RE(ACT)® CONGRESS 2018
INTERNATIONAL CONGRESS OF RESEARCH ON RARE AND ORPHAN DISEASES
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Undiagnosed and not diagnosed: a genetic view

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Undiagnosed diseases (UDN)
DEFINITION

"longstanding medical condition that eludes diagnosis by a referring physician can be considered undiagnosed and may be of interest to this clinical research program" (UDN International)

CONCEPTS

The concept of "diagnosis"

-clinical diagnosis (phenotype-phenomics)
-genetic diagnosis (genotype)

STATE OF THE ART

New NEXT GENERATION SEQUENCING strategies

WHOLE EXOME SEQUENCING
WHOLE GENOME SEQUENCING
GENE PANALES ANALYSIS

BOTTLENECKS

incomplete accuracy for

- copy number variations
- dynamic mutations
- epigenetics changes

Introducing a genetic view: how to categorize UDNs

PHENOTYPE DISCOVERY

-**KNOWN** PHENOTYPE ASSOCIATED WITH **KNOWN DISEASE GENE** **(diagnostics failure)**

(A) The case of **Calpain-3** gene

-**NEW** PHENOTYPE ASSOCIATED WITH **KNOWN DISEASE GENE** **(phenotype discovery)**

(B) The case of **VERSICAN** gene

GENE DISCOVERY

-**NOVEL** DISEASE GENE CAUSING **KNOWN PHENOTYPE** **(gene discovery)**

(C) The case of **POPDC1** gene

-**NOVEL** DISEASE GENE CAUSING **NOVEL PHENOTYPE** **(disease discovery)**

(D) The case of **MSTO** gene

CASE (A)

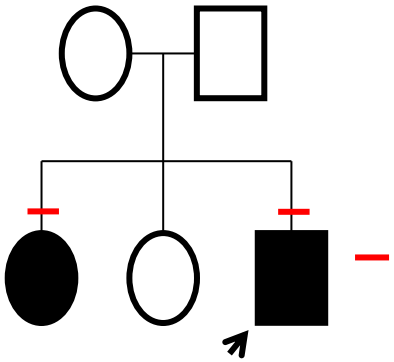
A KNOWN GENE CAUSING A KNOWN PHENOTYPE CALPAIN 3

#253600 MUSCULAR DYSTROPHY, PELVOFEMORAL
LEYDEN-MOEBIUS MUSCULAR DYSTROPHY
CALPAINOPATHY

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
15q15.1	Muscular dystrophy, limb-girdle, type 2A	253600	AR	3	CAPN3	114240

deCODE genetics

Family-of-4 with Limb-girdle muscular dystrophy

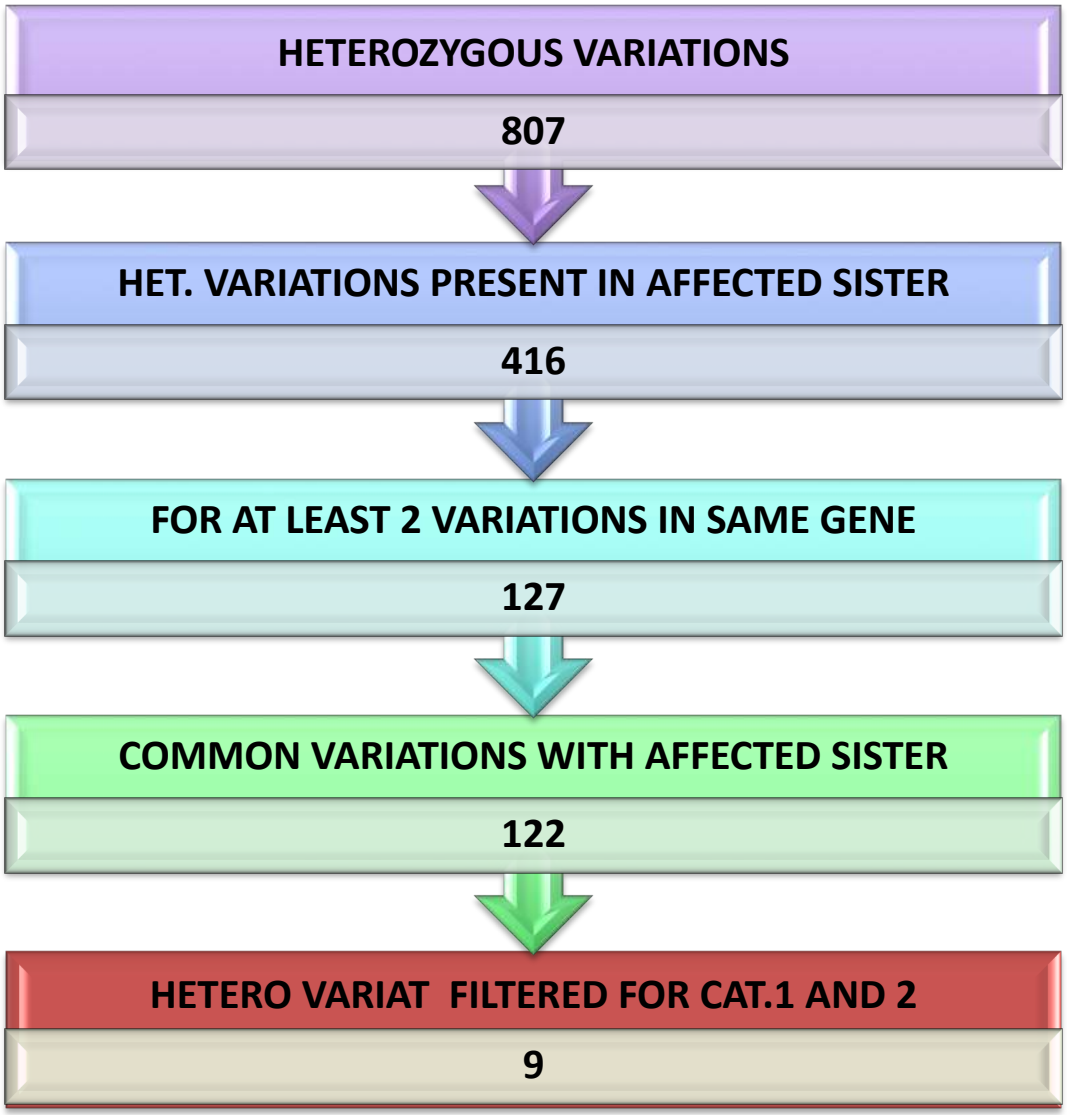


Previous
Gene panel testing
negative

Female aged 48 yrs (d.o.b.: 1968)
Onset 8-9 yrs with difficulty walking and climbing stairs, slowly progressive, wheelchair bound at the age of about 20 yrs.
The muscle biopsy showed a dystrophic picture**.**
At present: mild weakness of the neck flexors and extensors muscles, weakness of the deltoid, supraspinatus and infraspinatus. Weakness of quadriceps, iliopsoas and femoral adductor.
The distal muscles of the limbs are less involved.
CPK: 660 U/L
ECG: normal
Normal spirometry

Male aged 41 yrs
(d.o.b.: 1974**)**
Same clinical picture as the sister, slightly less severe disease progress.
Wheelchair bound

TOTAL SNPs 860
Prioritization for variants IN COMPOUND HETEROZYGOSIS



WGS ANALYSIS
Exons
Splice boundaries
5' and 3' UTRs

NeuroOmics

9 HETEROZYGOUS VARIATION FILTERED

chr12	9020954	G	A	het	NEU_FER0935	chr12:9020954, A2ML1 G>A, Cat2, het_sub, splice_donor_variant	true	Cat2
chr15	42676699	C	T	het	NEU_FER0935	chr15:42676699, CAPN3 c.(328,67)_C>T p.(110,23)_R>*, Cat1, het_sub, stop_gained	true	Cat1
chr15	42702195	T	A	het	NEU_FER0935	chr15:42702195, CAPN3 T>A, Cat2, het_sub, splice_donor_variant	true	Cat2
chr2	26700099	G	A	het	NEU_FER0935	chr2:26700099, OTOF c.(223,2464,394)_G>A p.(132,75,822)_R>W, Cat1, het_sub, mis	true	Cat1
chr22	24300059	G	A	het	NEU_FER0935	chr22:24300059, GSTT2B c.(544,586)_G>A p.(182,196)_R>*, Cat2, het_sub, stop_gair	true	Cat2
chr3	57440529	TG	T	het	NEU_FER0935	chr3:57440529, DNAH12 c.(3359,3428)_TG>T p.(1120,1143)_., Cat2, het_del, frames	true	Cat2
chr4	962068	A	C	het	NEU_FER0935	chr4:962068, DGKQ A>C, Cat2, het_sub, splice_donor_variant	true	Cat2
chr6	32487158	G	GCA	het	NEU_FER0935	chr6:32487158, HLA-DRB5 c.640-641_G>GCA p.214_., Cat2, het_ins, frameshift_vari	true	Cat2
chr6	32489940	G	A	het	NEU_FER0935	chr6:32489940, HLA-DRB5 c.112_G>A p.38_Q>*, Cat2, het_sub, stop_gained	true	Cat2

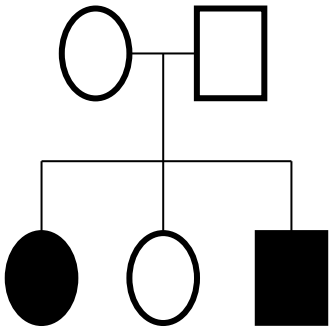
Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
15q15.1	Muscular dystrophy, limb-girdle, type 2A	253600	AR	3

CAPN3 c.328C>T p.R110*, stop gained with Clinical significance Pathogenic (already described)

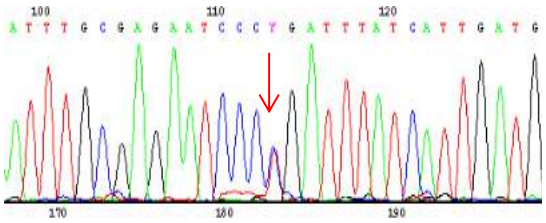
CAPN3 c.2115+2T>A, splice_donor_variant (not described)

VALIDATED

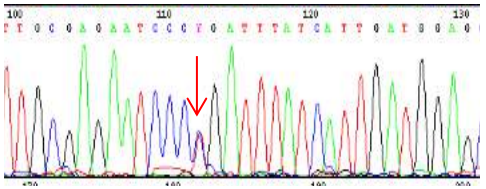


Diagnosis
LGMD2A

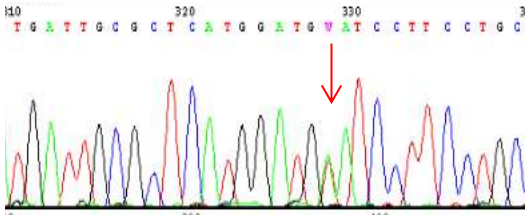
Exon 2 c.328C>T, p. Arg110*



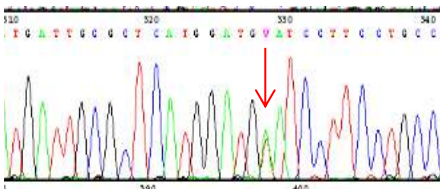
Exon 2 c.328C>T, p. Arg110*



Exon 19 c.2115+2T>A



Exon 19 c.2115+2T>A



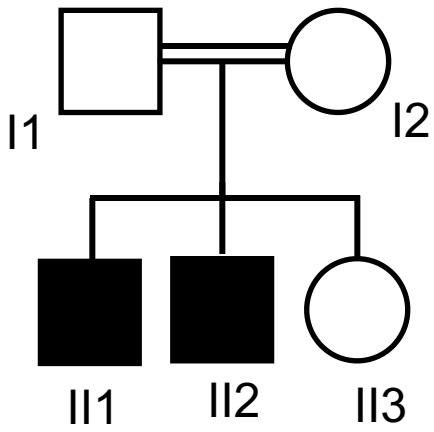
CASE (B)

A KNOWN GENE CAUSING A NEW PHENOTYPE Versican (VCAN)

143200
WAGNER VITREORETINOPATHY; WGVRP
Alternative titles; symbols
EROSIVE VITREORETINOPATHY; ERVR
WAGNER VITREORETINAL DEGENERATION
HYALOIDEORETINAL DEGENERATION OF WAGNER
WAGNER SYNDROME 1; WGN1

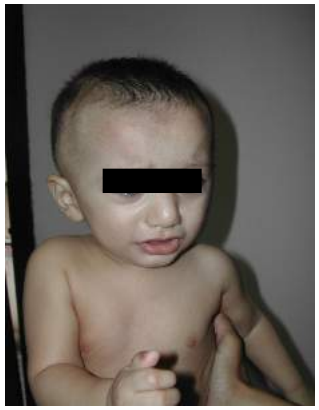
Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
5q14.2-q14.3	Wagner syndrome 1	143200	AD	3	VCAN	118661

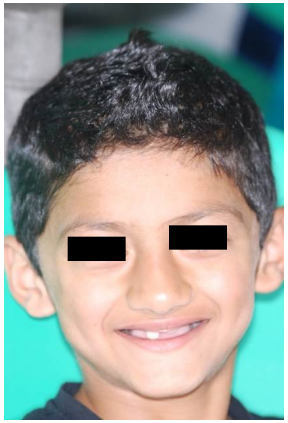
Fam 76 CONSANGUINEOUS FAMILY FROM PAKISTAN
TEETH ABNORMALITIES AND DYSMORPHIC FEATURES IN TWO SIBLINGS

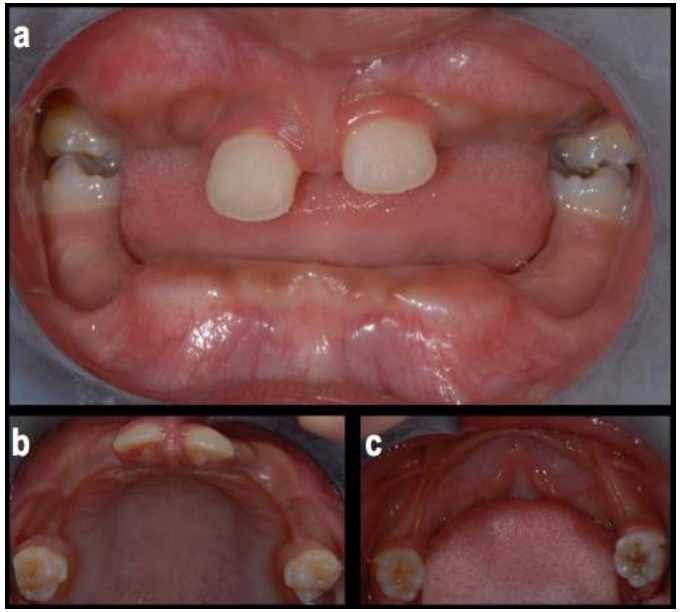


impaired tooth and periodontium development

- Loss of the maxillary central incisors
- Dental arches show a cutting-edge profile of the crest in the edentulous regions
- The root complex of exfoliated teeth is almost completely absent







WHOLE EXOME SEQUENCING ANALYSIS

FILTERS:

- **Homozygous** on patients (CONSANGUINITY), heterozygous on parents
- Exclusion of SNPs present on dbSNP132/1000 genomes/hapmap/YH project/BGI Db, Sanger Centre (UK), with frequency greater than 0.5%
- Non synonymous mutations/5'-3' UTR, splice site variations and small indels <20bp)

Table 1 Variants statistic according filtering step.

	Father_I1	*Mother_I2*	*Case_II1*	*Case_II2*
Total variants(SNVs & InDels)	122262+24123	122996+24206	119916+23175	121893+24064
MAF<0.5% (1K, ESP, ExAC)	27939	27451	26569	27200
Non-synonymous mutations, alterations at splice site and small insertion/deletions	1838	1841	1852	1843
Excluded variants could be found in Inhouse database	1084	1105	1097	1101
Shared genes (Homozgyous variants for cases, heterozygous for controls)	17 Genes			
Combined homozygous mapping result(Homozygous region for both affected)	14 Genes(*VCAN, RAET1L, SYNE1, TAGAP, C6orf123, MTPAP, RBP3, AGAP6, OR6C74, ITGA7, C15orf48, NARG2, HMG20B, TTC3*)			
Causative gene	***VCAN*** (c.7994A>T, p.His2665Leu)			

Undiagnosed Diseases Network INTERNATIONAL

RARER

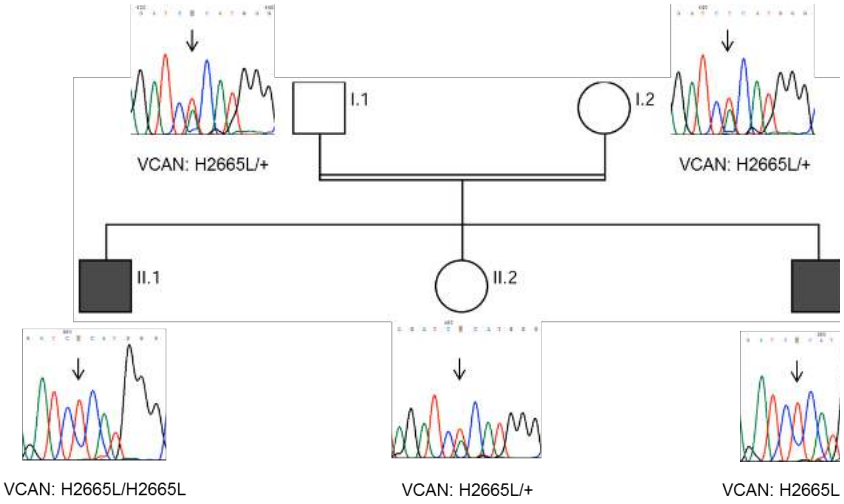
VCAN gene, homozygous missense mutation in exon 8 (c.7994A>T; p.His2665Leu; chromosome 5: 82836816; GRCh37 / hg19) (NM_004385.4)

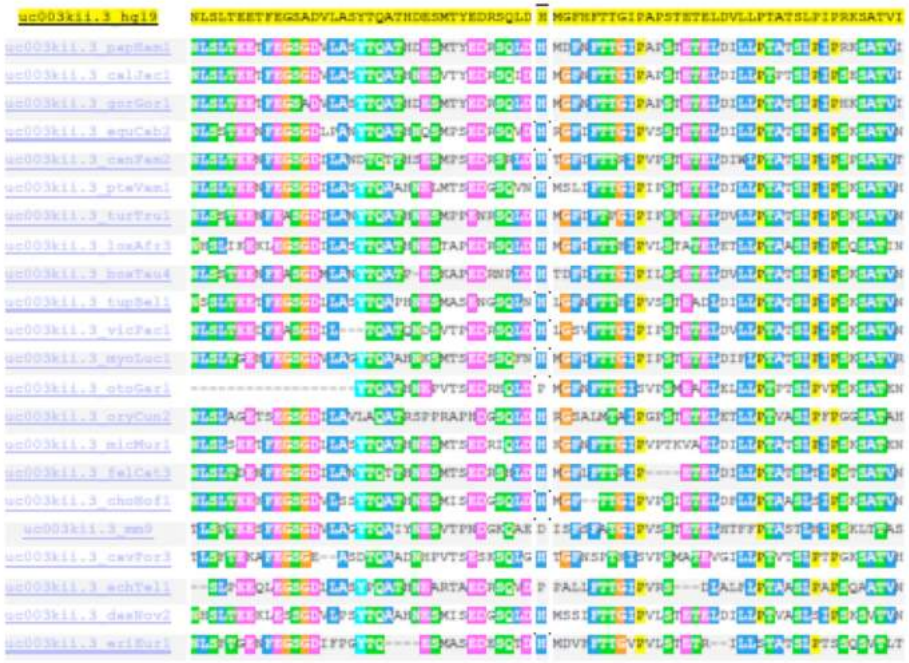
VCAN gene, homozygous missense mutation in exon 8 (c.7994A>T; p.His2665Leu; ***chromosome 5: 82836816***; GRCh37 / hg19) (NM_004385.4)

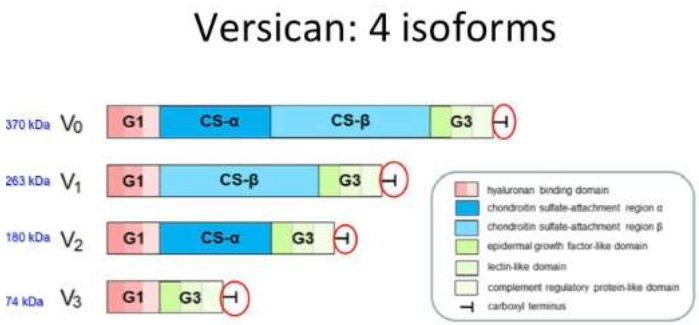
rs61754537	5:82836799	T/G	(-)	SNP	dbSNP		-	missense variant	D/E	1672	0.01	0.385	ENST00000343200.5
COSM3941392	5:82836799	COSMIC_MUTATION	(-)	somatic sequence alteration	COSMIC		-	coding sequence variant	-	1672	-	-	ENST00000343200.5
COSM4959186	5:82836806	COSMIC_MUTATION	(-)	somatic sequence alteration	COSMIC		-	coding sequence variant	-	1675	-	-	ENST00000343200.5
rs749126586	5:82836811	A/G	(-)	SNP	dbSNP		-	synonymous variant	L	1676	-	-	ENST00000343200.5
rs768723294	5:82836812	G/A	(-)	SNP	dbSNP		-	missense variant	D/N	1677	0.1	0.021	ENST00000343200.5
COSM3994502	5:82836813	COSMIC_MUTATION	(-)	somatic sequence alteration	COSMIC		-	coding sequence variant	-	1677	-	-	ENST00000343200.5
rs774497812	5:82836821	G/C	(-)	SNP	dbSNP		-	missense variant	G/R	1680	0.03	0.477	ENST00000343200.5
rs61733390	5:82836834	C/A/T	0.001 (A)	SNP	dbSNP		-	missense variant	T/K	1684	0.01	0.59	ENST00000343200.5
rs61733390	5:82836834	C/A/T	0.001 (A)	SNP	dbSNP		-	missense variant	T/I	1684	0.01	0.503	ENST00000343200.5
rs776687856	5:82836838	T/C	(-)	SNP	dbSNP		-	synonymous	T	1685	-	-	ENST00000343200.5

UNREPORTED IN ALL dbSNP databases

VERSICAN (VCAN) His2665 amino acid IS EXTREMELY CONSERVED AMONG SPECIES AND IS LOCATED IN THE PROTEIN C-TERMINUS DOMAIN







VCAN PROTEIN FUNCTIONS

VERSICAN: ROLE IN RAT TOOTH DEVELOPMENT SUPPORTS ITS PATHOGENIC ROLE in our PATIENTS

Journal of Molecular Histology (2005) 36: 281–288
DOI 10.1007/s10735-005-5534-2

Expression of versican and ADAMTS during rat tooth eruption

Shinya Sone[1,2], Megumi Nakamura[3], Yuriko Maruya[1], Ichiro Takahashi[4], Itaru Mizoguchi[5], Hideaki Mayanagi[1] & Yasuyuki Sasano[2,*]
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[2]*Division of Craniofacial Development and Regeneration, Graduate School of Dentistry, Tohoku University, Sendai, 980-9875, Japan*
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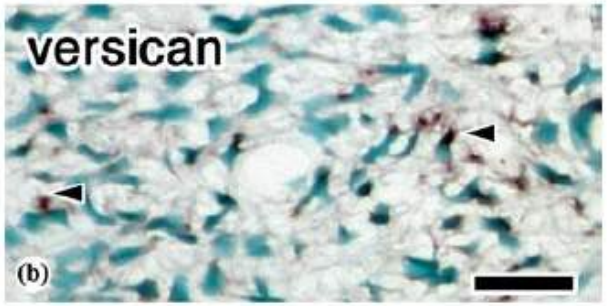
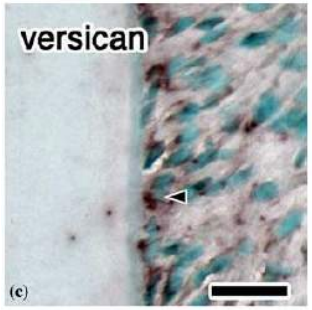
[5]*Department of Orthodontics, School of Dentistry, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido, 061-0293, Japan*

VERSICAN EXPRESSION IN RAT TOOTH

IN SITU HYBRIDIZATION OF VCAN AND ADAMTS1 IN **ODONTOBLASTS**

VCAN IS PRESENT ALSO IN **CEMENTUM**, ALVEOLAR BONE AND DENTAL PULP





VERSICAN: HIGHLY EXPRESSED IN RAT TOOTH

VERSICAN IS A KNOWN GENE DISEASE

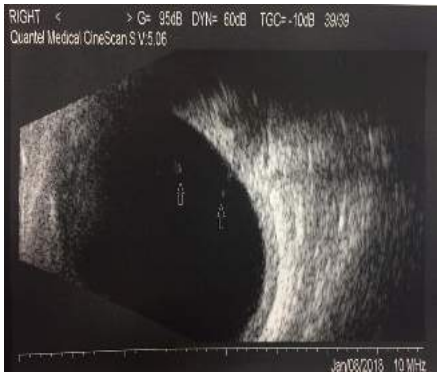
143200 5q14.2-q14.3 Wagner syndrome 1 143200 AD 3 VCAN 118661

WAGNER VITREORETINOPATHY; WGVRP
Alternative titles; symbols
EROSIVE VITREORETINOPATHY; ERVR WAGNER VITREORETINAL DEGENERATION HYALOIDEORETINAL DEGENERATION OF WAGNER WAGNER SYNDROME 1; WGN1

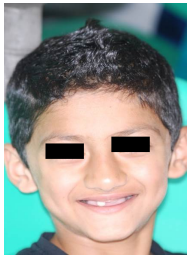
5 FAMILIES DESCRIBED
SPLICE SITE MUTATIONS ONLY OCCUR

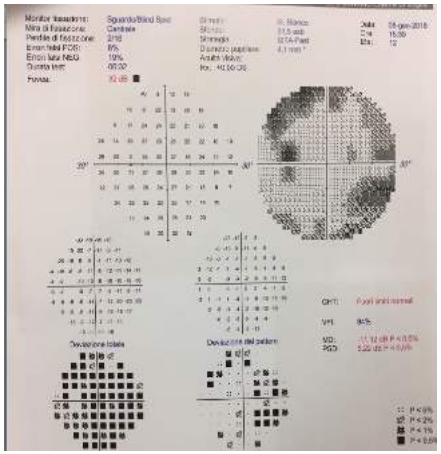
DOMINANT TRANSMISSION PEDIGRREE WAGNER

OPHTALMOLOGICAL EXAMINATION OF OUR PATIENT

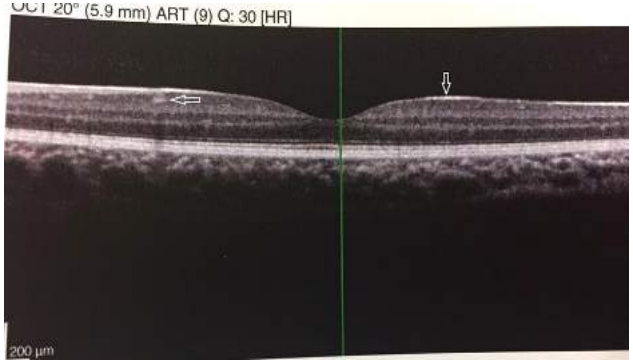


Bilaterally minimal peripheral vitreous condensation





(optical coherence tomography (OCT),
hypereflective inner limiting membrane with hypereflective foci within the ganglion cell layer.



Visual filed test showed bilaterally several points of **reduced retinal sensitivity**.

CONCLUSIONS: Reduced visual acuity in both eyes EARLY SIGNS OF VITREOPATHY AND RETINOPATHY, compatible with a pauci-asymptomatic stage of *WAGNER DISEASE*

CASE (C)

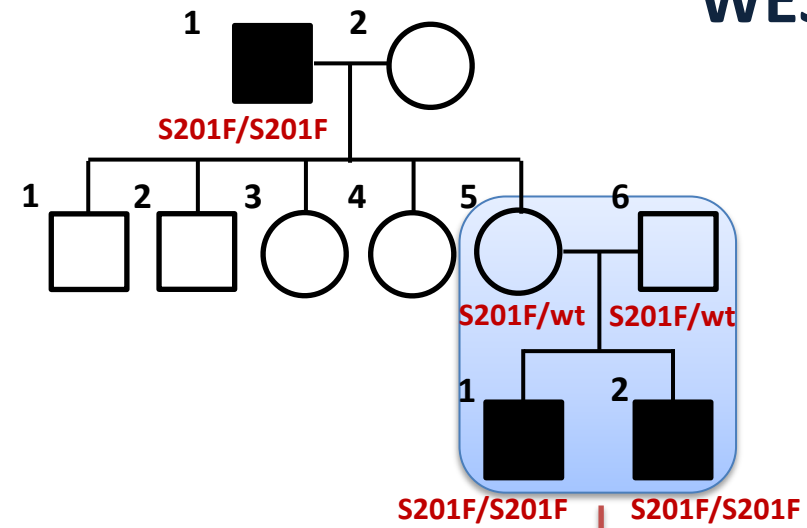
A NEW GENE CAUSING A KNOWN PHENOTYPE

BVES (POPDC1)

616812
MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2X; LGMD2X

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
6q21	Muscular dystrophy, limb-girdle, type 2X	616812	AR	3	BVES (POPDC1)	604577

FAMILY OF FOUR WITH LGMD AND AV BLOCK
WES STRATEGY



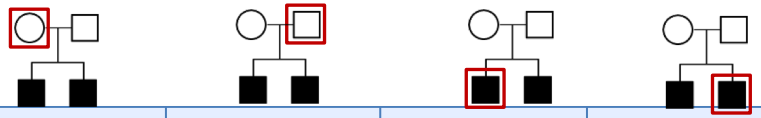
«family of four»
Whole Exome Sequencing

variant prioritization:
- recessive model
- mutation effect (missense, nonsense,splice site)
- population frequency < 0,01%
- pathogenicity prediction
- segregation analysis in the family

GENETICS

- Autosomal recessive inheritance
- Pseudodominant pedigree (Albanian community in Southern Italy))
- **PHENOTYPE**
- Limb Girdle Muscular dystrophy (LGMD)
- late onset (3-4th decade)
- Mild muscle phenotype (predominantly lower limbs)
- Severe AV block (requiring pacing)
- High CK (up to 7000 IU/L)

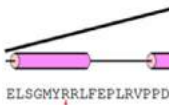
- **Homozygosity on patients (4, 5), heterozygosity on parents (2, 3) according to RECESSIVE MODEL**
- **SNP and indel calling**
- **Screening for mutations in coding regions, UTR and splice sites**
- **Exclusion of SNPs present on dbSNP132/1000 genomes/hapmap/YH project with frequency greater than 0.05%**
- **HMM prediction**
- **Aminoacid substitution prediction with SIFT**
- **Annotating candidate variations with GO and KEGG databases**



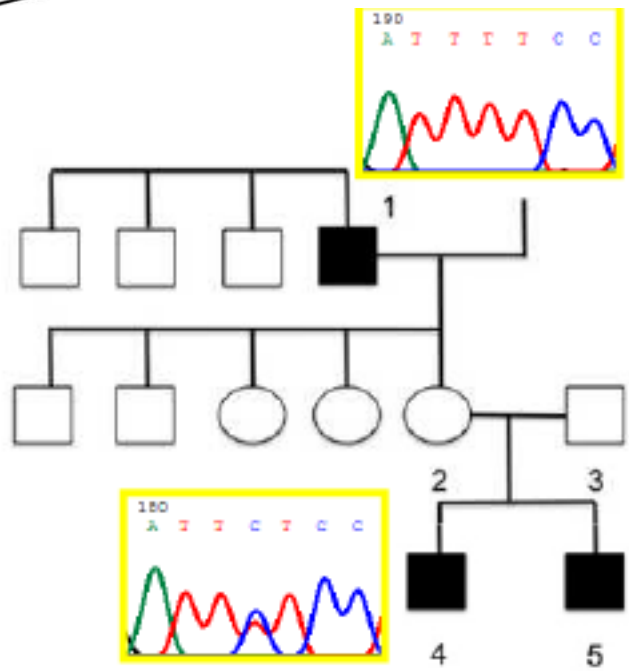
Chr	Position	Ref	Gene	Detailed Information for control MOTHER	Detailed Information for control FATHER	Detailed Information for case I	Detailed Information for case II	MutType	Prediction from SIFT	Codons	Substitution	Allele frequency
chr22	43035850	-2TT	ATP5L2	None	None	-2TT;Hom; 3-UTR	-2TT;Hom; 3-UTR	Indel	-	-	-	not reported
chr6	105572468	G	BVES	R99A36G32	R99G40A19	A99A84G0, Hom,missense	A87A74G0, Hom,missense	SNP	DAMAGING	TCT602TTT	S201F	not reported
chr16	57492109	G	COQ9	R99A8G6,5-UTR	R99A14G10,5-UTR	A63A24G0, Hom,5-UTR	A40A15C1, Hom,5-UTR	SNP	-	-	-	0.00004794
chr10	47915891	C	FAM21B	M99C29A28	M99A44C32	A72A76T2, Hom,missense	A68A69C1, Hom,missense	SNP	TOLERATED	TCC1298TAC	S433Y	not reported
chr6	98472445	C	MIR2113	Y99C27T25,,5-UTR	Y99T16C13,5-UTR	T95T64C0, Hom,5-UTR	T93T50C0, Hom,5-UTR	SNP	-	-	-	0.01551 (rs117428639)
chr14	23391533	N/A	PRMT5	+4ACAA;Het;3-UTR	+4ACAA;Het;3-UTR	+4ACAA; Hom;3-UTR	+4ACAA; Hom;3-UTR	Indel	-	-	-	not reported
chr12	118464907	T	RFC5	W99A15T7,5-UTR	W99T8A5,5-UTR	A57A22T0, Hom,5-UTR	A40A15T0, Hom,5-UTR	SNP	-	-	-	not reported
chr9	100854283	C	TRIM14	Y99T87C82	Y99T68C62	T99T191G1, Hom,missense	T64T188C1, Hom,missense	SNP	TOLERATED	AGC701AAC	S234N	0.001866 (rs145652674)

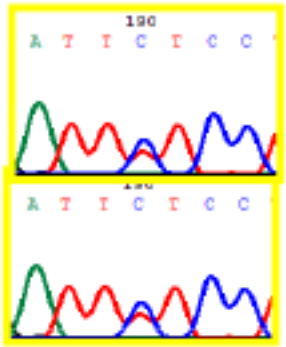
STRONGEST CANDIDATE : BVES (POPDC1)

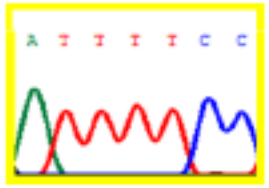
THE MISSENSE S201F MUTATION IS PREDICTED TO BE PATHOGENIC

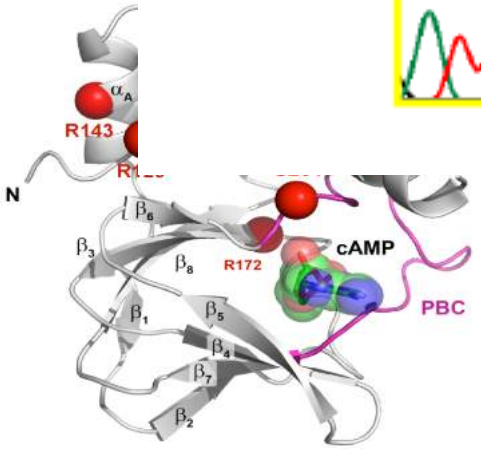


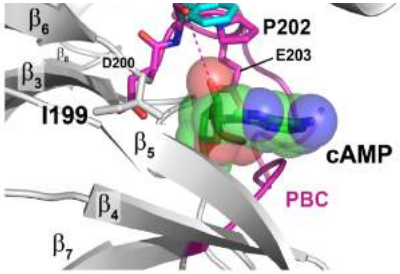
located in a functional







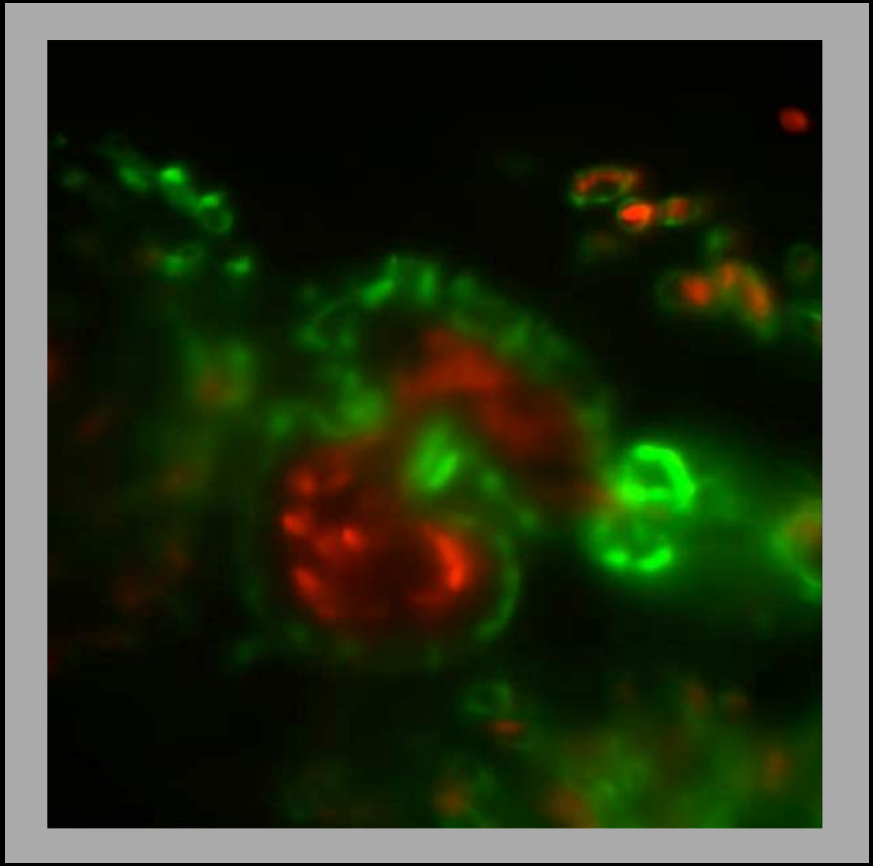




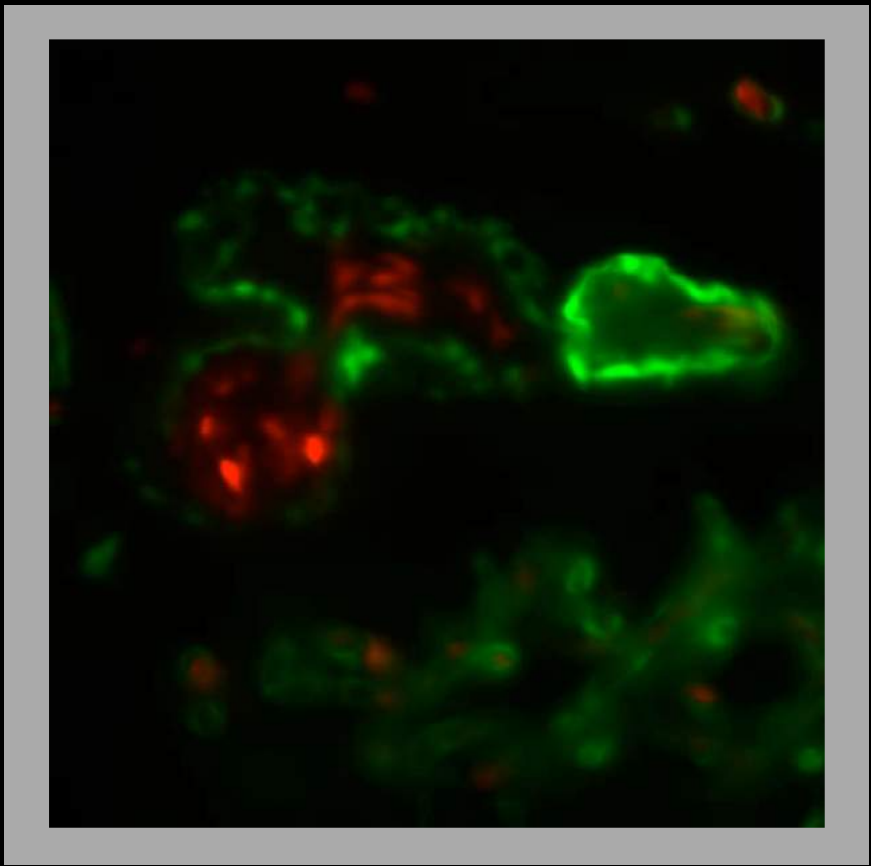
protein model predicting impaired cAMP binding

Cardiac arrhythmia in popdc1 zebrafish morphants

WT



PMO



FUNCTIONAL ASSAYS PERFORMED

- ***Null POPDC1 mice: described***
- ***Immunohistochemistry and western blot in patients' muscle***
- ***Ligand precipitation assay testing cAMP binding capac***
- ***FRET current measurement to test the effect on cAM***
- ***HL cells transfection with POPDC1^{S201F} and patch-clan polarization measurement***
- ***Xenopus Oocytes POPDC1-TREK-1 interaction studies***
- ***Zebrafish morphant for POPDC1 silencing***
- ***Zebrafish TALEN gene editing with POPDC1^{S201F}***

New type of LGMD: LGMD2X

The Journal of Clinical Investigation

RESEARCH ARTICLE

POPDC1^{S201F} causes muscular dystrophy and arrhythmia by affecting protein trafficking

Roland F.R. Schindler,[1] Chiara Scotton,[2] Jianguo Zhang,[3] Chiara Passarelli,[2,4] Beatriz Ortiz-Bonnin,[5] Subreena Simrick,[1] Thorsten Schwerte,[6] Kar-Lai Poon,[1] Mingyan Fang,[3,7] Susanne Rinné,[5] Alexander Froese,[8] Viacheslav O. Nikolaev,[8,9] Christiane Grunert,[1] Thomas Müller,[10] Giorgio Tasca,[4] Padmini Sarathchandra,[1] Fabrizio Drago,[4] Bruno Dallapiccola,[4] Claudio Rapezzi,[11] Eloisa Arbustini,[12] Francesca Romana Di Raimo,[2] Marcella Neri,[2] Rita Selvatici,[2] Francesca Gualandi,[2] Fabiana Fattori,[4] Antonello Pietrangelo,[13] Wenyan Li,[3] Hui Jiang,[3] Xun Xu,[3] Enrico Bertini,[4] Niels Decher,[5] Jun Wang,[3,14,15] Thomas Brand,[1] and Alessandra Ferlini[2,16]

CASE (D)

A NEW GENE CAUSING A NEW PHENOTYPE

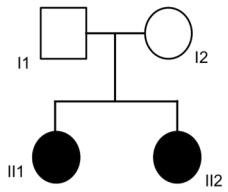
Misato 1 (MSTO1)

OMIM# 617675
MYOPATHY, MITOCHONDRIAL, AND ATAXIA; MMYAT

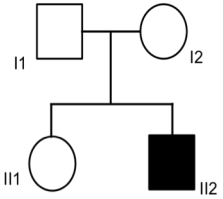
Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
1q22	Myopathy, mitochondrial, and ataxia	617675	AD, AR	3	MSTO1	617619

CLINICIANS
Prof E. Mercuri
Prof.ssa Donati

Family A (Italy)

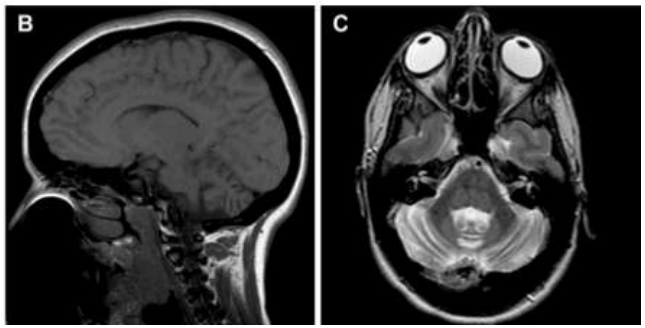


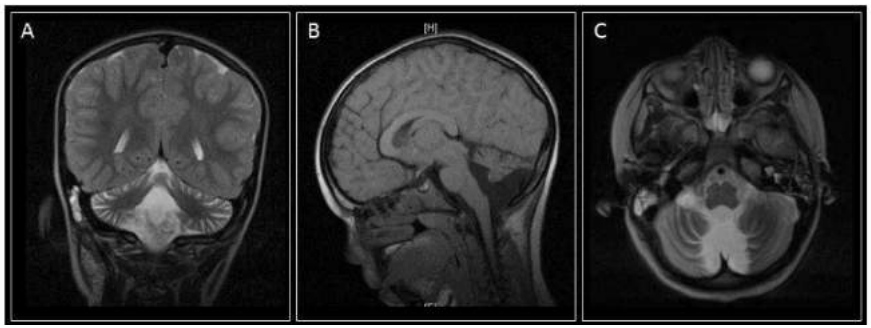
Family B (UK)
Clinician Prof Muntoni



MAIN CLINICAL FEATURES

- congenital MYOPATHY
-growth and motor delay
-cerebellar hypotrophy and ATAXIA
- mental retardation
-SCOLIOSIS
-dystrophic features on muscle biopsy and high CK

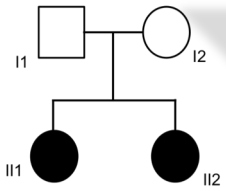




Brain MRI (hypotrophy of cerebellar vermis, enlarged cisterna magna, hyperintense signals in periventricular white matter.

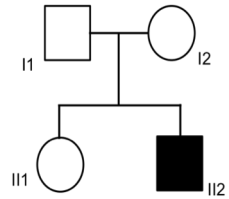
NOVEL GENE AND NOVEL PHENOTYPE DISCOVERY THE MSTO GENE OMIM 617619

Family A (Italy)

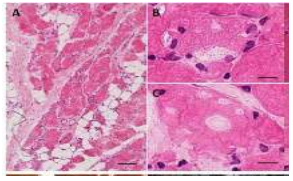


R345C/F376L VARIANTS
HIGH INTER-SPECIES CONSERVATION
NOT REPORTED IN ALL GENOMIC VARIANTS DATABASES

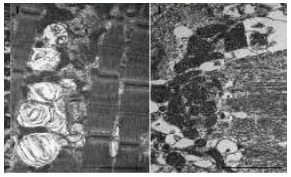
Family B (UK)



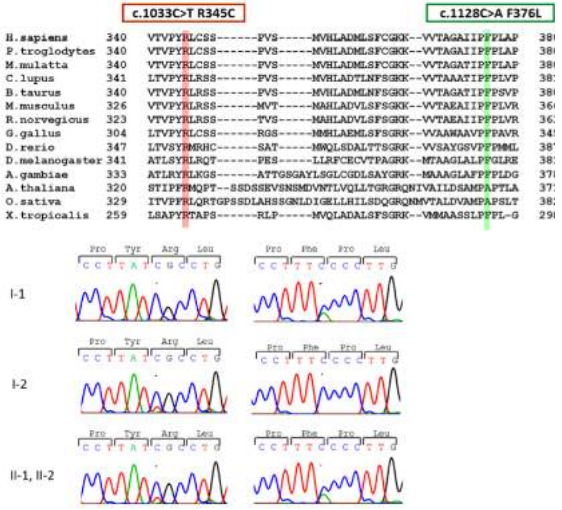
T324I/c.996+1G>A VARIANTS
HIGH INTER-SPECIES CONSERVATION
NOT REPORTED IN ALL GENOMIC VARIANTS DATABASES



MUSCLE BIOPSY
showing dystrophic changes ,patchy fatty infiltrat ion fibrosis, increased variation in fibre size, empt y vacuoles



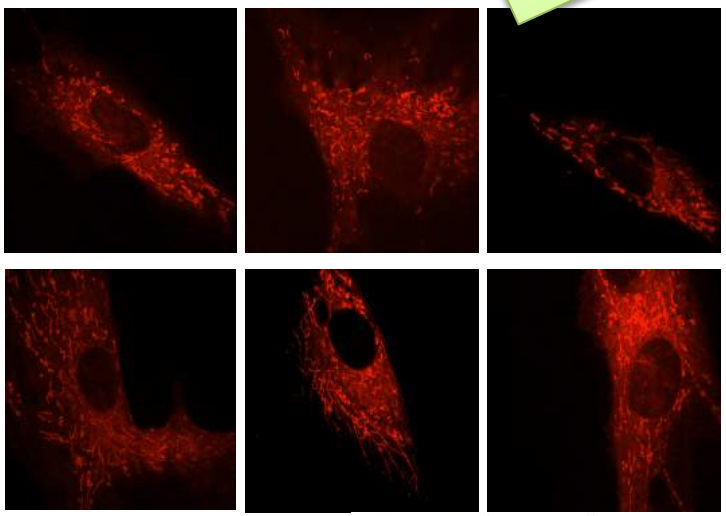
Ultrastructural examination :
AGGREGATES OF MITOCHONDRIA with vacuolar degeneration



MSTO1 GENE IS A NEW GENE DISEASE CAUSING A NOVEL PHENOTYPE with MULTISYSTEMIC DISEASE DUE TO ABNORMAL MITOCHONDRIAL NETOWRK

NEW GENE,
NEW DISEASE
MMYAT

MISATO (MSTO) gene
DROSOPHILA MELANOGASTER homologous region
GTPase family
ubiquitously distributed
Localized in mitochondria



patients

CTRL

MITOCHONDRIAL MORPHOLOGY (obtained with MitoTracker red):

FILAMENTOUS mitochondrial network of fibroblasts from a control (CT)
FRAGMENTED network in patients' cells, (family A) grown in glucose medium

Received: 16 November 2016 | Revised: 10 May 2017 | Accepted: 12 May 2017
DOI: 10.1002/humu.23262

BRIEF REPORT

WILEY HGVS

Recessive mutations in *MSTO1* cause mitochondrial dynamics impairment, leading to myopathy and ataxia

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UNIFE OVERVIEW OF GENE/PHENOTYPE DISCOVERY STUDIES by WHOLE SEQUENCING (exome or genome)

RARER

PROJECT
Next-generation sequencing and gene therapy to diagnose and cure rare diseases in Regione Emilia Romagna (RER)

N=18

NeurOmics

PROJECT
An Integrated European-Omics research project for the diagnosis and therapy in rare neuromuscular and neurodegenerative diseases

N=12

Undiagnosed Diseases Network INTERNATIONAL

N=1

(Francesco Brancati L'Aquila, Italy)

•SUMMARY OF RESULTS, WES OR WGS ANALYSIS

- CASE A (KNOWN PHENO-KNOWN GENE) **N= 7**
- CASE B (NEW PHENO-KNOWN GENE) **N=4**
- CASE C (NEW GENE-KNOWN PHENO) **N=2**
- CASE D (NEW GENE-NEW PHENO) **N=4 NEW DISEASE**
- CASE E DIGENIC INHERITANCE **N=2**

TOTAL SOLVED 19 (59%)

STILL UNSOLVED 12 (41%)

SolveRD

NEW EU H2020 PROJECT: Solving the unsolved

REFLECTIONS

-extensively exploring **all mutation types in known genes**, reaching accuracy close to 95%, as for a diagnostic test

-we need implementation for **CNVs** identification

-designing **exhaustive strategies to identify new genes (functional studies)**

AVENUES

-Family analysis
-patients cohorts with very homogenous phenotype grouped and studies
-others?

Challenges

ChiP Sequencing for detecting epigenetic causes
RNA sequencing (appropriate source of RNA)
Digenic inheritance or modifiers

Università di Ferrara
fondata nel 1391

Azienda Ospedaliero-Universitaria S'Anna - Ferrara

Rete dei Servizi di Genetica Medica

European Reference Network
for rare or low prevalence complex diseases
Network
Neuromuscular Diseases (ERN EURO-NMD)
Member
AOU di Ferrara — Italia

Euro-NMD ERN
GENETIC TASK Chair

RARER

NeurOmics

SolveRD

Undiagnosed Diseases Network INTERNATIONAL

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