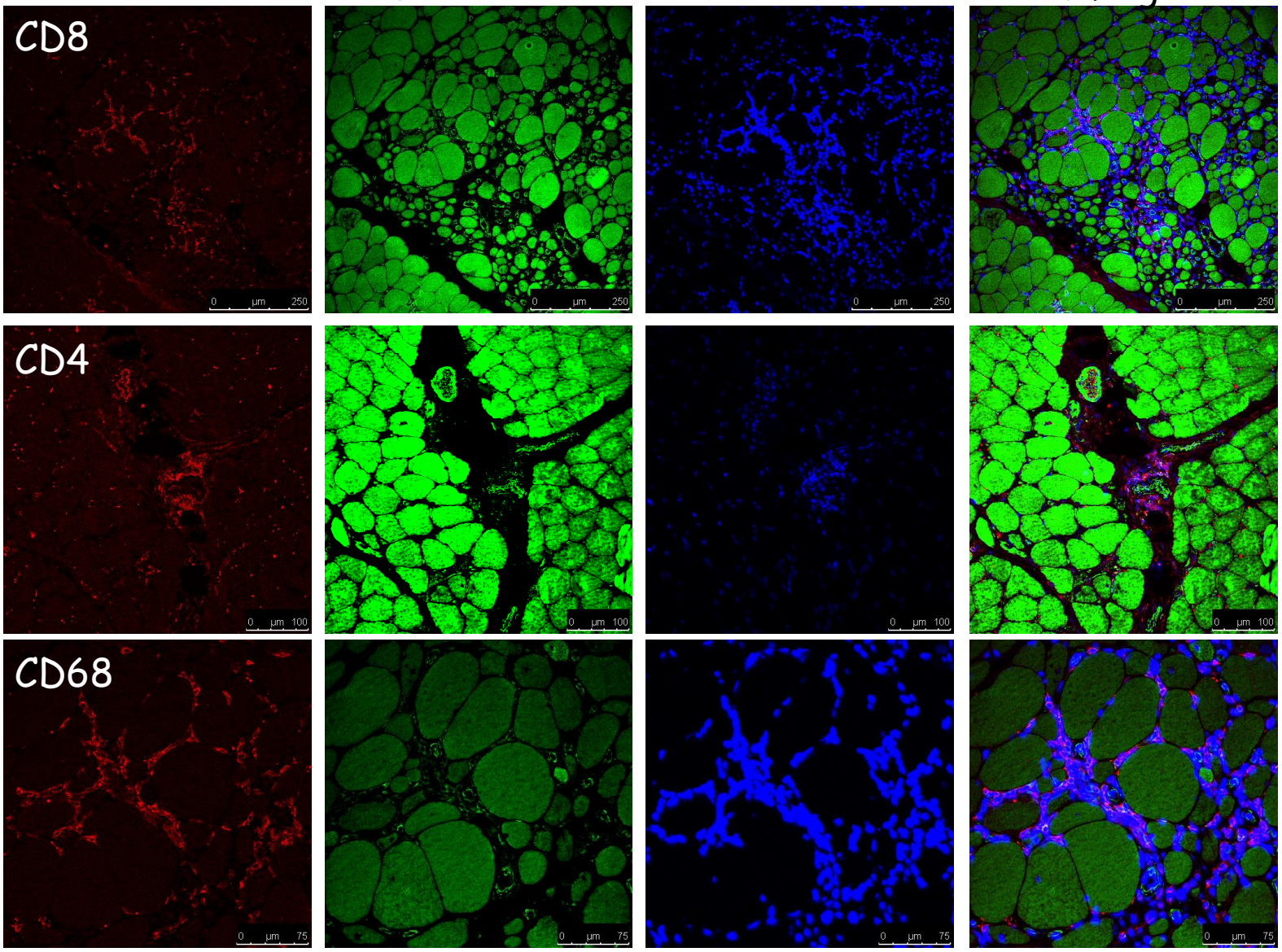








DM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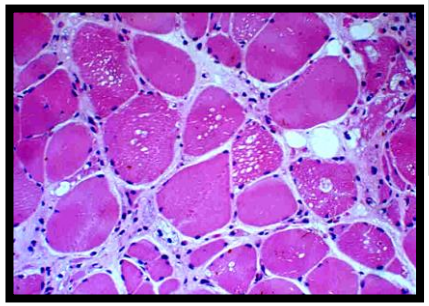
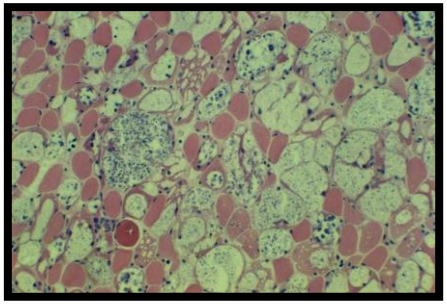
Miopatie metaboliche





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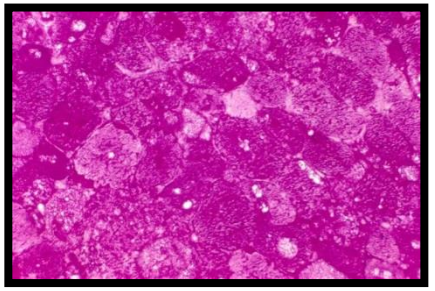
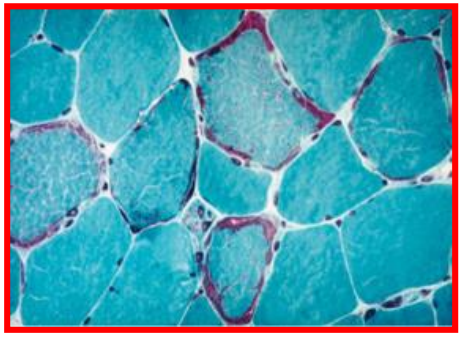
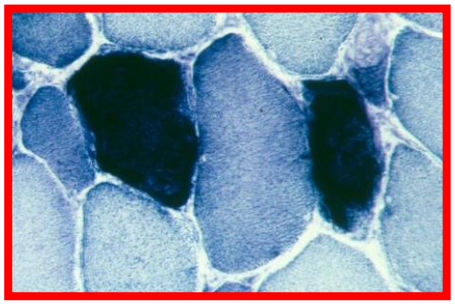
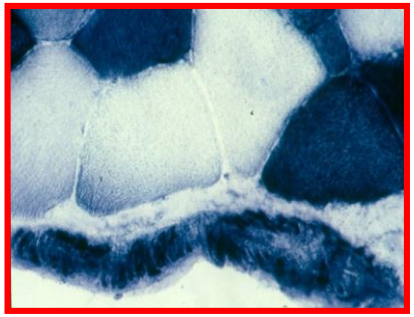


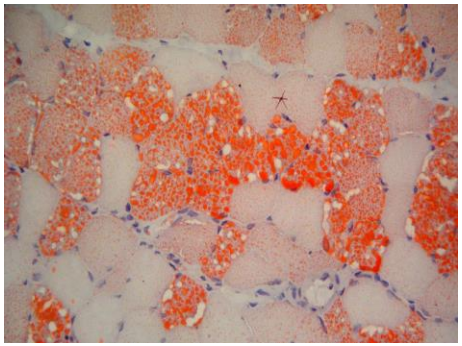


miopatia mitocondriali

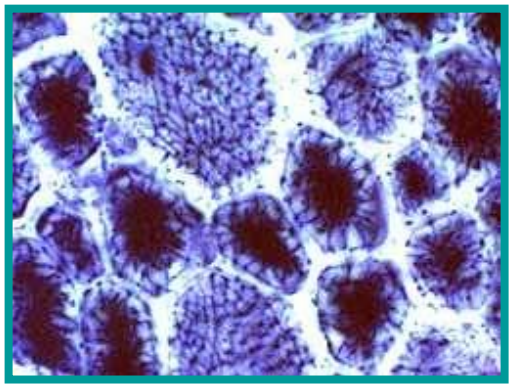




miopatia da accumulo di lipidi

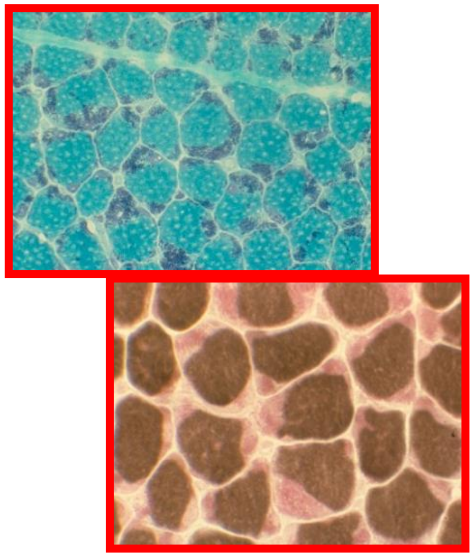


Miopatia miotubulare: arresto maturativo delle fibre muscolari con assenza della migrazione dei nuclei alla periferia (simili ai miotubi alla 22°-24° sett. eta' gestazionale) -> marcato aumento dei **nuclei centralizzati** presenti nel 30-95% delle fibre



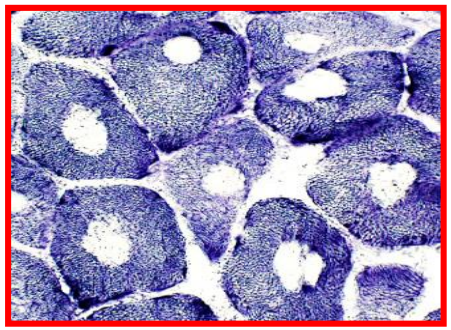
Geni: MTM1, DNM2, BIN1, RYR1; TTN, SPEG, CCDC78, CACNA1S

Miopatia nemalinica
corpi nemalinici →inclusioni intracitoplasmatiche eosinofile che contengono a-actinina (maggiore componente della linea Z) a disposizione subsarcolemmale o perinucleare; predominanza fibre di tipo 1

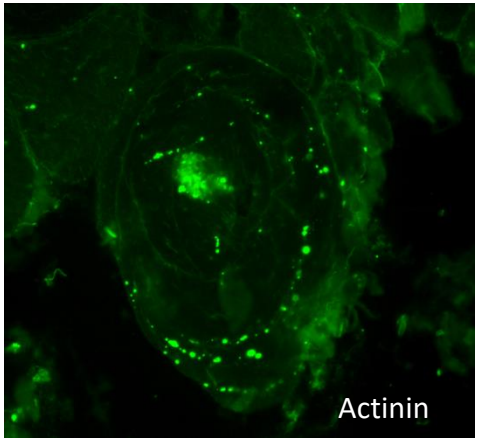


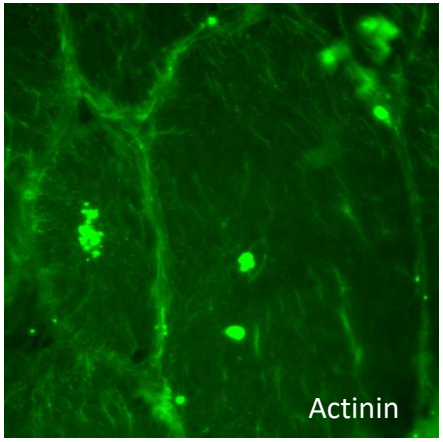
Geni: NEB, ACTA1, TPM3, TPM2, CFL2, KLHL40, KLHL41, KBTBD13, TNNT1; MYPN, LMOD3, MYO18B

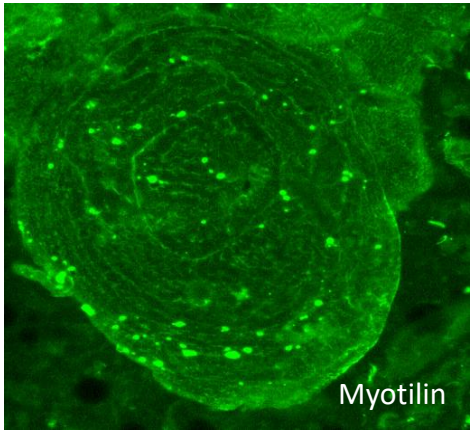
Miopatia central core
"**Core**" all'interno delle fibre, per tutto il decorso
- alterazione dei dischi Z
- nei "core" assenza di attività enzimatica ossidativa e mitocondri

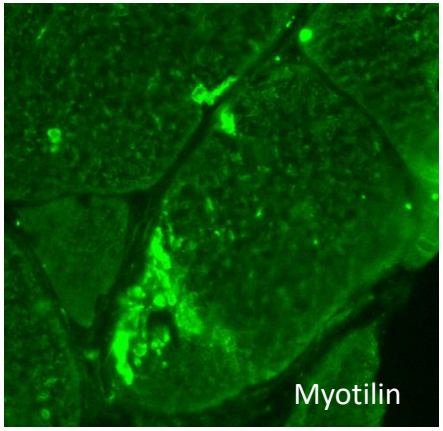


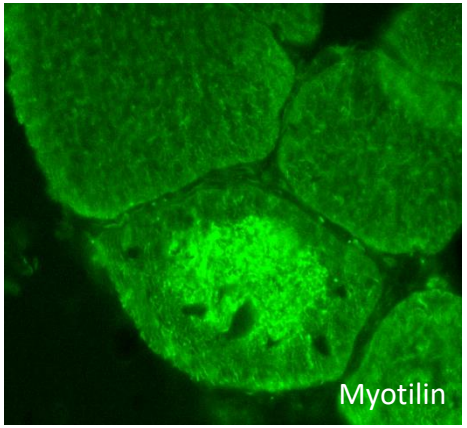
Geni: RYR1, SEPN1, MYH7, ACTA1, TTN, CFL2; MYH2, MEGF10, ACADS, TRIP4

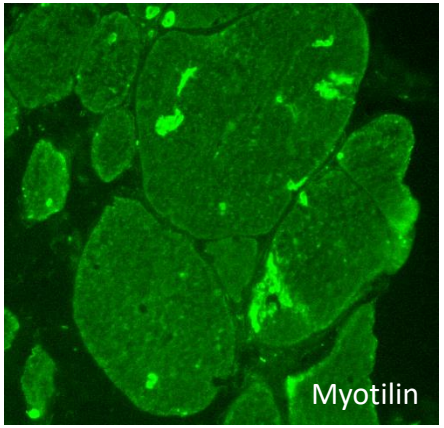


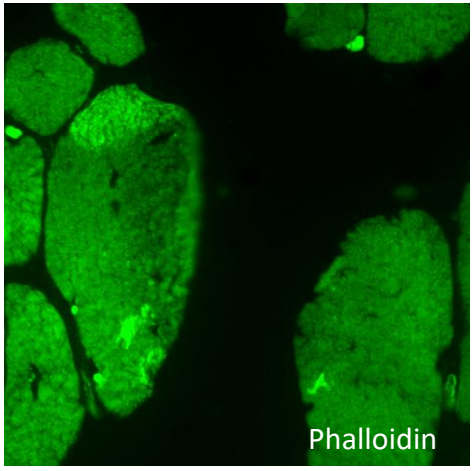


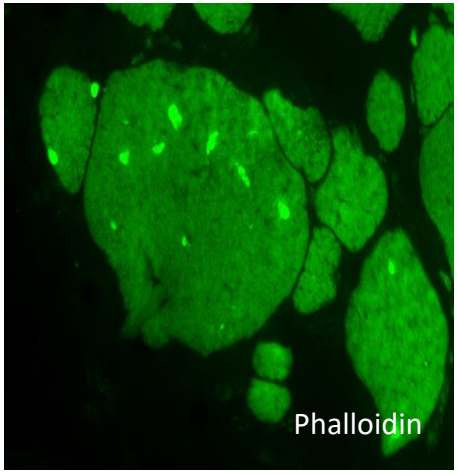






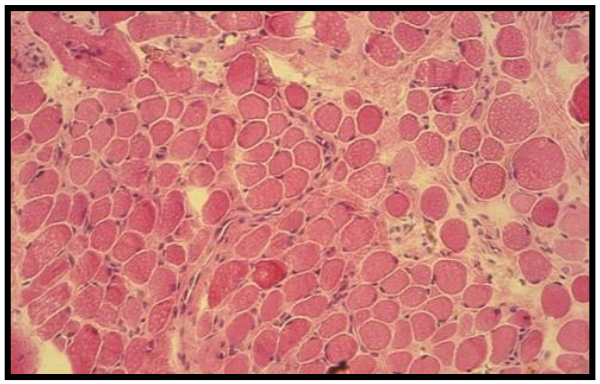


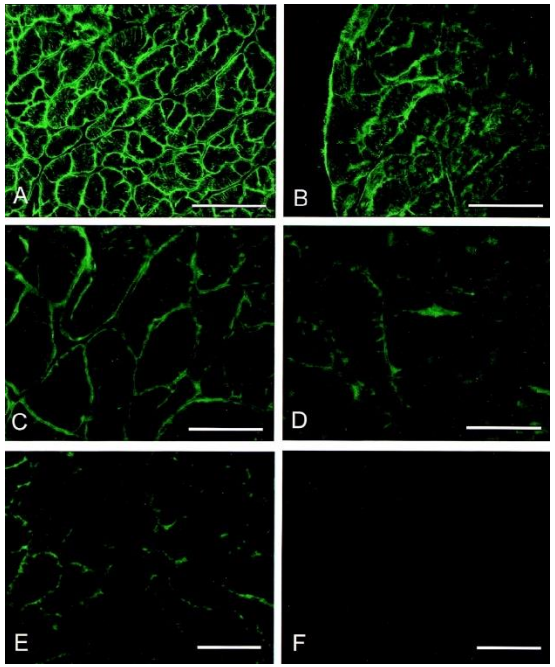




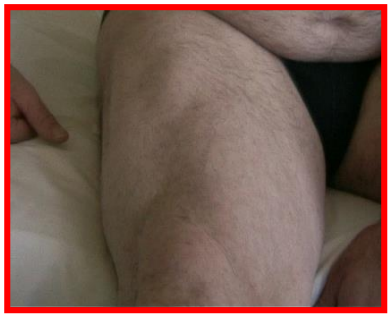
Miopatia nemalinica

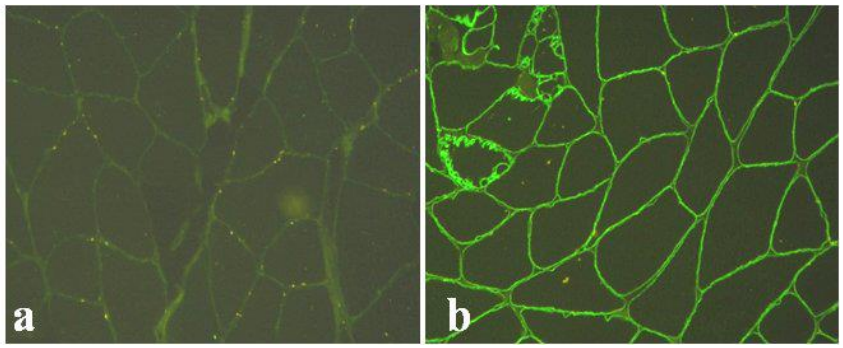
Acta1



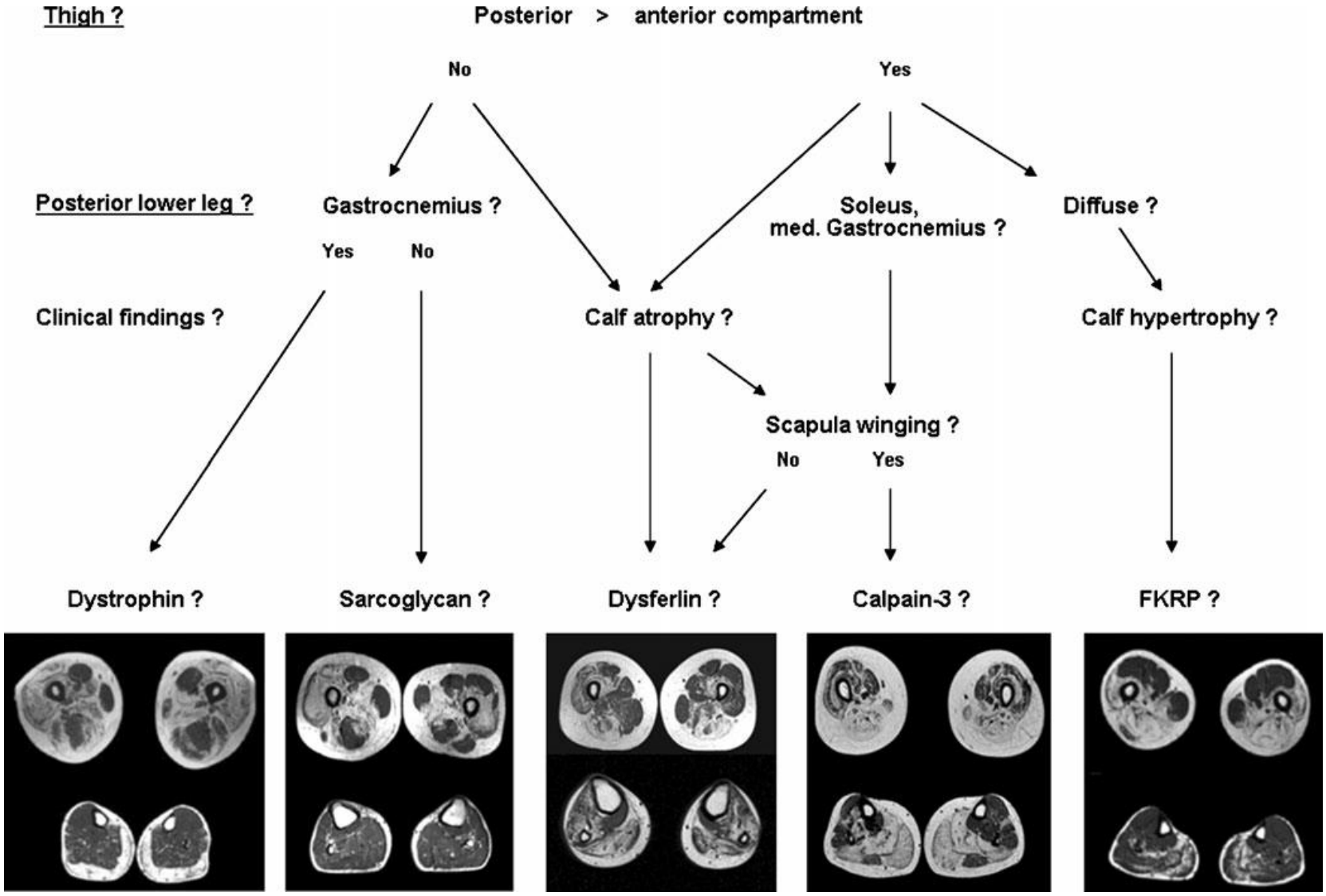


LGMD2 C,D,E,F -> sarcoglicanopatie (AR)
IC: a volte evidenzia uno specifico difetto, spesso difetti multipli di tutti i sarcoglicani





LGMD1C - caveolinopatia
AD: mutazioni eterozigoti nel gene CAV3



Wattjes et al. 2010

Miopatie -> diagnosi

Con le nuove tecnologie di **NGS** è possibile effettuare un'indagine genetica estesa senza dover necessariamente ipotizzare un gene responsabile *a priori*.

Problematiche

a) **Mancata individuazione delle <espansioni di triplette>**

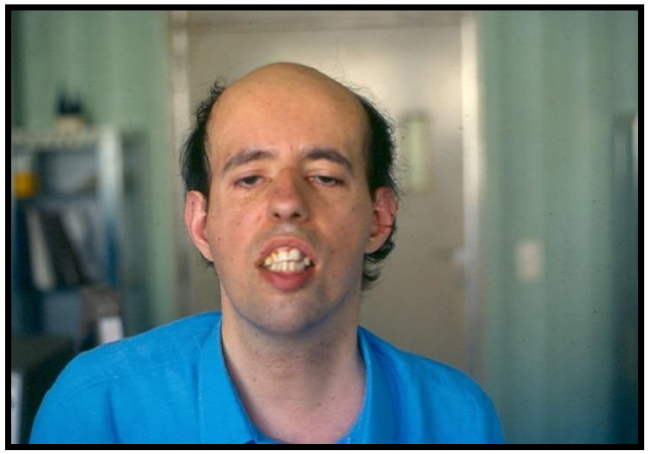
b) Identificazione di varianti non correlate al fenotipo

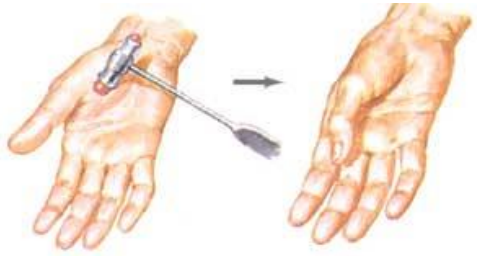
c) Non completa copertura dei geni

d) Numero elevato di varianti non riportate

❖Distrofia Miotonica tipo 1 (DM1)

- trasmissione autosomica dominante
- gene (19q13.3) che codifica la miotonina protein kinasi
- espansione di ripetizione di una tripletta basi (CTG)
- La tripletta è ripetuta > 50 volte -> migliaia
- ➢ il numero di ripetizioni è proporzionale alla gravità del fenotipo clinico
- ➢ Miopatia + miotonia
- Multisistemica (muscolo scheletrico e liscio, cuore, cristallino, sistema nervoso centrale, endocrinopatie)
- Esordio clinico variabile
- Anticipazione della malattia in successive generazioni (esordio più precoce, fenotipo più grave)





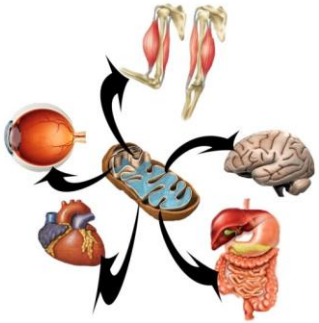
❖Distrofia Miotonica tipo 2 (DM2) o Miopatia Miotonica Prossimale (PROMM)

- trasmissione autosomica dominante
- espansione di ripetizione CCTG nell'introne 1 del gene CNBP (3q21) > 55 -> migliaia
- deficit prossimale senza coinvolgimento facciale o bulbare; frequentemente mialgie

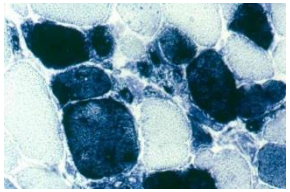
DIAGNOSI: CLINICA + EMG + GENETICA

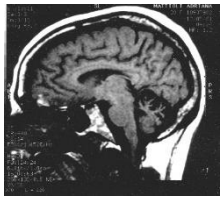
Malattie mitocondriali clinicamente eterogenee

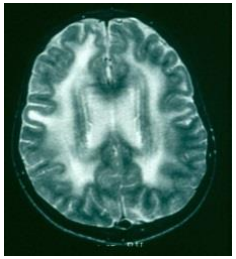
- sindromiche e non-sindromiche
- spesso multisistemiche
- esordio: dalla nascita alla vecchiaia

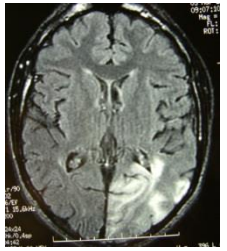


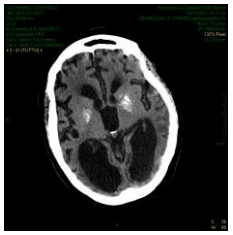
1. il sistema più frequentemente colpito è il sistema nervoso periferico (muscolo e nervo)
2. a seguire il sistema nervoso centrale
3. e poi… orecchio, apparato endocrino, cuore, occhio, intestino, rene, midollo osseo…

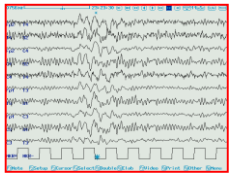










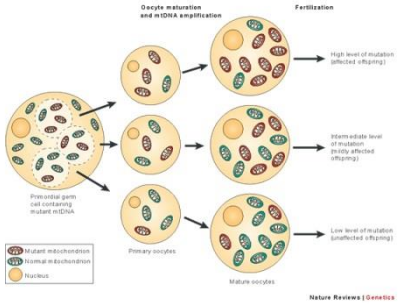


➢I mitocondri sono ubiquitari (solo i globuli rossi non hanno mitocondri)

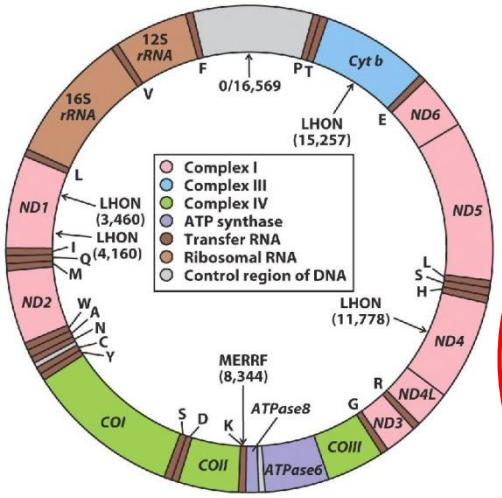
Malattie mitocondriali geneticamente eterogenee

Doppio contributo genomico

- 1500 proteine mitocondriali; solo 13 codificate dal DNA mitocondriale
- Negli adulti: prevalenza per le mutazioni del DNAmt 1:5000; per le mutazioni del DNA nucleare 2.9: 100.000 (Gorman et al. 2015)



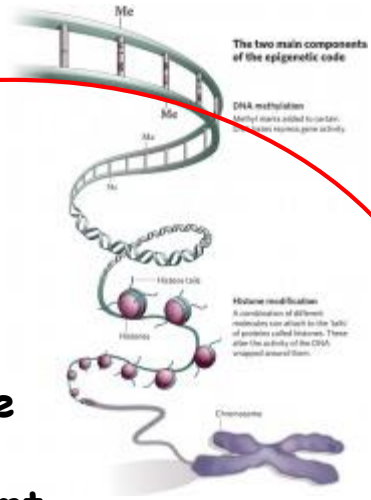
•trasmissione materna
•eteroplasmia
•segregazione mitotica
• effetto soglia



- delezione singola del DNAmt
- mutazioni puntiformi DNAmt

cross-talk

- delezioni multiple DNAmt
- deplezione DNAmt



DNAmt normale

mendeliana

Malattie mitocondriali in sintesi

Fenotipi più comuni o meglio definiti

- Progressive External Ophthalmoplegia (PEO)
- Kearns Sayre Syndrome (KSS)
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Myoclonic epilepsy and ragged red fibres (MERRF)
- Leber's hereditary optic neuropathy (LHON)
- Sindrome di Leigh

Mutazioni del DNA mitocondriale più comuni

- Delezione singola sporadica -> il difetto genetico più comune nell'adulto
- Mutazione A3243G (MELAS, PEO, Encefalopatia, Cardiopatia, Diabete/sordità) -> la mutazione puntiforme più comune
- Mutazione A8344G (MERRF, PEO, miopatia, encefalomiopatia, Leigh)

Geni nucleari più comunemente coinvolti

- POLG1, Twinkle, OPA1

delezione singola DNAmt sporadica

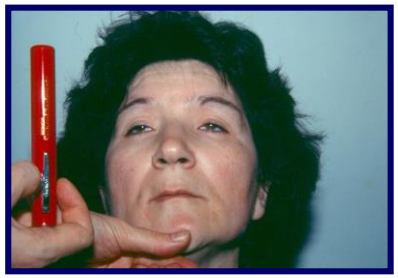
Del-S, sporadica, Mut.Punt., materna, Del-Mul dominante recessiva

delezione singola DNAmt sporadica

PEO → PEO plus → KSS

lieve miopatia

lentamente progressiva



miopatia > = < CNS

multi sistemica

variabile gravità e progressione

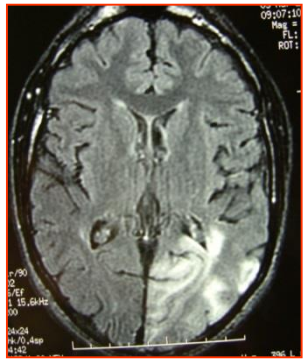
CNS >>>> miopatia

multi sistemica grave

PEO manifestazione clinica più comune delle malattie mitocondriali

Età d'esordio infanzia -> vecchiaia

- La **mutazione A3243G** è presente nell'80% dei casi di MELAS
- È la più comune mutazione puntiforme del DNAmt



PEO ⟷ **MELAS**

deletion
3243
4274
4285
5692
5703
12311
12315

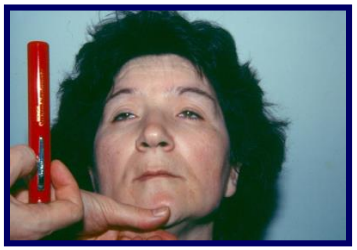
583
1642
3243
3252
3260
3271
3291
5814
9957
13513

diabete/ipoacusia neurosensoriale (MIDD)

3243
8296
duplicazione

3243
3254
3260
3303
4295
9997

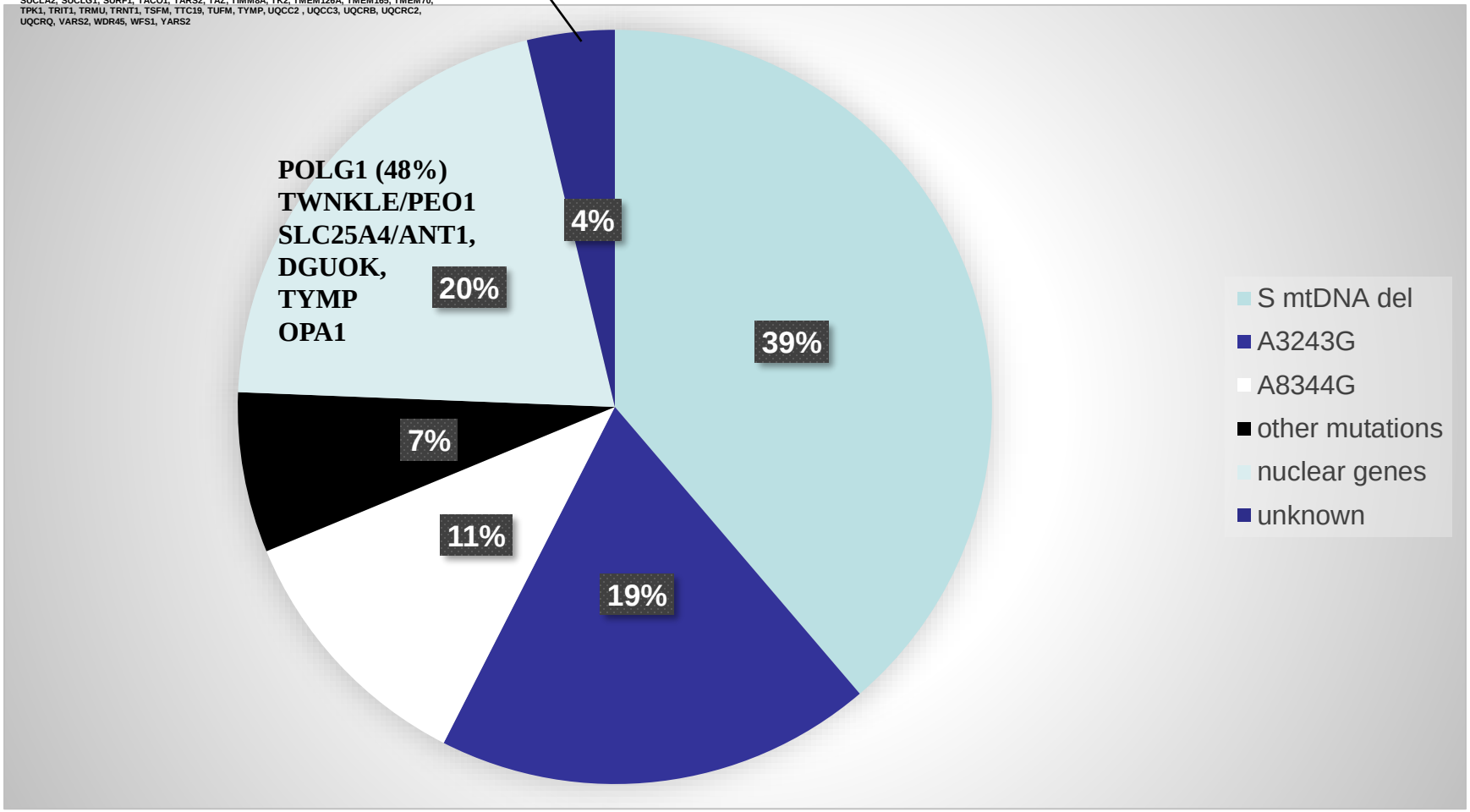
cardiomiopatia

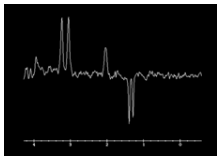


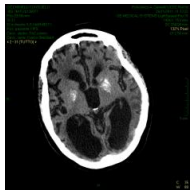
160 consecutive adult patients with PMM

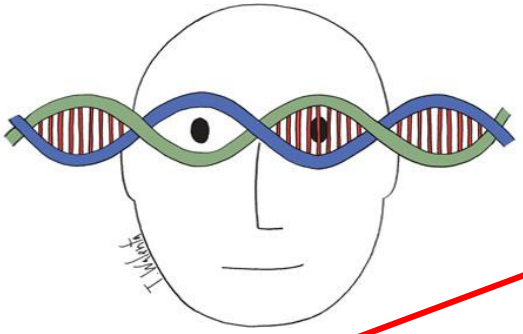
AARS, AARS2, ABCB11, ABCB4, ABCB7, ABCD4, ACAD9, ACADM, ACADVL, ACO2, ACSF3, ADCK3 (CABC1; COQ8), ADCK4, AFG3L2, AGK, AGL, AIFM1, ALAS2, ALDOA, ALDOB, ALG1, ALG11, ALG13, ALG2, ALG3, ALG6, ALG9, AMACR, APOPT1, APTX, ARG1, ASL, ASS1, ATP5A1, ATP5E, ATP7B, ATP8B1, ATPAF2 (ATP12), AUH, B4GALT1, BCKDHA, BCKDHB, BCS1L, BOLA3, C10ORF2, C12ORF65, C19orf12, CA5A, CARS2, CHKB, CISD2, CLPB, COA5 (C2ORF64), COA6, COASY, COG4, COG5, COG6, COG7, COG8, COQ2, COQ4, COQ6, COQ9, COX10, COX14 (C12ORF62), COX15, COX20 (FAM36A), COX4I2, COX6A1, COX6B1, COX7B, CPS1, CPT1A, CPT2, CYC1, DARS, DARS2, DBT, DDHD1, DDHD2, DDOST, DGUOK, DLAT, DLD, DMGDH, DNA2, DNAJC19, DNM1L, DNM2 , DOLK, DPAGT1, DPM1, DPM3, EARS2, ECHS1, ELAC2, ENO3, ETFA, ETFB, ETFDH, ETHE1, FAH, FARS2, FASTKD2, FBP1, FBXL4, FDX1L, FH, FLAD1, FOXRED1, G6PC, GAA, GAMT, GARS, GATM, GBE1, GCDH, GFER, GFM1 (EFG1), GFM2, GLRX5, GMPPA, GSS, GTPBP3, GYG1, GYG2, GYS1, GYS2, HADHA, HADHB, HARS2, HCFC1, HIBCH, HLCS, HMGCL, HMGCS2, HSD17B10, HSPD1, IARS2, IBA57, ISCA2, ISCU, IVD, LAMP2, LARS, LARS2, LDHA, LIAS, LIPT1, LMBRD1, LRPPRC, LYRM4, LYRM7, MARS, MARS2, MCCC1, MCCC2, MCEE, MFF, MFN2, MGAT2, MGME1, MICU1, MLYCD, MMAA, MMAB, MMACHC, MMADHC (C2ORF25) , MOGS, MPC1 (BRP44L), MPDU1, MPI, MPV17, MRPL12, MRPL3, MRPL44, MRPS16, MRPS22, MRPS7, MTFMT, MTO1, MTPAP, MTR, MTRR, MUT, NADK2, NAGS, NARS2, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3 (C3ORF60), NDUFAF4 (C6ORF66), NDUFAF5, NDUFAF6, NDUFAF7 (C2ORF56), NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFS1, NFU1, NGLY1, NR2F1, NUBPL, OPA1, OPA3, OTC, PARS2, PC, PCCA, PCCB, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PET100, PFKM, PGAM2, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PMM2, PNPT1, POLG, POLG2, PRKAG2, PRPS1, PTRH2, PUS1, PYGM, QARS, RANBP2, RARS, RARS2, REEP1 (C2ORF23), RFT1, RMND1, RRM2B, SARS2, SCO1, SCO2, SDHA, SDHAF1, SERAC1, SFXN4, SLC19A2, SLC19A3, SLC22A5, SLC25A1, SLC25A13, SLC25A15, SLC25A19, SLC25A20, SLC25A22, SLC25A3 (PHC), SLC25A38, SLC25A4, SLC2A2, SLC35A1, SLC35A2, SLC35C1, SLC37A4, SLC6A8, SLC7A7, SPAST, SPG7, SPTLC1, SRD5A3, SSR4, STT3A, STT3B, STXBP1, SUCLA2, SUCLG1, SURF1, TACO1, TARS2, TAZ, TIMM8A, TK2, TMEM126A, TMEM165, TMEM70, TPK1, TRIT1, TRMU, TRNT1, TSFM, TTC19, TUFM, TYMP, UQCC2 , UQCC3, UQCRB, UQCRC2, UQCRQ, VARS2, WDR45, WFS1, YARS2

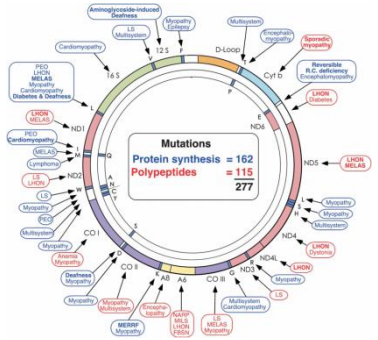
nuclear genes panel





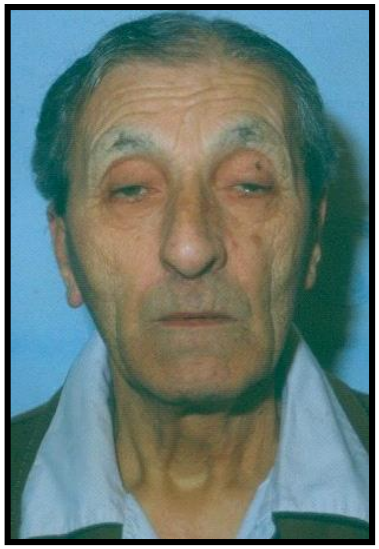


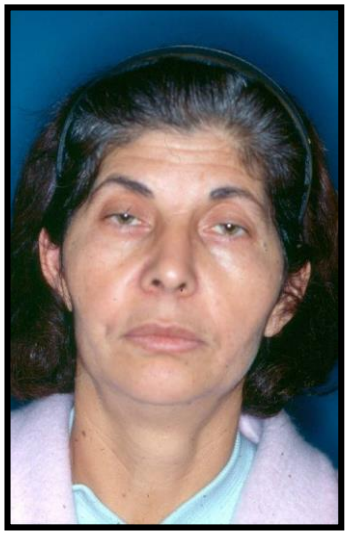


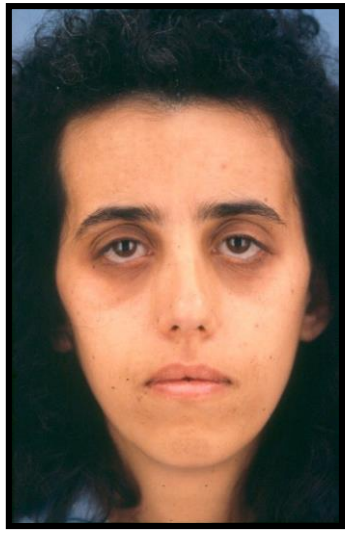


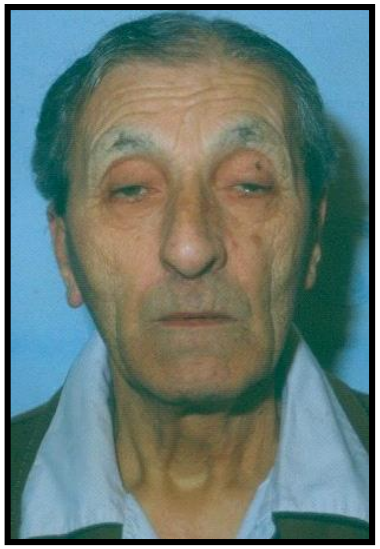
protocollo clinico diagnostico

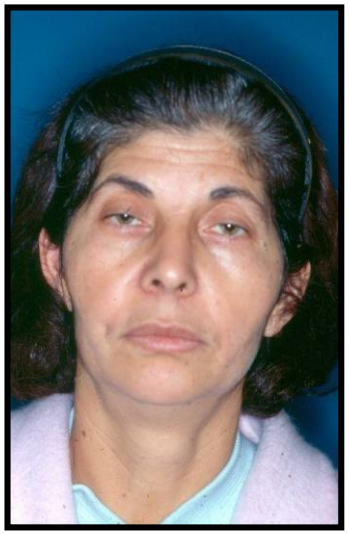
AARS, AARS2, ABCB11, ABCB4, ABCB7, ABCD4, ACAD9, ACADM, ACADVL, ACO2, ACSF3, ADCK3 (CABC1; COQ8), ADCK4, AFG3L2, AGK, AGL, AIFM1, ALAS2, ALDOA, ALDOB, ALG1, ALG11, ALG13, ALG2, ALG3, ALG6, ALG9, AMACR, APOPT1, APTX, ARG1, ASL, ASS1, ATP5A1, ATP5E, ATP7B, ATP8B1, ATPAF2 (ATP12), AUH, B4GALT1, BCKDHA, BCKDHB, BCS1L, BOLA3, C10ORF2, C12ORF65, C19orf12, CA5A, CARS2, CHKB, CISD2, CLPB, COA5 (C2ORF64), COA6, COASY, COG4, COG5, COG6, COG7, COG8, COQ2, COQ4, COQ6, COQ9, COX10, COX14 (C12ORF62), COX15, COX20 (FAM36A), COX4I2, COX6A1, COX6B1, COX7B, CPS1, CPT1A, CPT2, CYC1, DARS, DARS2, DBT, DDHD1, DDHD2, DDOST, DGUOK, DLAT, DLD, DMGDH, DNA2, DNAJC19, DNM1L, DNM2 , DOLK, DPAGT1, DPM1, DPM3, EARS2, ECHS1, ELAC2, ENO3, ETFA, ETFB, ETFDH, ETHE1, FAH, FARS2, FASTKD2, FBP1, FBXL4, FDX1L, FH, FLAD1, FOXRED1, G6PC, GAA, GAMT, GARS, GATM, GBE1, GCDH, GFER, GFM1 (EFG1), GFM2, GLRX5, GMPPA, GSS, GTPBP3, GYG1, GYG2, GYS1, GYS2, HADHA, HADHB, HARS2, HCFC1, HIBCH, HLCS, HMGCL, HMGCS2, HSD17B10, HSPD1, IARS2, IBA57, ISCA2, ISCU, IVD, LAMP2, LARS, LARS2, LDHA, LIAS, LIPT1, LMBRD1, LRPPRC, LYRM4, LYRM7, MARS, MARS2, MCCC1, MCCC2, MCEE, MFF, MFN2, MGAT2, MGME1, MICU1, MLYCD, MMAA, MMAB, MMACHC, MMADHC (C2ORF25) , MOGS, MPC1 (BRP44L), MPDU1, MPI, MPV17, MRPL12, MRPL3, MRPL44, MRPS16, MRPS22, MRPS7, MTFMT, MTO1, MTPAP, MTR, MTRR, MUT, NADK2, NAGS, NARS2, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA4, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3 (C3ORF60), NDUFAF4 (C6ORF66), NDUFAF5, NDUFAF6, NDUFAF7 (C2ORF56), NDUFB3, NDUFB9, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFS1, NFU1, NGLY1, NR2F1, NUBPL, OPA1, OPA3, OTC, PARS2, PC, PCCA, PCCB, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PET100, PFKM, PGAM2, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PMM2, PNPT1, POLG, POLG2, PRKAG2, PRPS1, PTRH2, PUS1, PYGM, QARS, RANBP2, RARS, RARS2, REEP1 (C2ORF23), RFT1, RMND1, RRM2B, SARS2, SCO1, SCO2, SDHA, SDHAF1, SERAC1, SFXN4, SLC19A2, SLC19A3, SLC22A5, SLC25A1, SLC25A13, SLC25A15, SLC25A19, SLC25A20, SLC25A22, SLC25A3 (PHC), SLC25A38, SLC25A4, SLC2A2, SLC35A1, SLC35A2, SLC35C1, SLC37A4, SLC6A8, SLC7A7, SPAST, SPG7, SPTLC1, SRD5A3, SSR4, STT3A, STT3B, STXBP1, SUCLA2, SUCLG1, SURF1, TACO1, TARS2, TAZ, TIMM8A, TK2, TMEM126A, TMEM165, TMEM70, TPK1, TRIT1, TRMU, TRNT1, TSFM, TTC19, TUFM, TYMP, UQCC2 , UQCC3, UQCRB, UQCRC2, UQCRQ, VARS2, WDR45, WFS1, YARS2

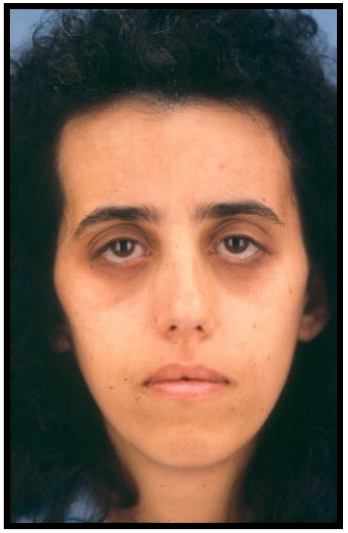


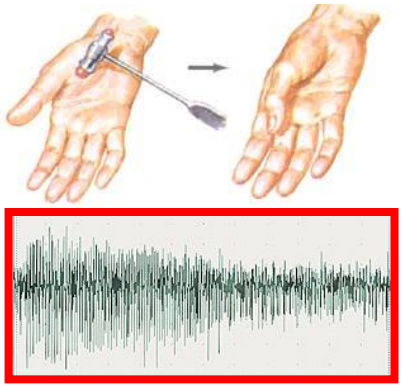


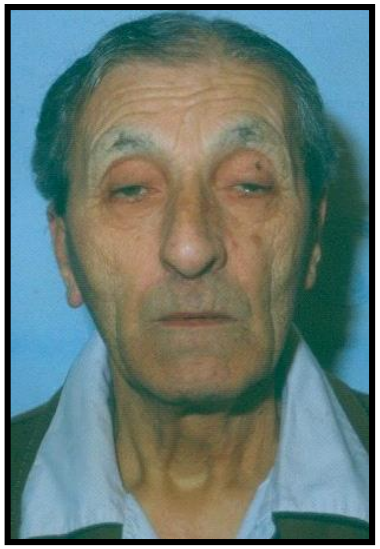


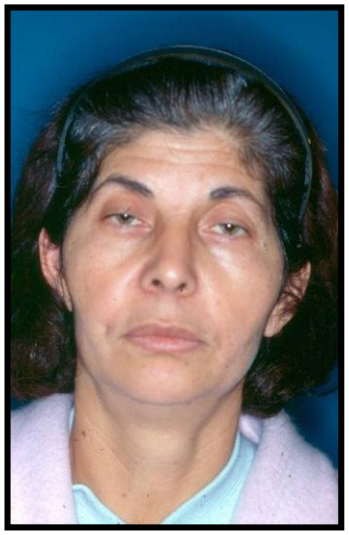


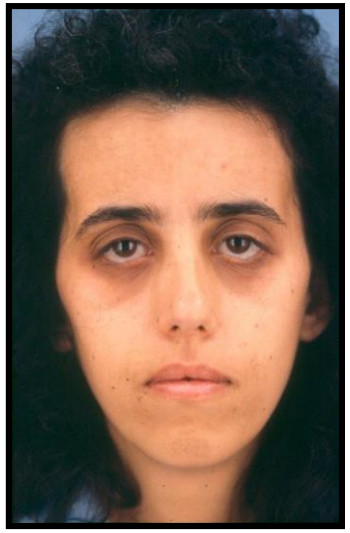


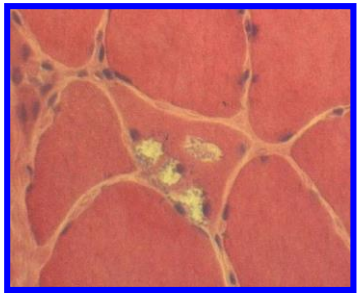


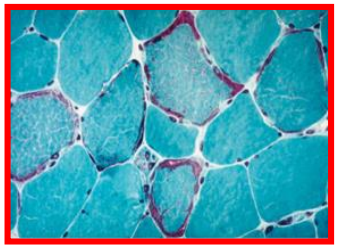


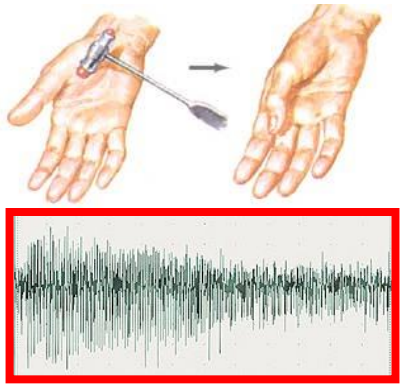


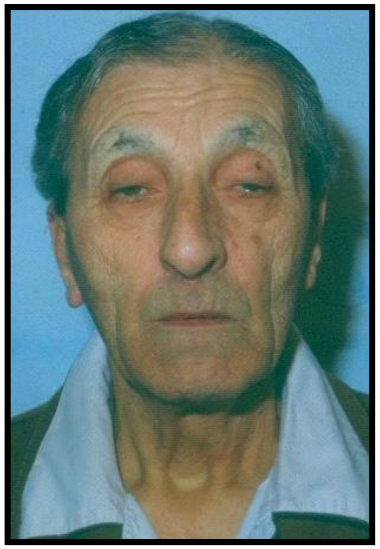


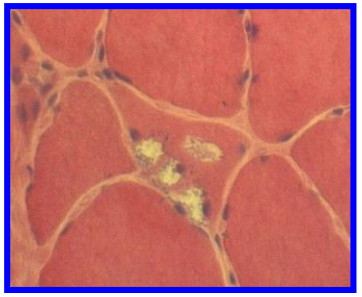






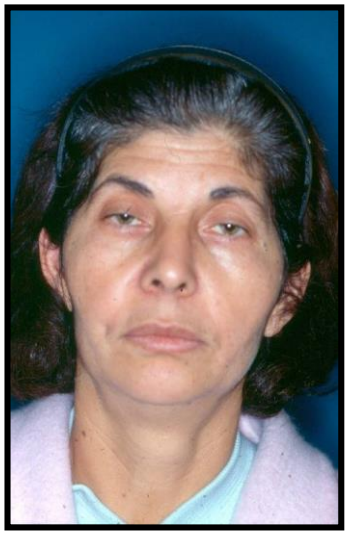


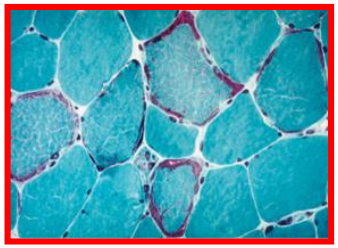




espansione
CGC ex1 PABN1
14q11.2-q13

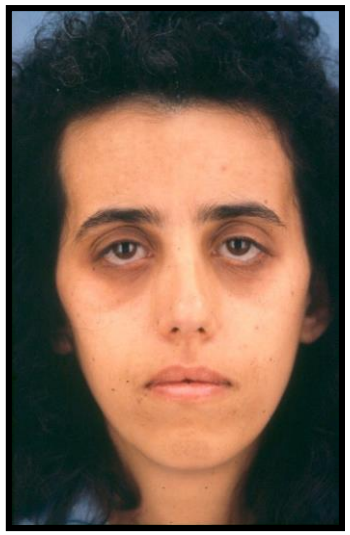
OPMD

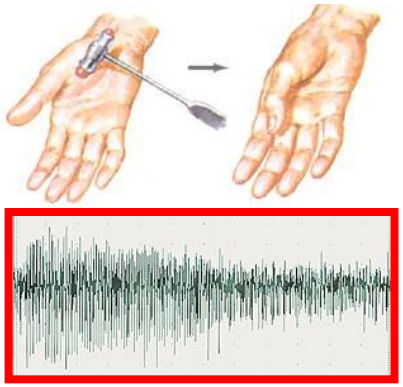




A8344G
tRNAlys
DNAmt

MERRF





espansione
CTG >50 in DMPK
19q13.3

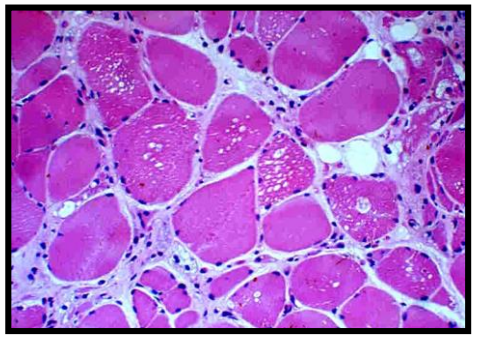
DM1

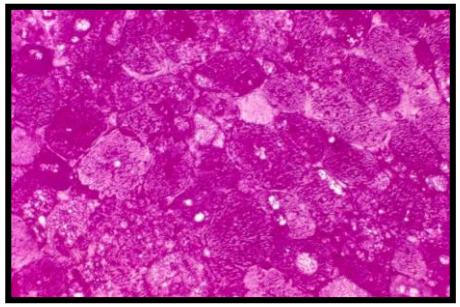
distrofie muscolari tipo "cingoli" (LGMD)

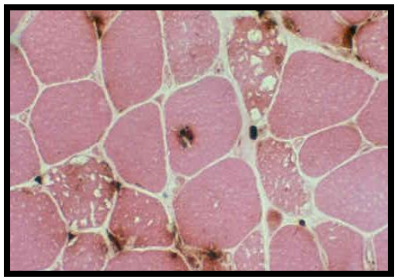
- LGMD2: Recessive
  - 2A: CAPN; 15q15
  - 2B: Dysferlin; 2p13.1
  - 2C: γ-Sarcoglycan; 13q12
  - 2D: α-Sarcoglycan; 17q21
  - 2E: β-Sarcoglycan; 4q12
  - 2F: δ-Sarcoglycan; 5q33
  - 2G: Telethonin; 17q11-12
  - 2H: TRIM32; 9q31-q33
  - 2I: FKRP; 19q13.3
  - 2J: Titin; 2q31
  - 2K: POMT1; 9q34
  - 2L: anoctamina 5; 11p13-p12
  - 2M: Fukutin; 9q31
  - 2N: POMT2; 14q24
  - 2O: POMGnT1; 1p34.1
  - 2V: GAA; 17q21-q23 (Pompe)
  - 2Z
- LGMD1: Dominanti
  - 1A: Myotilin; 5q31; Dysarthria
  - 1B: Lamin A/C; 1q21; + Cardiac
  - 1C: Caveolin-3; 3p25; Child onset
  - 1D: 7q Dilated Cardiomyopathy
  - (?1E): 6q23
  - 1F: TNP03; 7q32
  - 1G: 4p21
  - 1H: 3p23
  - 1I: CAPN

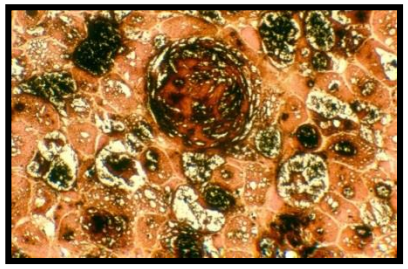
POMPE

- dosaggio biochimico della maltasi acida
- genetica -> analisi del gene *GAA*









Le distrofie muscolari - LGMD

Fenotipo comune

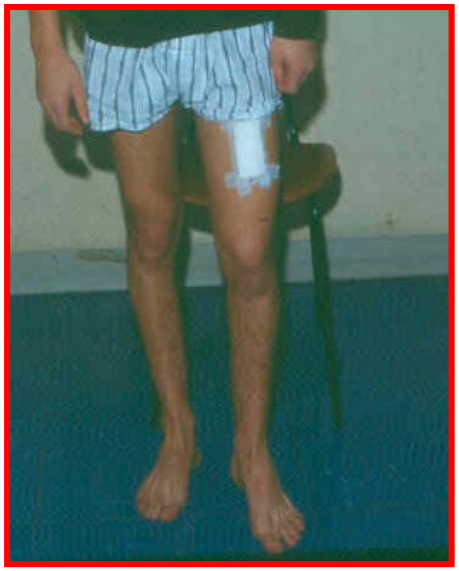
- Debolezza muscolare generalmente prossimale e simmetrica
- Ipertrofia dei polpacci
- Muscoli oculomotori risparmiati
- Debolezza dei mm. mimici assente nelle prime fasi della malattia, ma può manifestarsi nelle fasi più avanzate

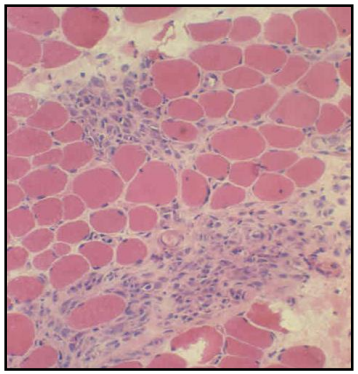
LGMD
debolezza a distribuzione distale

Deficit distali soprattutto in

✓forme dominanti: LGMD1A (miotilina), 1C (caveolina), 1E (desmina)

✓forme recessive: deficit distale talora > prossimale in LGMD2B (disferlina) e 2L (anoctamina 5) -> miopatia distale tipo Miyoshi



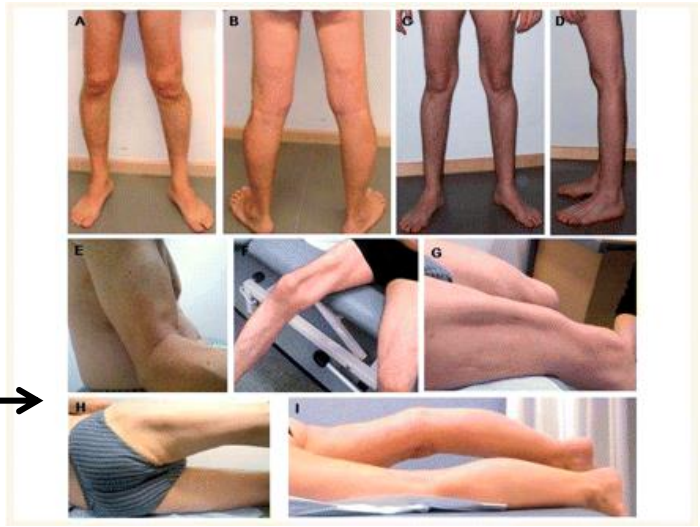


DYSF 2p12p13

LGMD
asimmetria

Deficit tipicamente simmetrico, ma asimmetria in

- portatrici manifeste DMD
- FSHD > quasi sempre
- LGMD2L (anoctamina 5) → > nella maggioranza dei pazienti



- LGMD2A (calpaina), LGMD2B (disferlina) > abbastanza frequente

The genetic basis of undiagnosed muscular dystrophies and myopathies

Results from 504 patients

ABSTRACT

Objective: To apply next-generation sequencing (NGS) for the investigation of the genetic basis of undiagnosed muscular dystrophies and myopathies in a very large cohort of patients.

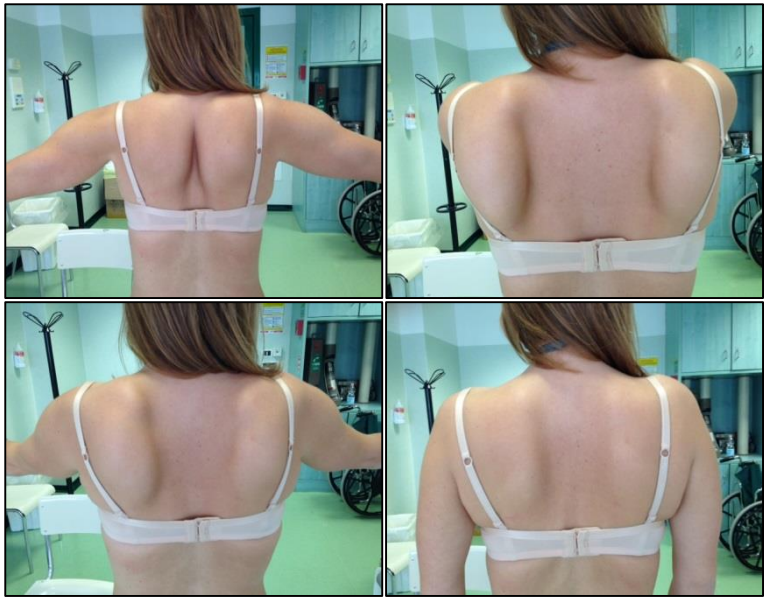
Methods: We applied an NGS-based platform named MotorPlex to our diagnostic workflow to test muscle disease genes with a high sensitivity and specificity for small DNA variants. We analyzed 504 undiagnosed patients mostly referred as being affected by limb-girdle muscular dystrophy or congenital myopathy.

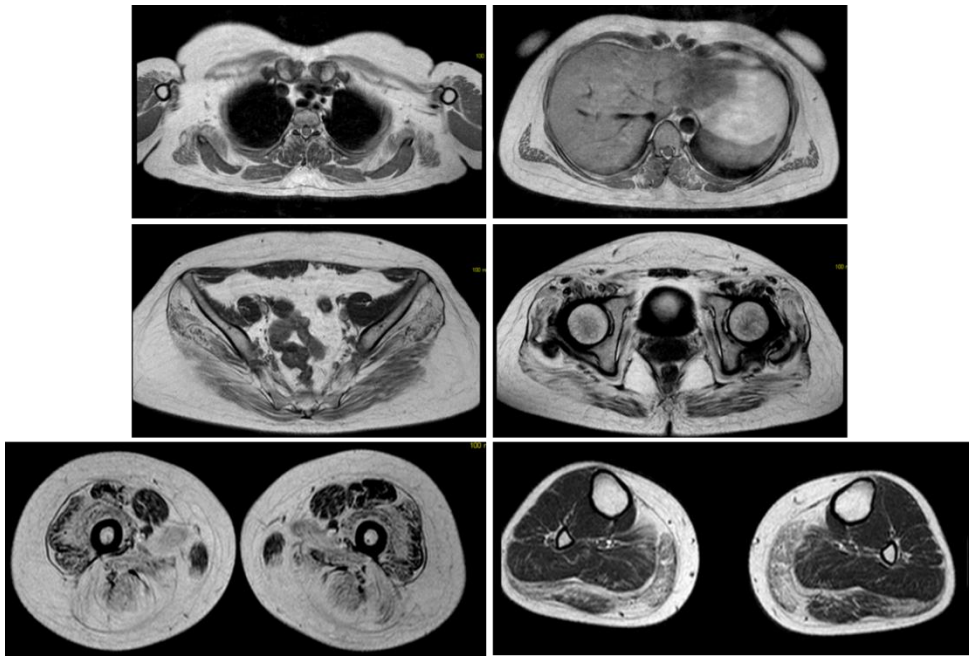
Results: MotorPlex provided a complete molecular diagnosis in 218 cases (43.3%). A further 160 patients (31.7%) showed as yet unproven candidate variants. Pathogenic variants were found in 47 of 93 genes, and in more than 30% of cases, the phenotype was nonconventional, broadening the spectrum of disease presentation in at least 10 genes.

Conclusions: Our large DNA study of patients with undiagnosed myopathy is an example of the ongoing revolution in molecular diagnostics, highlighting the advantages in using NGS as a first-tier approach for heterogeneous genetic conditions. ***Neurology*® 2016;87:71-76**

Table 1 LGMD genes[22]

Disease	Locus	Gene	No. of patients
LGMD1B	1q22	*LMNA*	3
LGMD1C	3p25.3	*CAV3*	2
LGMD2A	15q15	*CAPN3*	22
LGMD2B	2p13.2	*DYSF*	15
LGMD2C	13q12	*SGCG*	4
LGMD2D	17q21	*SGCA*	10
LGMD2E	4q12	*SGCB*	6
LGMD2G	17q12	*TCAP*	1
LGMD2H	9q33.1	*TRIM32*	1
LGMD2I	19q13.3	*FKRP*	7
LGMD2J	2q24.3	*TTN*	5
LGMD2K	9q34.1	*POMT1*	1
LGMD2L	11p13	*ANO5*	15
LGMD2M	9q31	*FKTN*	2
LGMD2N	14q24	*POMT2*	6
LGMD2R	2q35	*DES*	1
LGMD2S	4q35.1	*TRAPPC11*	2
LGMD2T	3p21	*GMPPB*	2
LGMD2V	17q25	*GAA*	10





Gene	*Locus*	*Genotipo*	*Variante*		*rsID*
LMNA	chr1:156104230	**Eterozigote**	**c.550C>T**	**p.Gln184X**	-
CAPN3	chr15:42680000	**Eterozigote**	**c.550delA**	**p.Thr184Argfs**	rs80338800
CAPN3	chr15:42700421	**Eterozigote**	**c.1813G>C**	**p.Val605Leu**	-

Mutazioni Calpaina: compatibili con il fenotipo muscolare

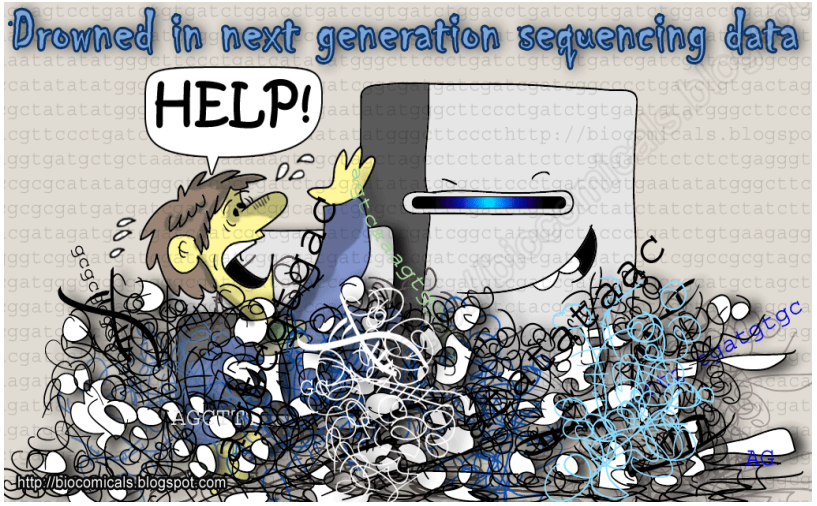
Mutazione Lamina: nuova ma classificata come patogena

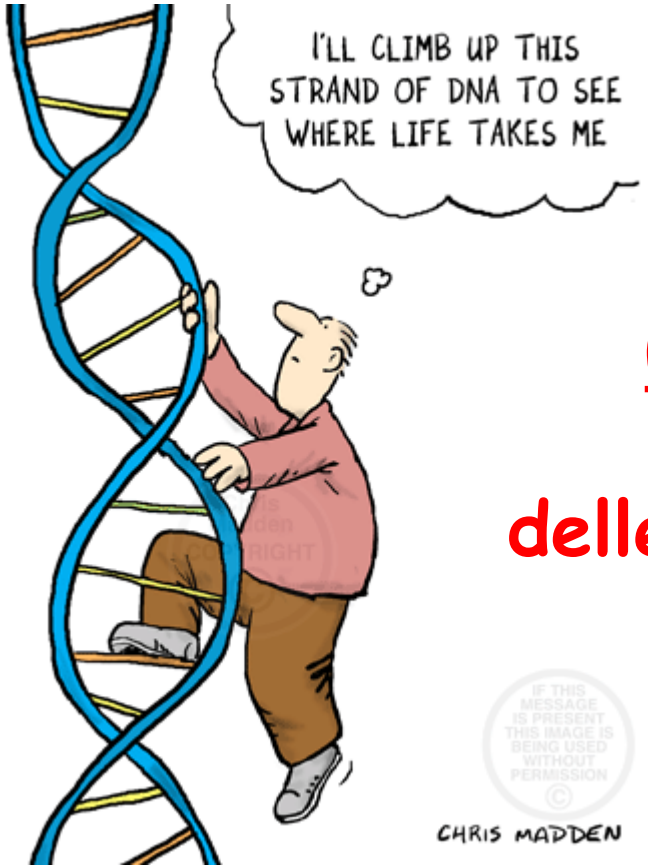
- la sequenza dell'esoma e tutte le altre tecnologie di NGS e «*omiche*» sono nuove e potenti strategie in grado di identificare nuovi geni e biomolecole

<u>ma</u>

- necessaria l'analisi e l'interpretazione di numerosissimi dati per far emergere dal rumore di fondo specifici geni o biomolecole
- l'uso improprio di tali tecnologie può condurre a errori diagnostici o erronea attribuzione di una data manifestazione clinica ad una certa mutazione

➢ necessaria una corretta fenotipizzazione attraverso una collezione estensiva di dati clinici, patologici e di *imaging*





La genetica e la clinica: un imprescindibile connubio nella diagnosi delle malattie muscolari complesse