Pathologie de la dynamique mitochondriale

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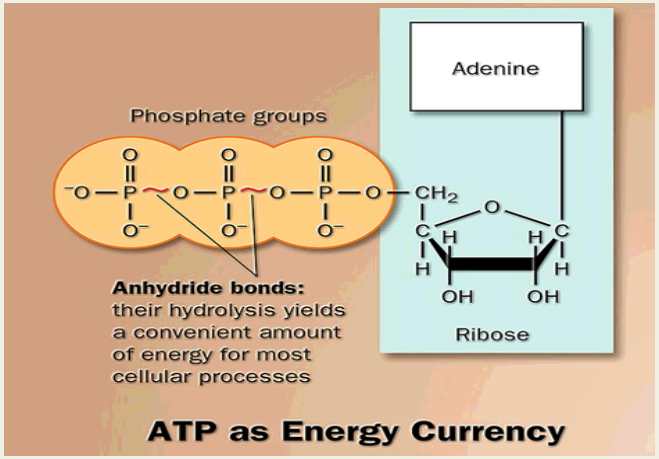
université angers

mitolab

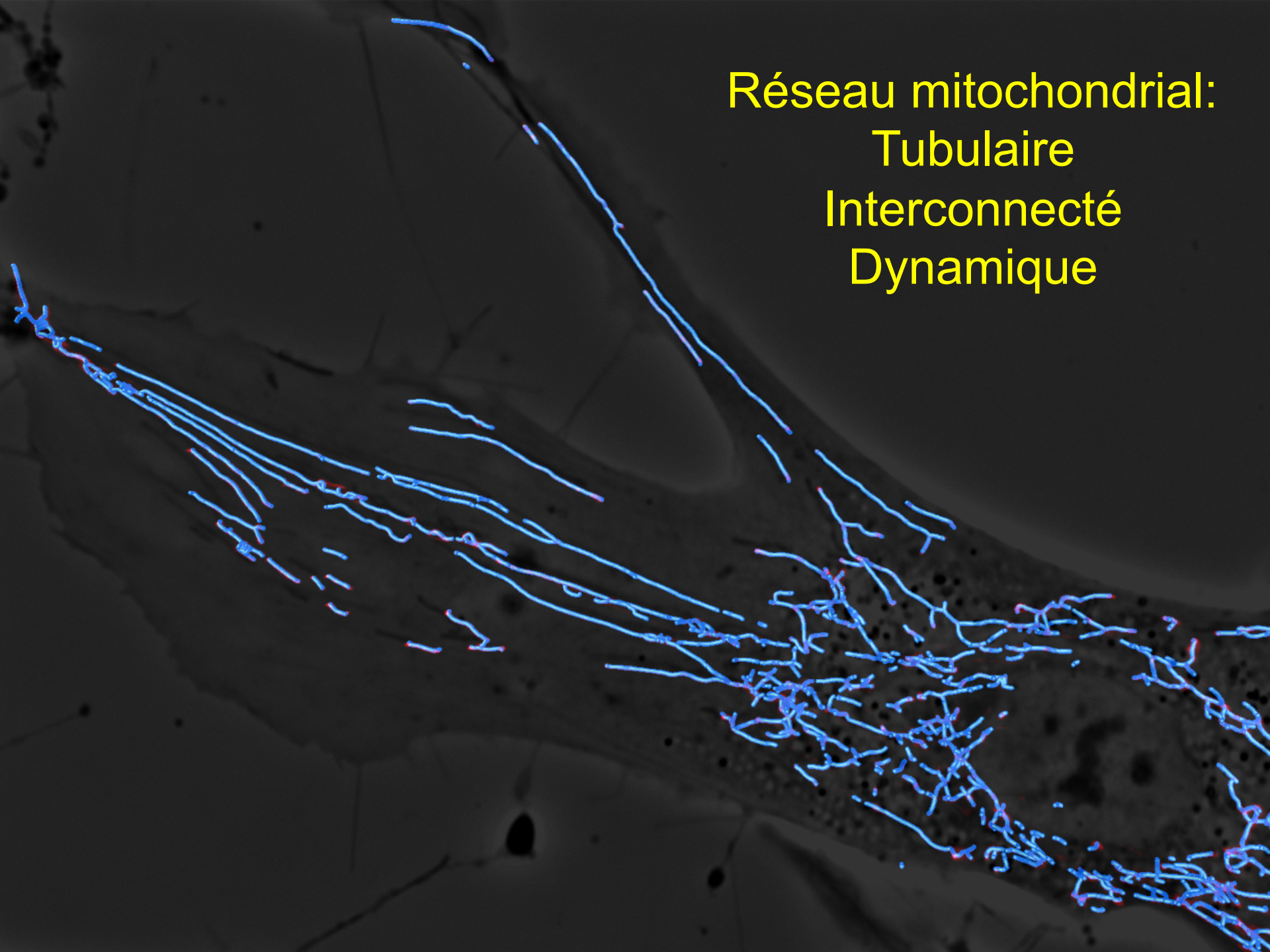
CHU ANGERS CENTRE HOSPITALIER UNIVERSITAIRE

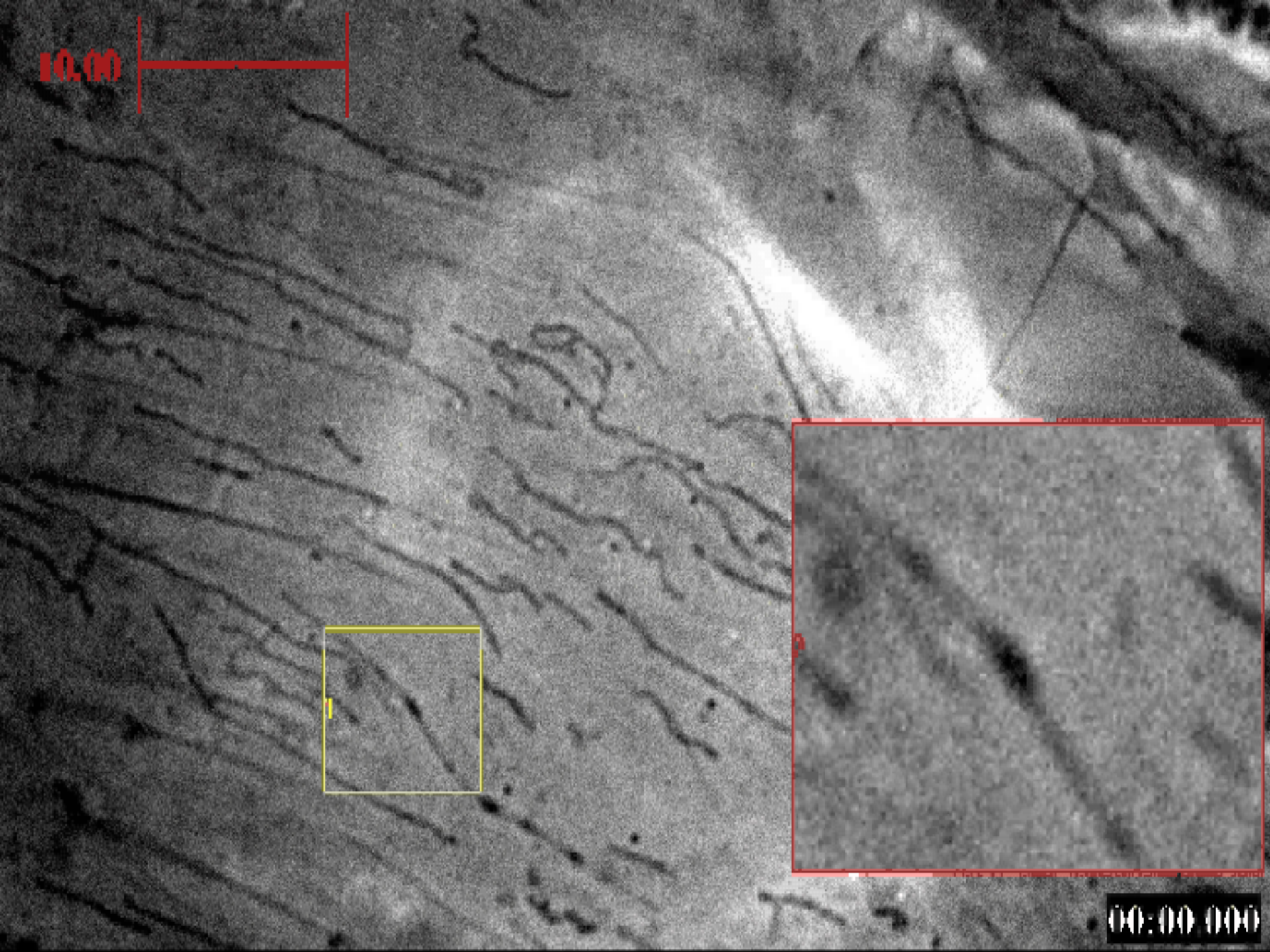
Dynamique mitochondriale: FUSION – FISSION – MOBILITE

Dans nos cellules, c'est la centrale énergétique qui se déplace !



Ex: Axones et Synapses


Réseau mitochondrial:
Tubulaire
Interconnecté
Dynamique


100.00
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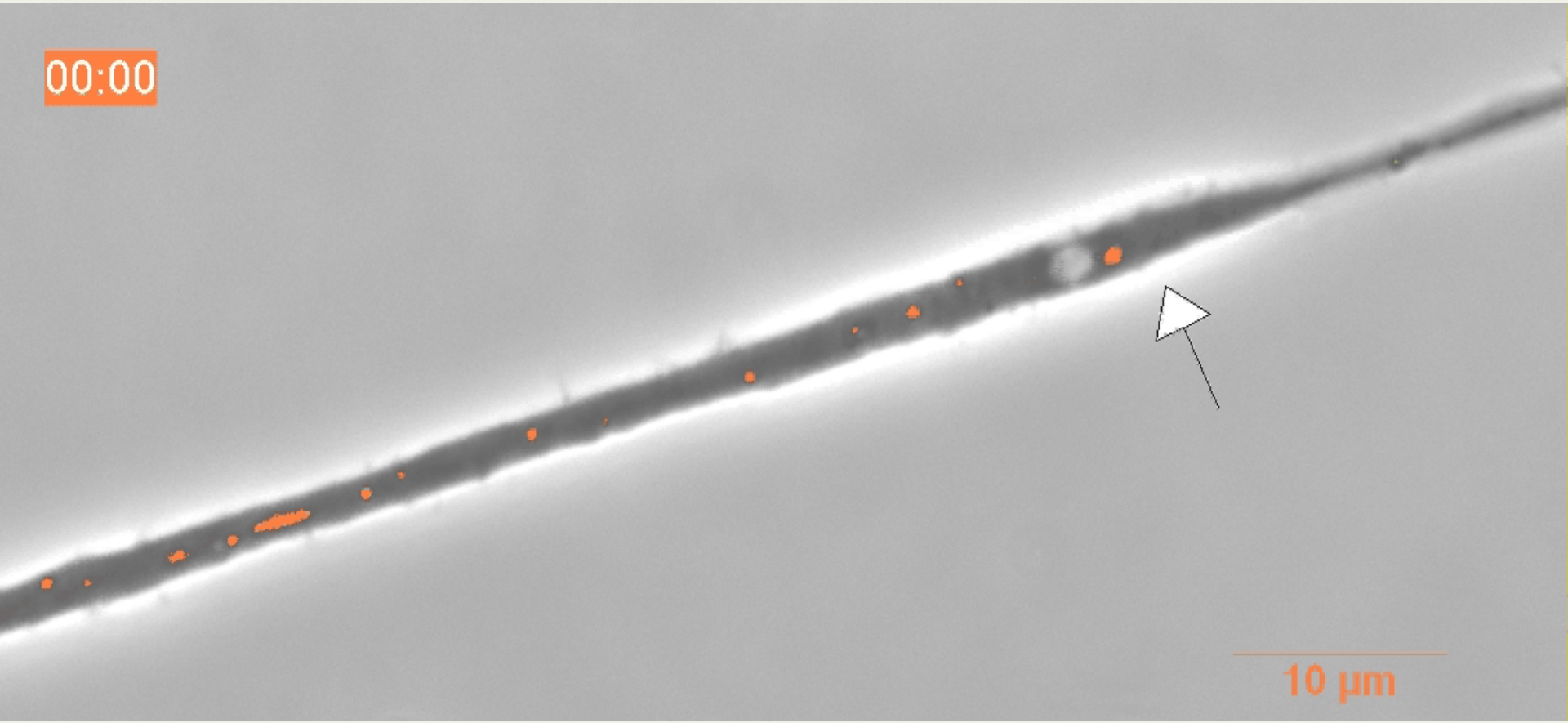
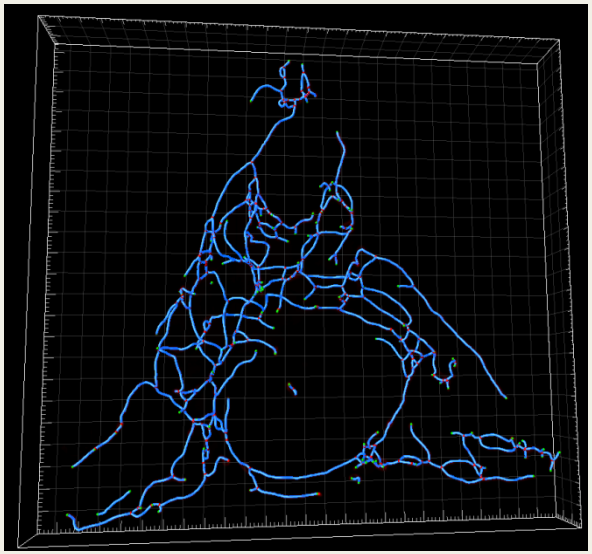
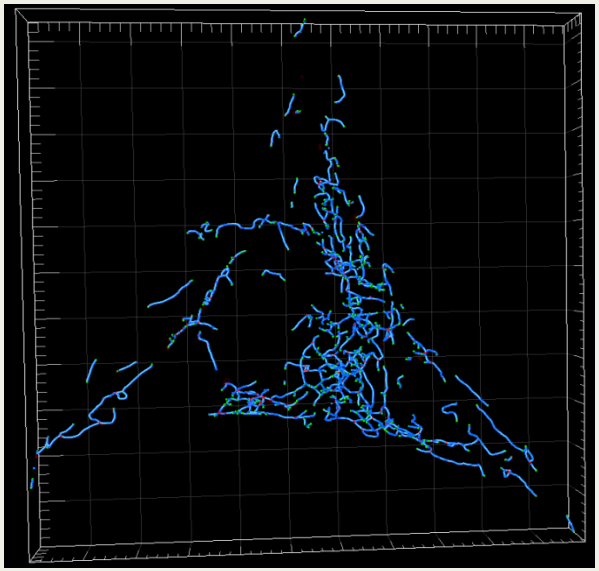
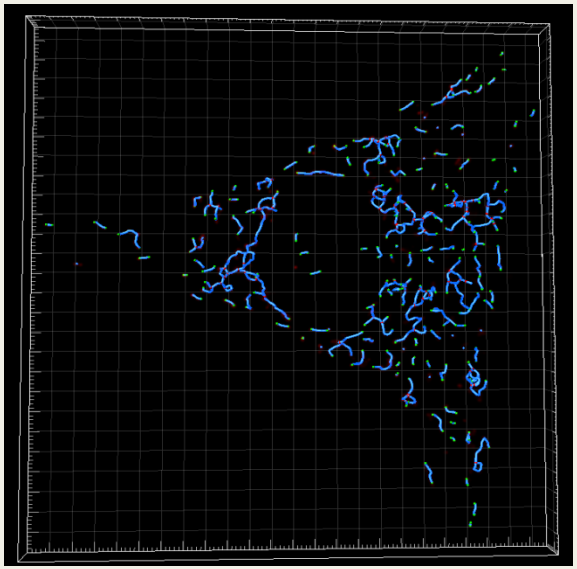
Transport axonal

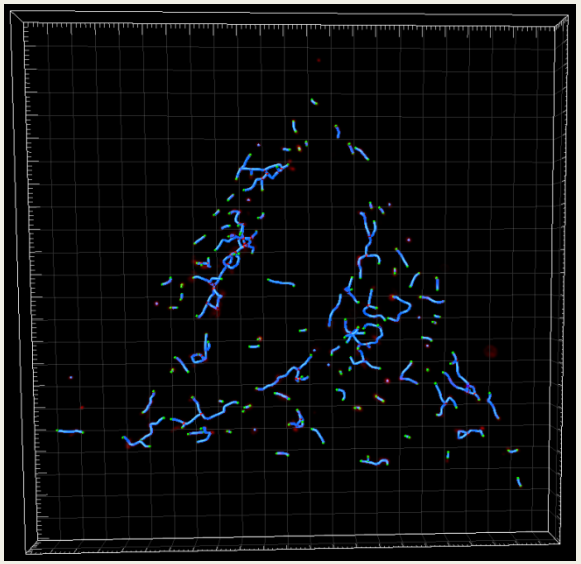


Varie selon l'état métabolique cellulaire et en réponse au stress

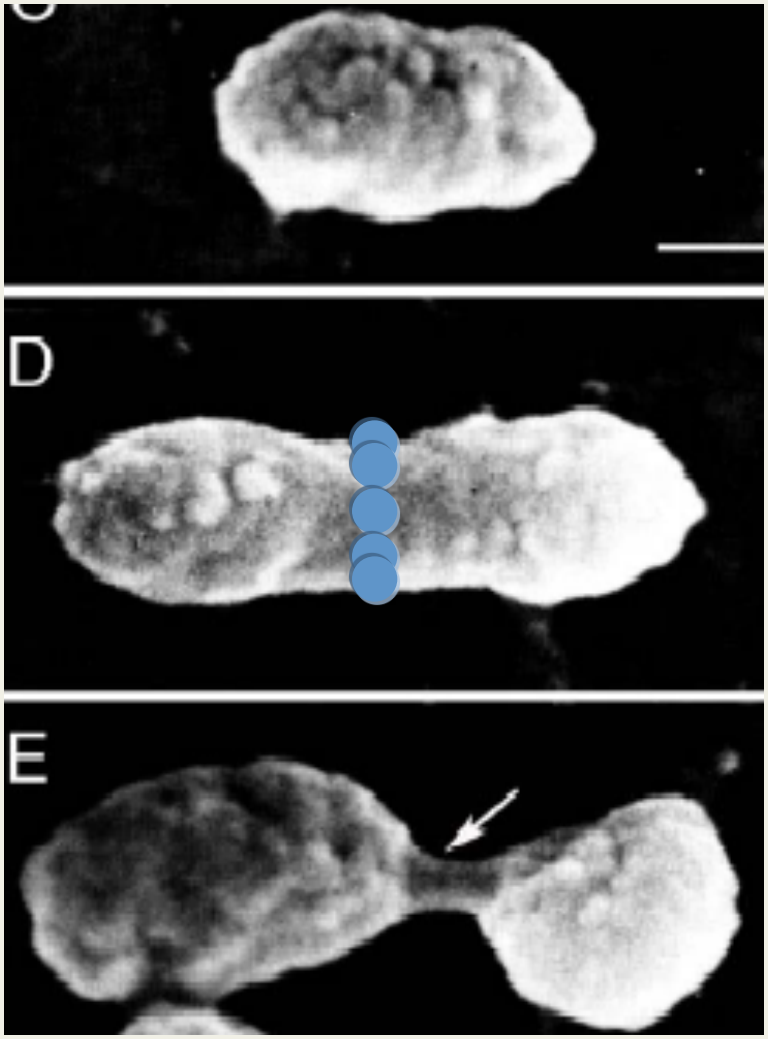




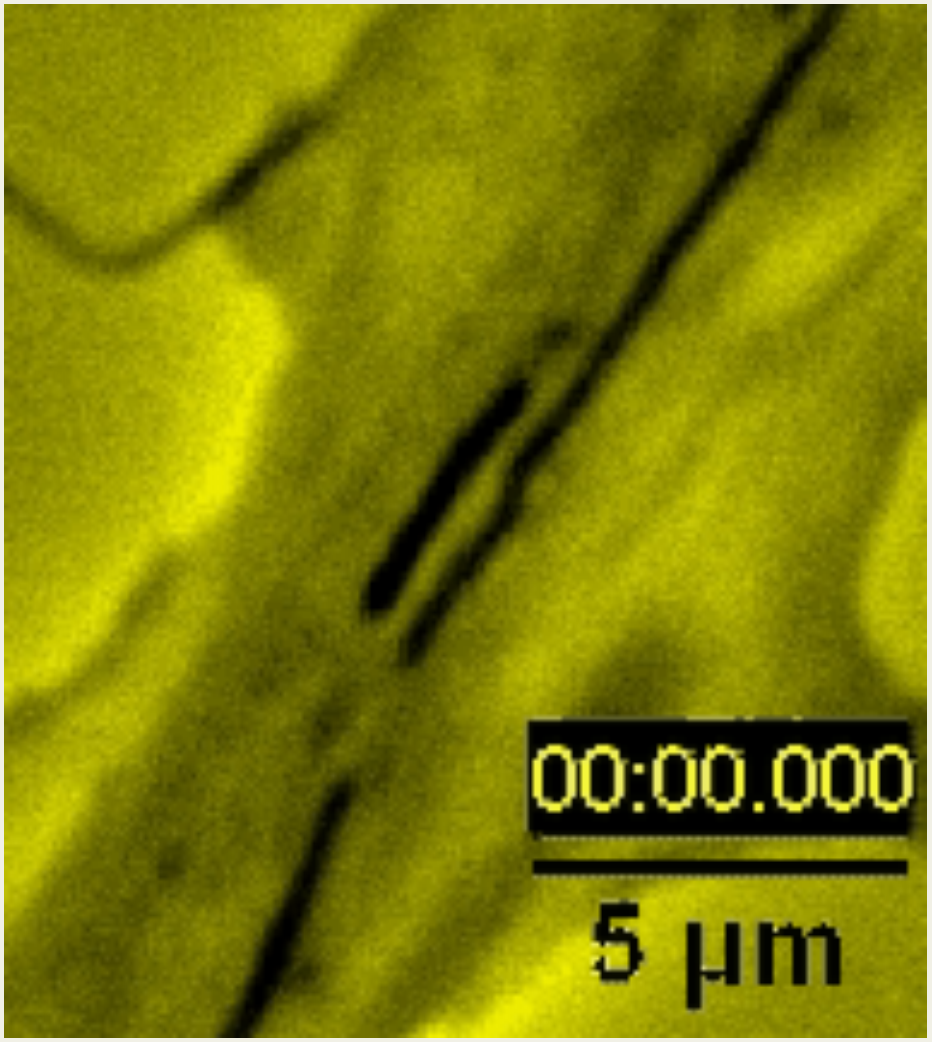




Plasticité mitochondriale ← Équilibre
forces antagonistes de fusion et de fission

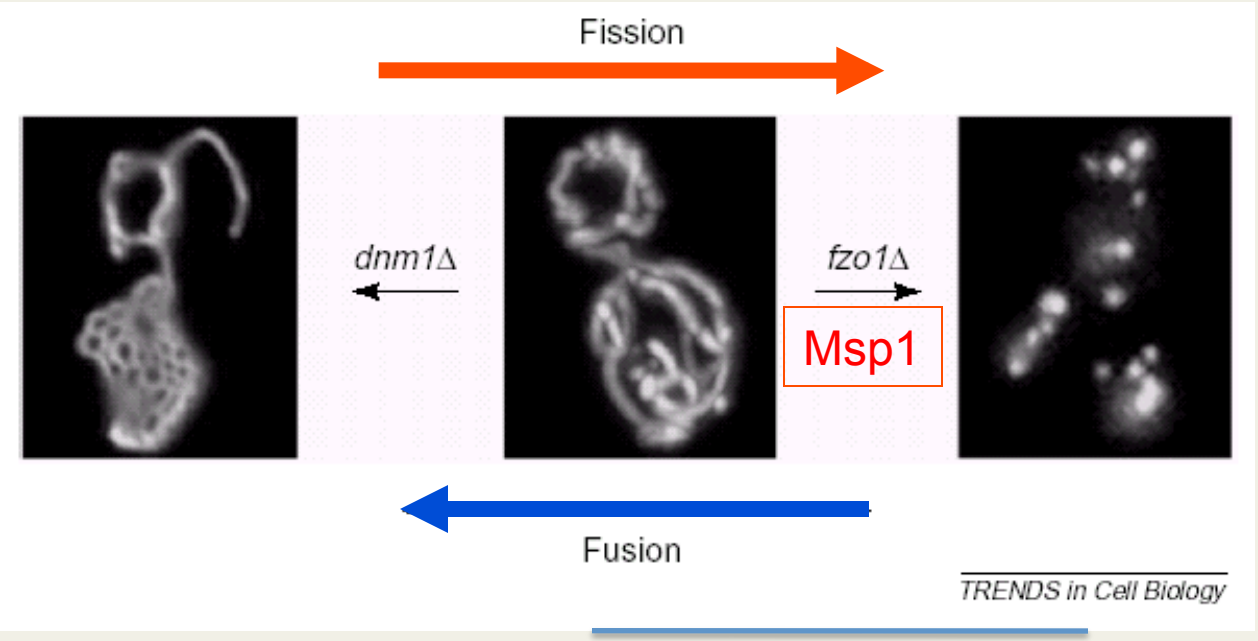


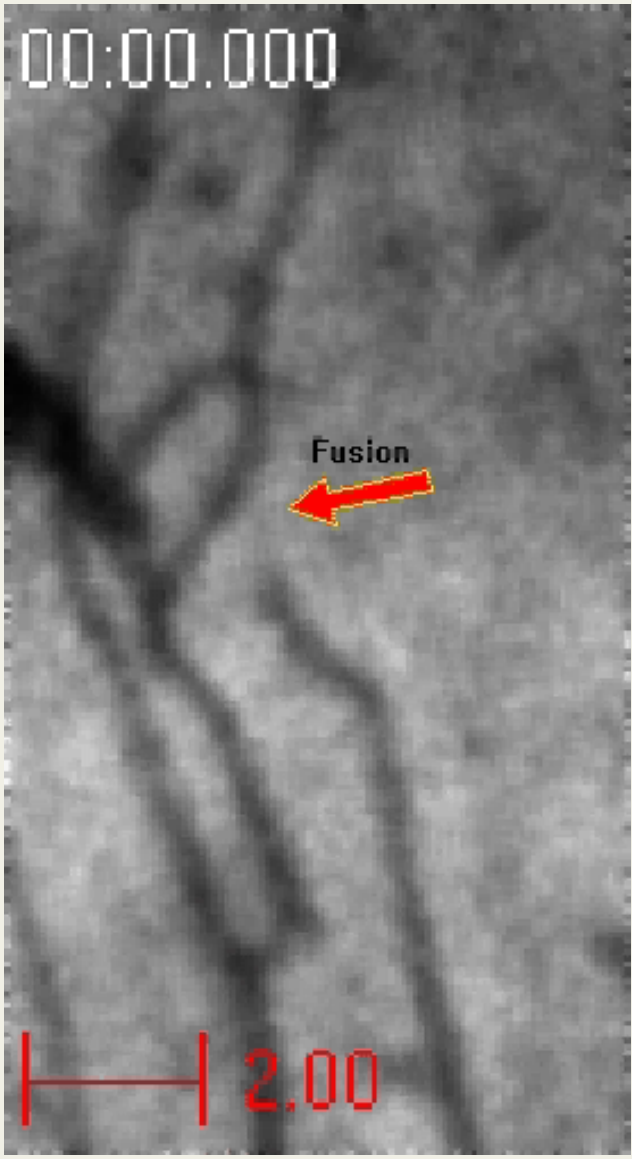
Fission



Fusion

Années 90: Identification des mutants de levure





2000:
Première description d'une pathologie de la dynamique mitochondriale

Msp1 = OPA1 (OPtic Atrophy1)
Atrophie Optique Dominante

letter

Nuclear gene *OPA1*, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy

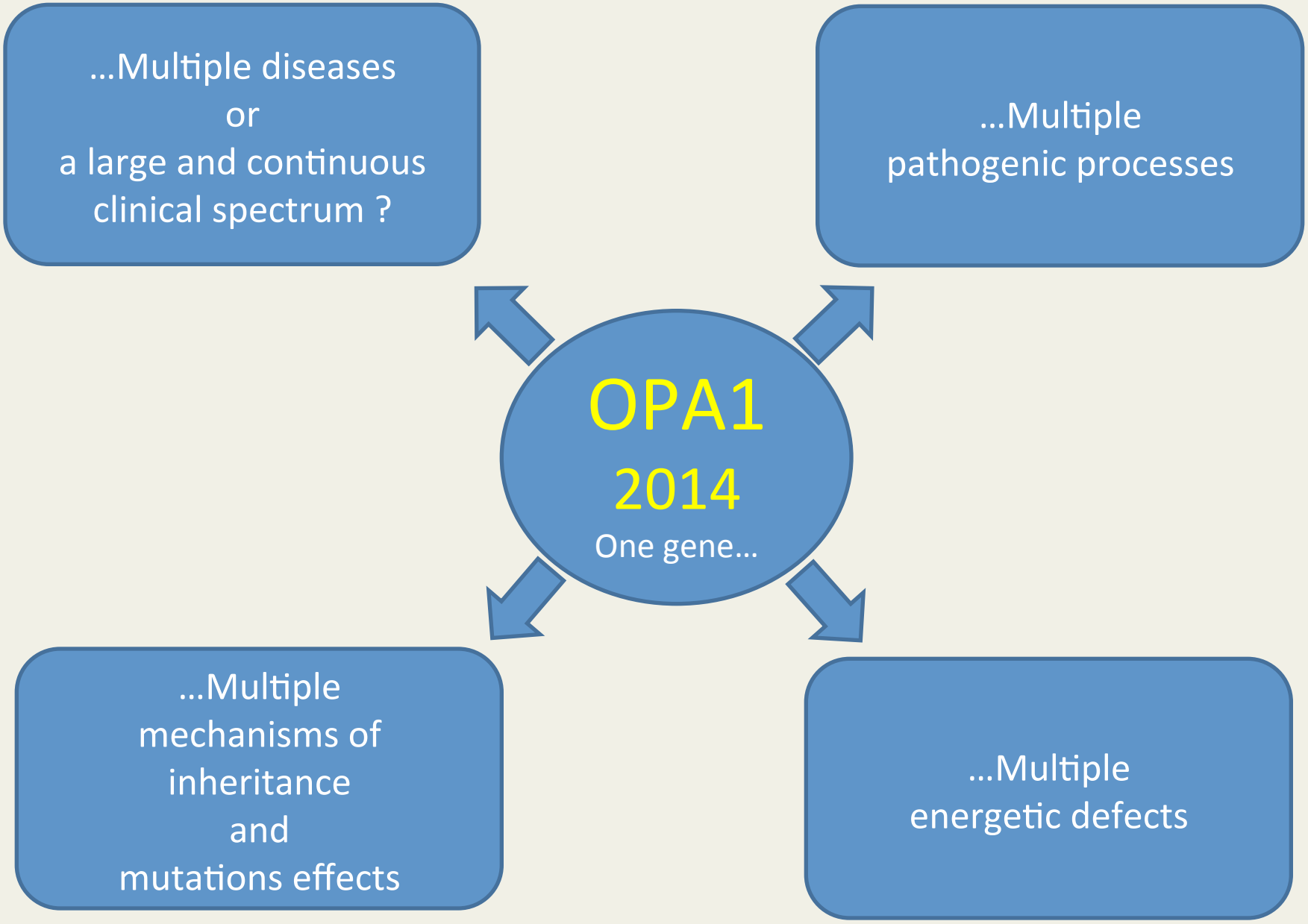
Cécile Delettre[1]*, Guy Lenaers[2]*, Jean-Michel Griffoin[1], Nadine Gigarel[3], Corinne Lorenzo[2], Pascale Belenguer[2], Laetitia Pelloquin[2], Josiane Grosgeorge[4], Claude Turc-Carel[4], Eric Perret[5], Catherine Astarie-Dequeker[6], Laetitia Lasquellec[7], Bernard Arnaud[7], Bernard Ducommun[2], Josseline Kaplan[3] & Christian P. Hamel[1,7]

*These authors contributed equally to this work.

letter

OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28

Christiane Alexander[1,2], Marcela Votruba[1,3], Ulrike E.A. Pesch[2], Dawn L. Thiselton[1], Simone Mayer[2], Anthony Moore[3,4], Miguel Rodriguez[5], Ulrich Kellner[6], Beate Leo-Kottler[7], Georg Auburger[8], Shomi S. Bhattacharya[1] & Bernd Wissinger[2]


…Multiple diseases
or
a large and continuous clinical spectrum ?
…Multiple pathogenic processes
OPA1
2014
One gene…
…Multiple mechanisms of inheritance
and
mutations effects
…Multiple energetic defects

OPA1

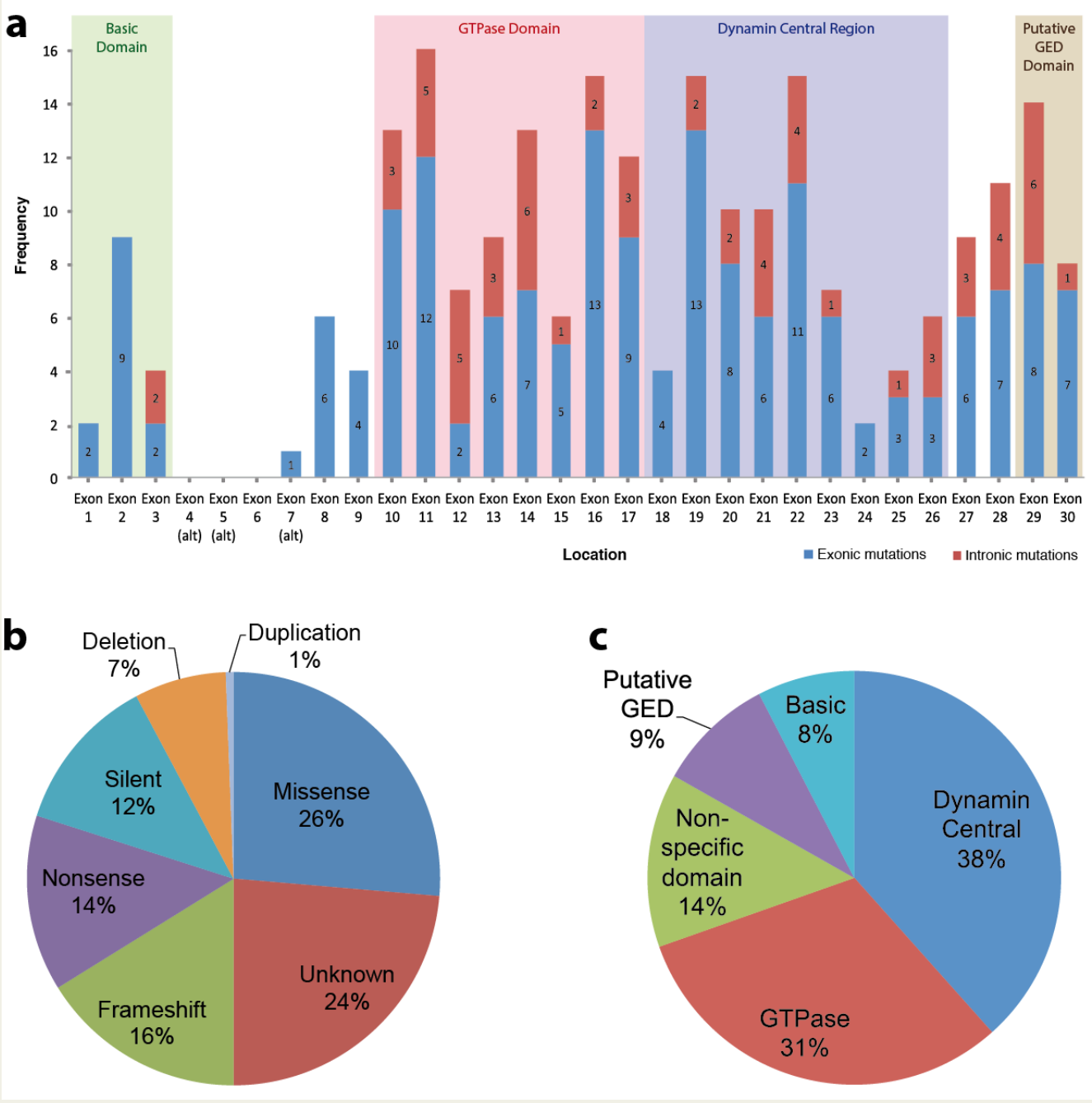
One gene…

30 exons (3q28-29)

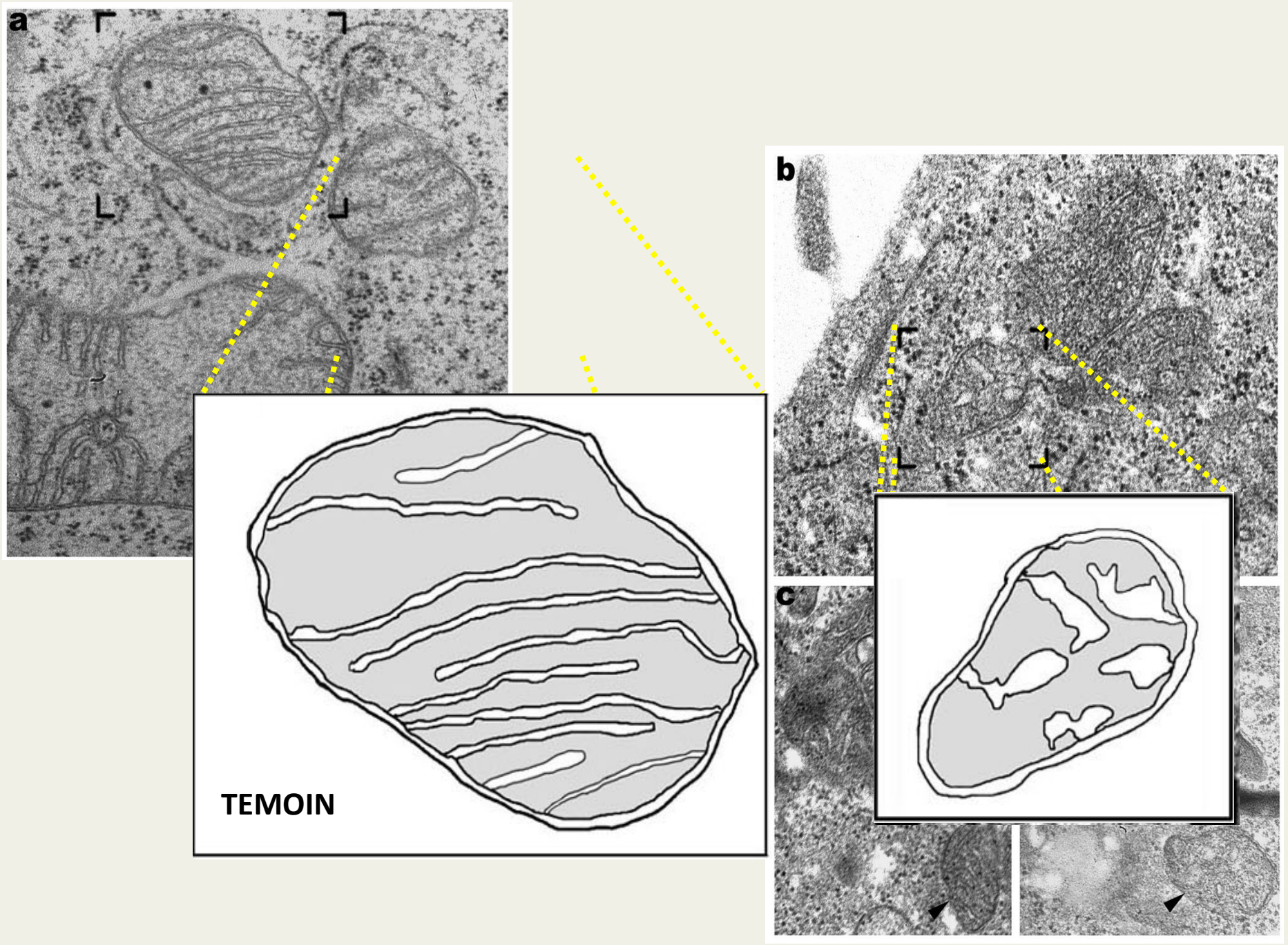
8 protein isoforms

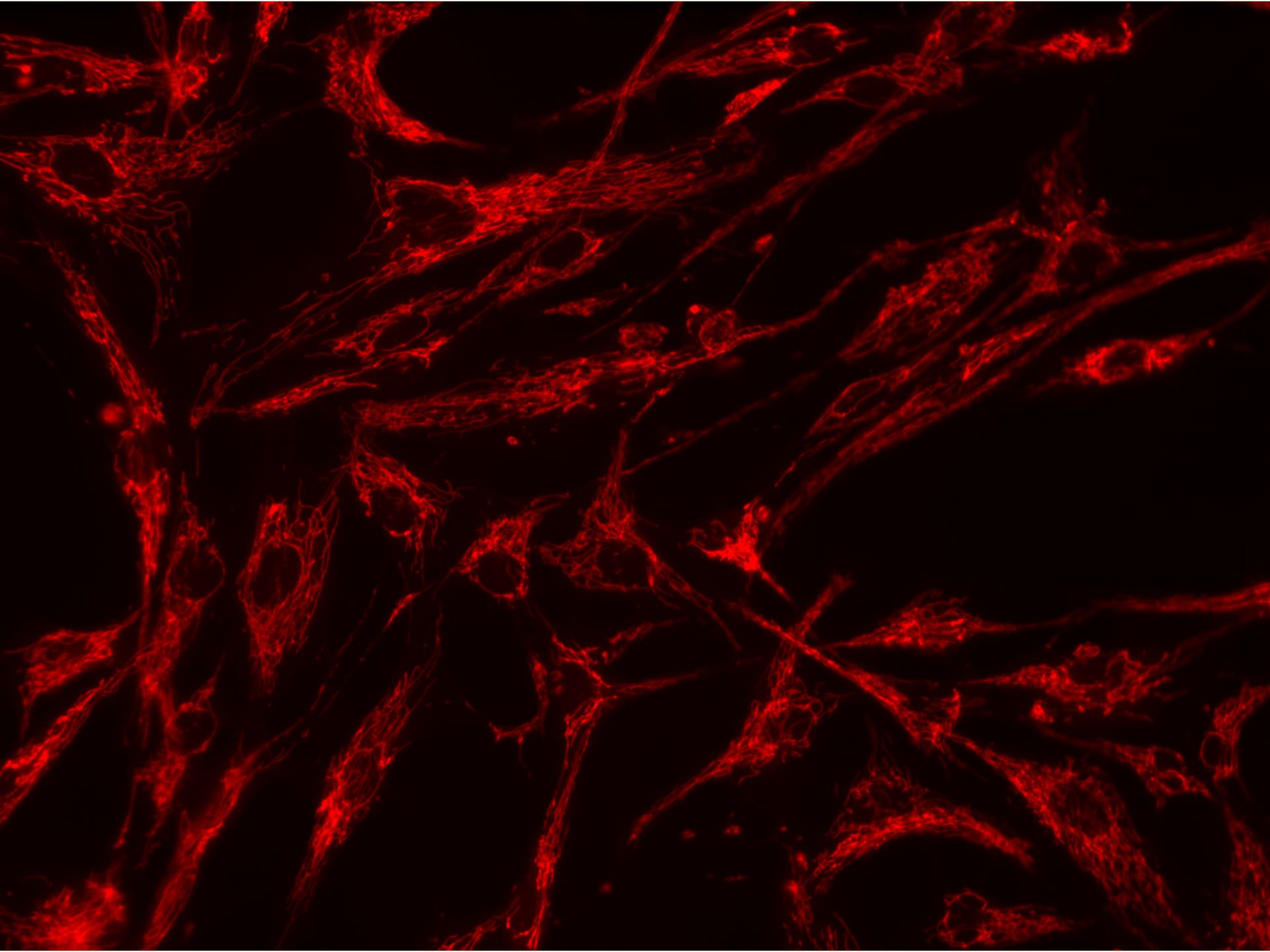
MIM processing

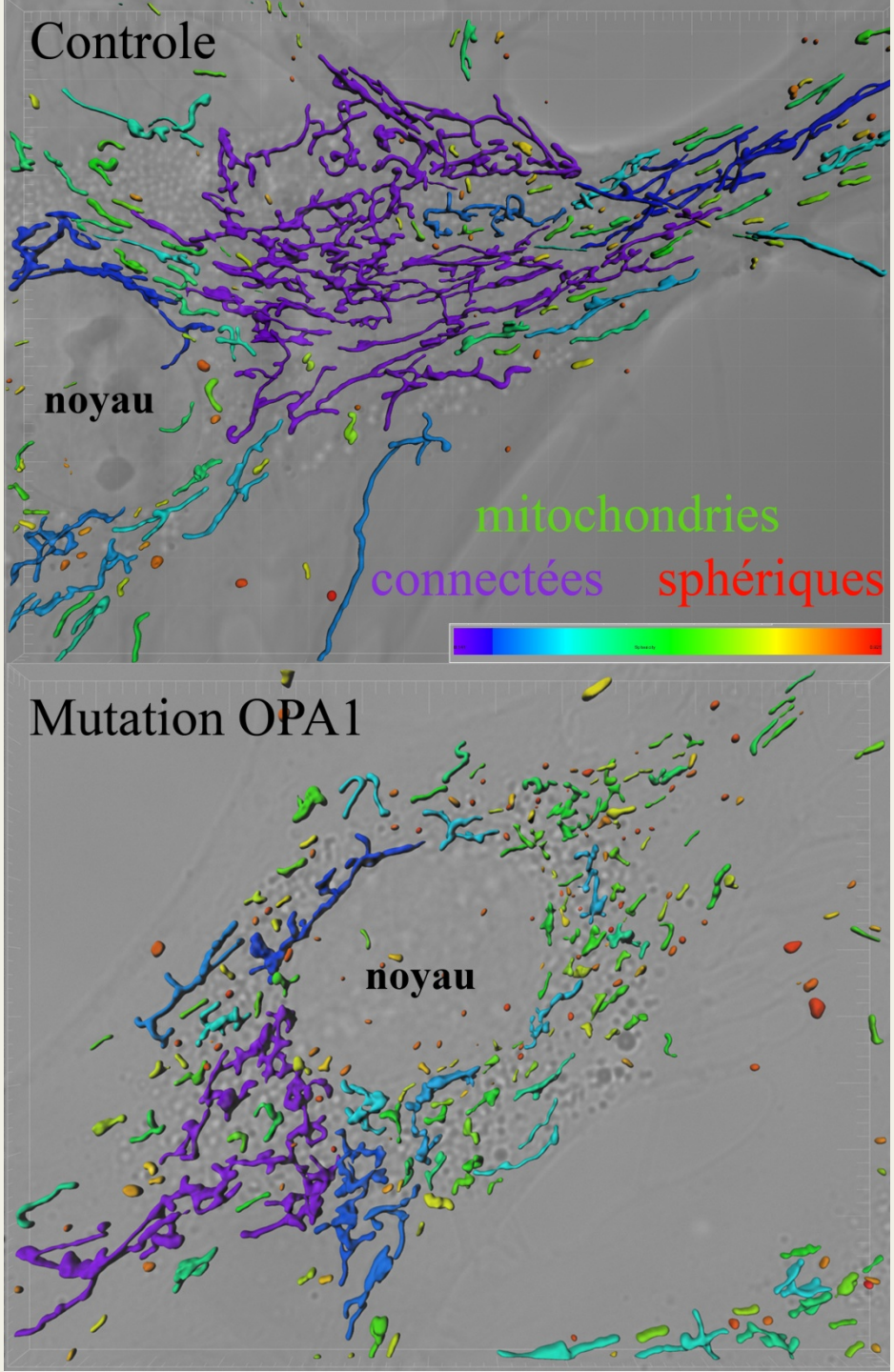
2014: **241** pathogenic variants



Database eOPA1 : Ferré et al Hum Mutat, 2005, 2009, 2014

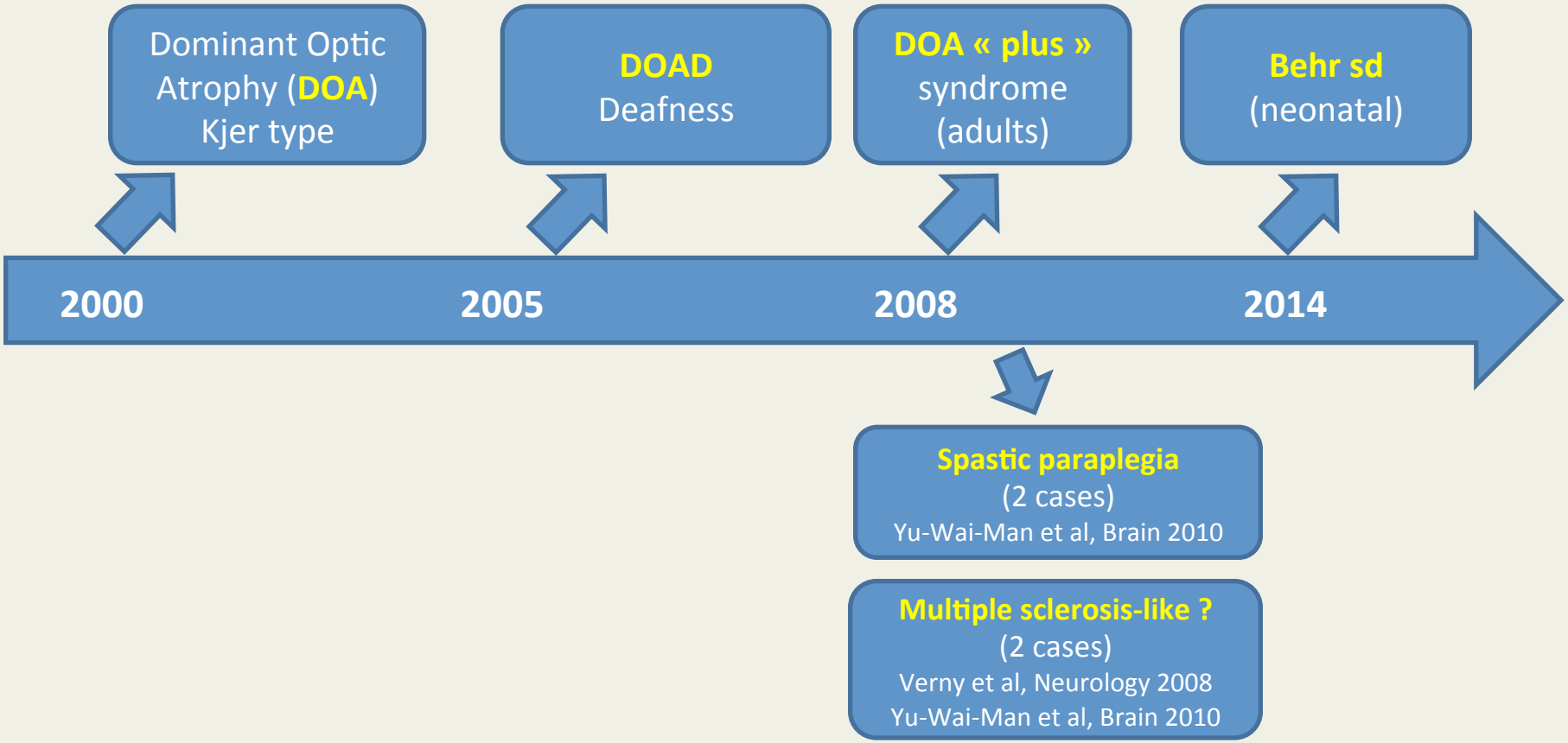

a
b
c
TEMOIN




Controle
noyau
mitochondries
connectées
sphériques
Mutation OPA1
noyau

…Multiple

diseases or a large and continuous clinical spectrum ?



DOAD, Deafness (2005)

doi:10.1093/brain/aws340 Brain 2013: 136; 1–6 | e236

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Sensorineural hearing loss in *OPA1*-linked disorders

Stéphanie Leruez,[1] Dan Milea,[1,2,3,4,5] Sabine Defoort-Dhellemmes,[6] Estelle Colin,[4,7] Martine Crochet,[6] Vincent Procaccio,[2,3,4,7] Marc Ferré,[2,3,4,7] Julie Lamblin,[8] Valérie Drouin,[9] Catherine Vincent-Delorme,[10] Guy Lenaers,[11] Christian Hamel,[11] Catherine Blanchet,[12] Gitte Juul,[5,12] Michael Larsen,[5,12] Christophe Verny,[2,3,4,14] Pascal Reynier,[2,3,4,7] Patrizia Amati-Bonneau[2,3,4,7] and Dominique Bonneau[2,3,4,7]

6,4% OPA1 patients with hearing impairment (21/327)

→ Due to Auditory neuropathy

→ Mean age at diagnosis: 13,8 (range: 2-30)
→ Progressive
→ Mild (66%) to severe

→ hearing impairment before OA: 54%

DOA plus adults (2008)

doi:10.1093/brain/awq007 Brain 2010: Page 1 of 16 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Multi-system neurological disease is common in patients with *OPA1* mutations

P. Yu-Wai-Man,[1,2] P.G. Griffiths,[1,2] G.S. Gorman,[1] C.M. Lourenco,[3] A.F. Wright,[4] M. Auer-Grumbach,[5] A. Toscano,[6] O. Musumeci,[6] M.L. Valentino,[7] L. Caporali,[7] C. Lamperti,[8] C.M. Tallaksen,[9] P. Duffey,[10] J. Miller,[11] R.G. Whittaker,[1] M.R. Baker,[11,12] M.J. Jackson,[11] M.P. Clarke,[2] B. Dhillon,[13] B. Czermin,[14] J.D. Stewart,[1] G. Hudson,[1] P. Reynier,[15,16] D. Bonneau,[15,16] W. Marques Jr,[3] G. Lenaers,[17] R. McFarland,[1] R.W. Taylor,[1] D.M. Turnbull,[1] M. Votruba,[18,19] M. Zeviani,[8] V. Carelli,[7] L.A. Bindoff,[20,21] R. Horvath,[1,22] P. Amati-Bonneau[15,16] and P.F. Chinnery[1,23]

→ ~20% of mutation carriers

Optic atrophy
+Deafness
+Ataxia
+Myopathy
+Peripheral neuropathy
+Progressive external ophthalmoplegia (PEO)

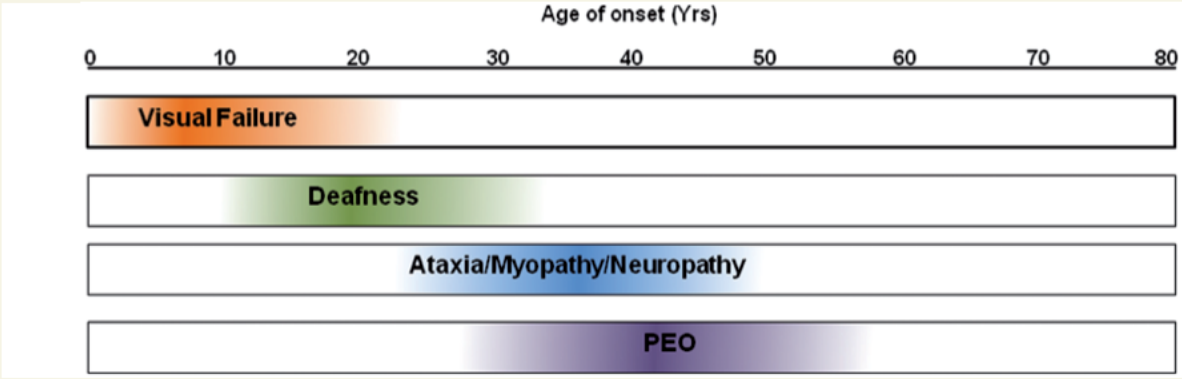


Figure 7 Evolution of the major clinical features observed in DOA+ syndromes.

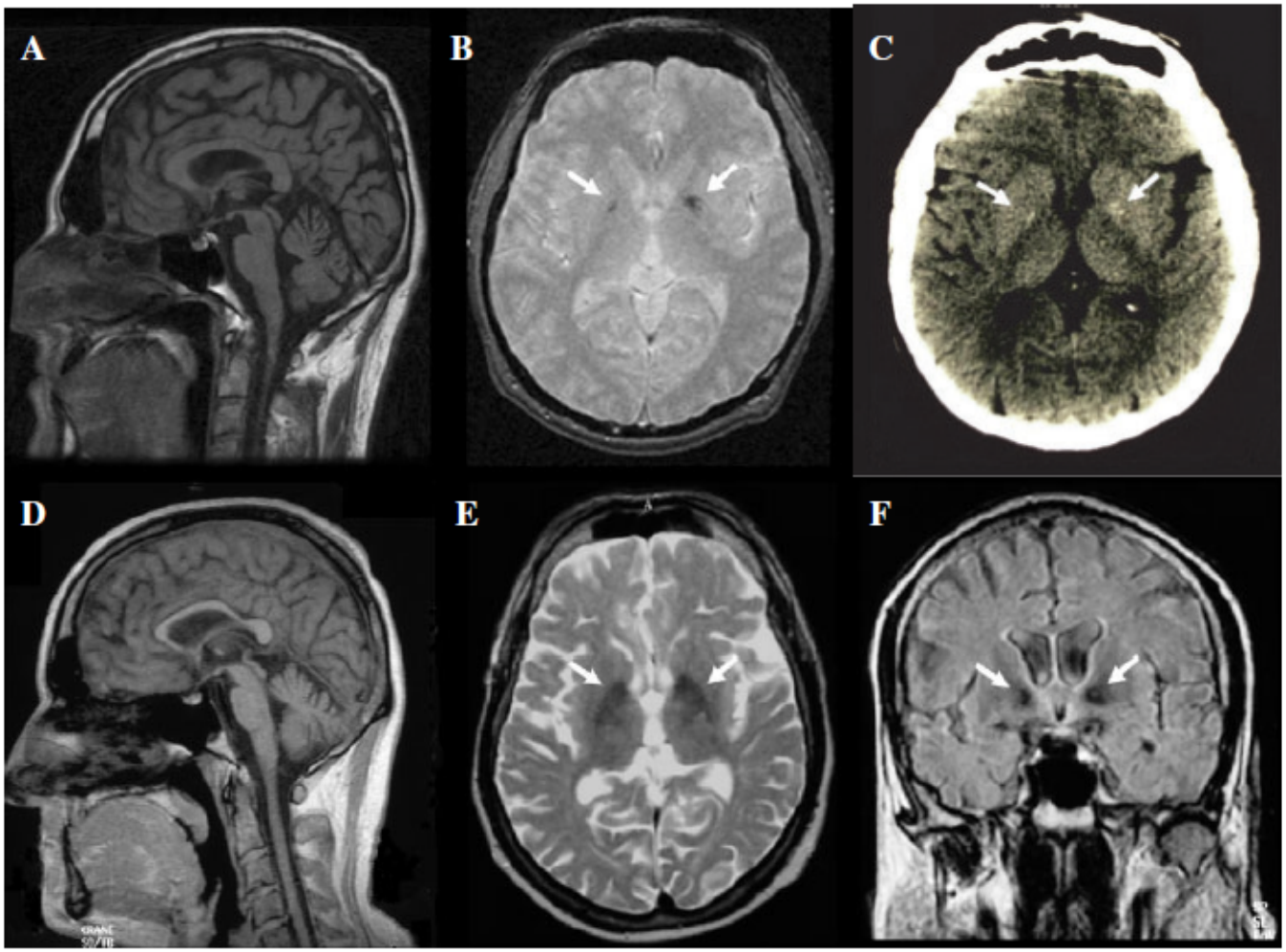


Fig. 3 Brain MRI and CT scan. (**A**), (**B**) and (**C**) refer to the proband from Family I. In panel A a mid-sagittal TI-weighted brain MRI scan shows variable degrees of atrophy affecting cerebral cortex, brainstem and cerebellum. In panel B the axial gradient echo MRI scan shows bilateral hypointensity within the globi pallidi (arrows), which is detected as depositions of calcium in the CT scan (arrows) shown in panel C. (**D**), (**E**) and (**F**) refer to the proband from Family 5. In panel D a mid-sagittal TI-weighted brain MRI scan shows a thin corpus callosum as well as brainstem and cerebellar atrophy. In panel E the axial T2-weighted scan shows bilateral hypointensity within the globi pallidi, which are also detected in the coronal scan (arrows) shown in panel F.

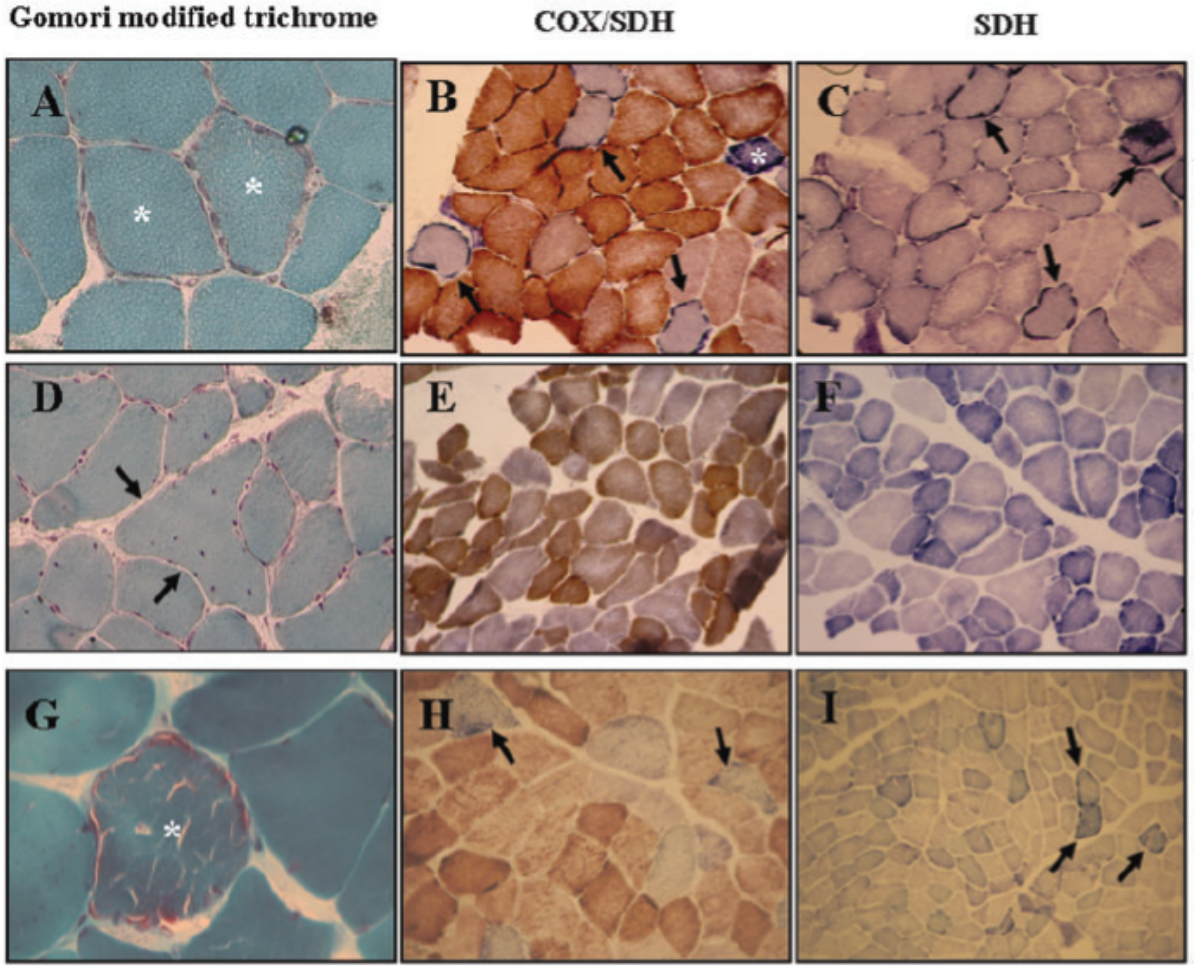


Fig. 2 Muscle histopathology (Gomori modified trichrome, COX/SDH and SDH stain). (**A**), (**B**) and (**C**) refer to the proband of Family I. In panel A two fibres displaying increased eosinofilic material with subsarcolemmal distribution, which resemble RRFs are shown (asterisks). In panel B, at the double COX/SDH stain some COX-deficient fibres are recognized by the prevalent SDH violet stain (arrows), and one hyperintense SDH fibre is also shown (asterisk). In panel C, a section serial to the previous in panel B shows numerous fibres with increased SDH stain, in particular in the subsarcolemmal region (arrows). (**D**), (**E**) and (**F**) refer to the proband of Family 2. In panel D a hypertrophic fibre is shown with numerous centralized nuclei (arrows), whereas this patient did not present RRFs. Panels E and F also show the great variability of fibre size, but no clear COX-deficient or hyperintense SDH fibres were present. However, a prevalent SDH stain was frequent in some fibres at COX/SDH double stain, as well as some parcellar increase of SDH only stain was evident in a few fibres. (**G**), (**H**) and (**I**) refer to the proband of Family 3. In panel G a typical RRFs is shown (asterisk). In panel H frequent COX-deficient fibres are seen (arrows), and in panel I increased subsarcolemmal staining of SDH is present in numerous fibres (arrows).

Behr syndrome (2014)

doi:10.1093/brain/awq306 Brain 2011: 134; 1–2 | e169

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Heterozygous *OPA1* mutations in Behr syndrome

Cecilia Marelli,[1,2,3,4] Patrizia Amati-Bonneau,[5] Pascal Reynier,[5] Valérie Layet,[6] Antoine Layet,[7] Giovanni Stevanin,[1,2,3,4] Etienne Brissaud,[8] Dominique Bonneau,[5] Alexandra Durr[1,2,3,4] and Alexis Brice[1,2,3,4]

Molecular Genetics and Metabolism 103 (2011) 383–387

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Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

ELSEVIER

Early-onset severe neuromuscular phenotype associated with compound heterozygosity for *OPA1* mutations

Christian P. Schaaf [a], Maria Blazo [b], Richard Alan Lewis [a,c], Ross E. Tonini [d], Hidehiro Takei [e], Jing Wang [a], Lee-Jun Wong [a], Fernando Scaglia [a,*]

doi:10.1093/brain/awu184 Brain 2014: Page 1 of 4 | e1

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Early-onset Behr syndrome due to compound heterozygous mutations in *OPA1*

Dominique Bonneau,[1] Estelle Colin,[1] Florine Oca,[1] Marc Ferré,[1] Arnaud Chevrollier,[1] Naïg Guéguen,[1] Valérie Desquiret-Dumas,[1] Sylvie N'Guyen,[2] Magalie Barth,[1] Xavier Zanlonghi,[3] Marlène Rio,[4] Isabelle Desguerre,[5] Christine Barnerias,[5] Marta Momtchilova,[6] Diana Rodriguez,[7] Abdelhamid Slama,[8] Guy Lenaers,[9] Vincent Procaccio,[1] Patrizia Amati-Bonneau[1] and Pascal Reynier[1]

Multiple etiologies
and patterns of inheritance

Early-onset OA
Spinocerebellar degeneration (ataxia)
Pyramidal signs
Peripheral neuropathy
Developmental delay

Distinct disorders or continuous clinical spectrum ?
3 clinical entities

DOA

Isolated OA

DOAD

OA
+Deafness

Adult DOAplus

OA
+Deafness
+Ataxia
+Peripheral neuropathy
+Myopathy
+CPEO

Neonatal Behr syndrome

OA
+Ataxia (cerebellar atrophy)
+Peripheral neuropathy
+Dysphagia, Gastrointestinal dysmobility

Clinical expression similar to « classical » mitochondrial OXPHOS disorders

The “DOA plus” phenotype is reproduced by an OPA1$^{+/-}$ mouse model

doi:10.1093/brain/aws303 Brain 2012: 135; 3599–3613 | 3599

BRAIN
A JOURNAL OF NEUROLOGY

The human *OPA1*^{delTTAG} mutation induces premature age-related systemic neurodegeneration in mouse

Emmanuelle Sarzi,[1] Claire Angebault,[2] Marie Seveno,[1] Naïg Gueguen,[2] Benjamin Chaix,[1] Guy Bielicki,[3] Nathalie Boddaert,[4] Anne-Laure Mausset-Bonnefont,[5] Chantal Cazevieille,[6] Valérie Rigau,[7] Jean-Pierre Renou,[3] Jing Wang,[1] Cécile Delettre,[1] Philippe Brabet,[1] Jean-Luc Puel,[1] Christian P. Hamel,[1] Pascal Reynier[2] and Guy Lenaers[1]

Age-related:

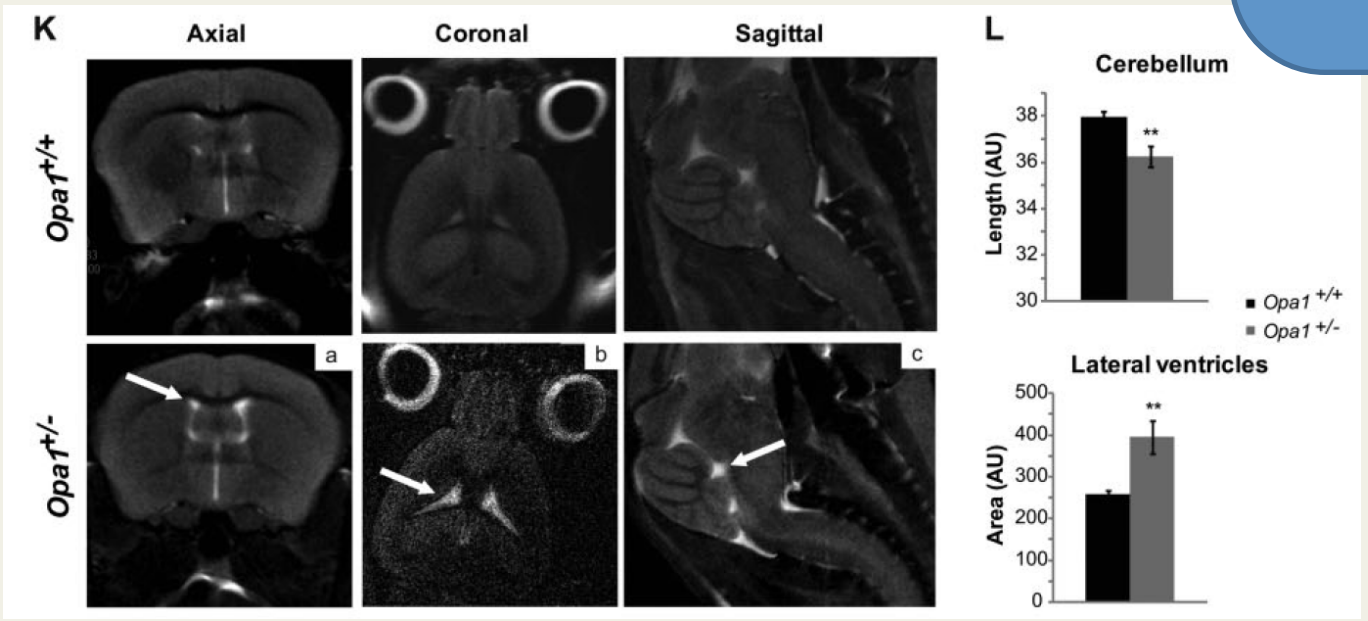
Visual failure

Deafness

Encephalopathy

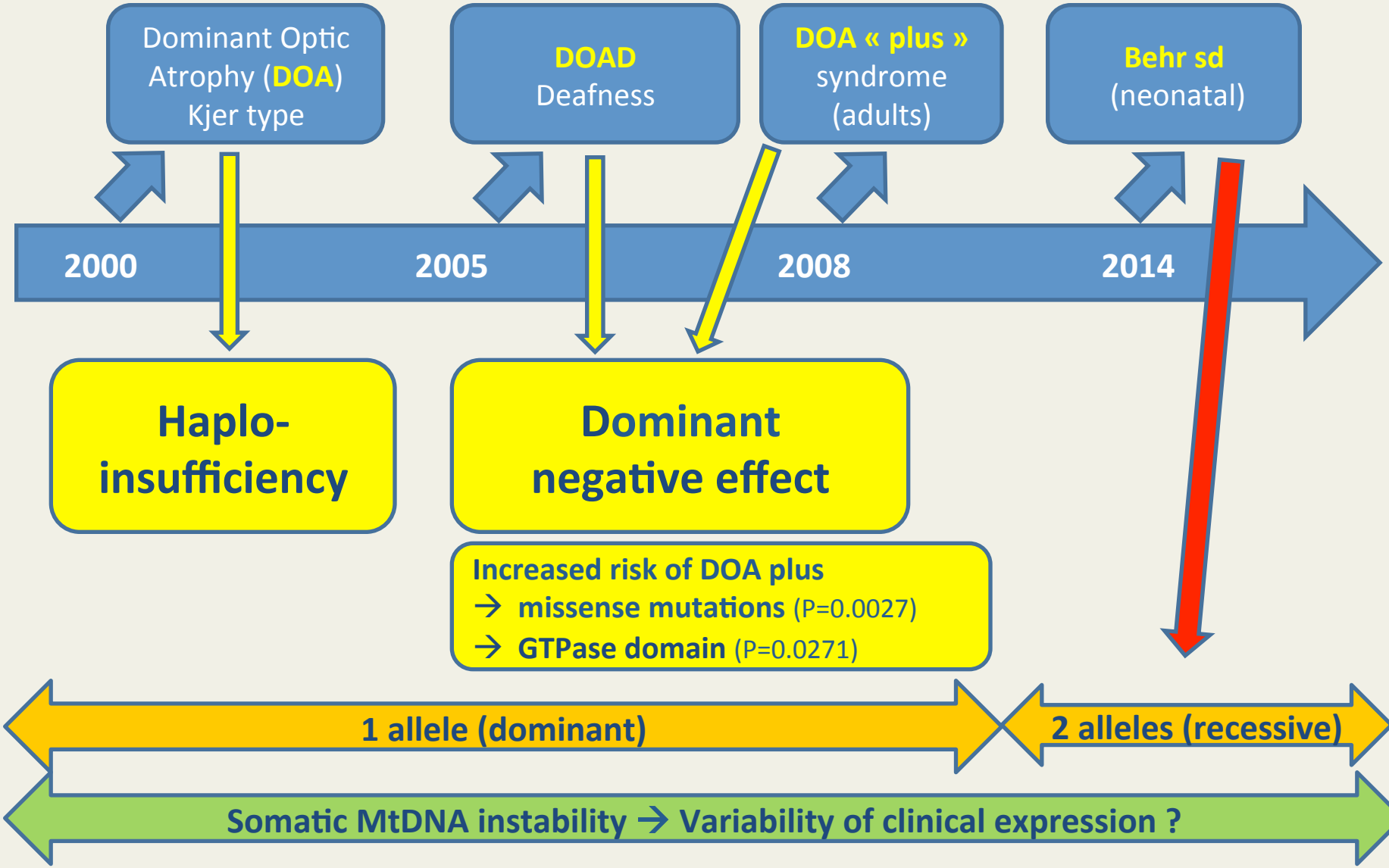
Peripheral neuropathy

Myopathy



Mouse brain MRI: cerebral and cerebellar atrophy

…Multiple mechanisms of inheritance and mutations effects

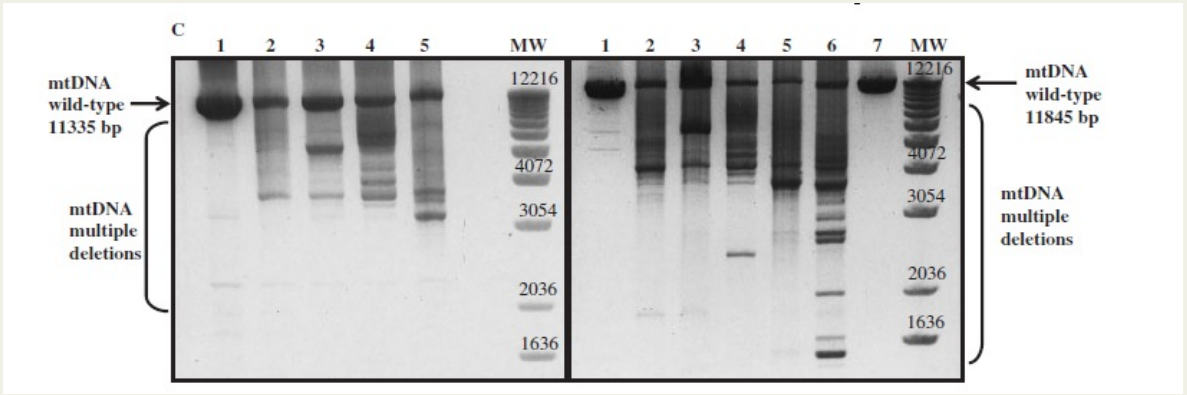


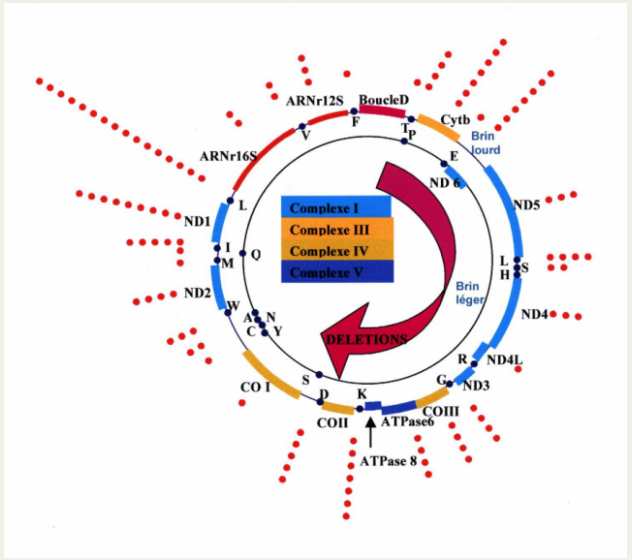
Instabilité de l'ADN mitochondrial

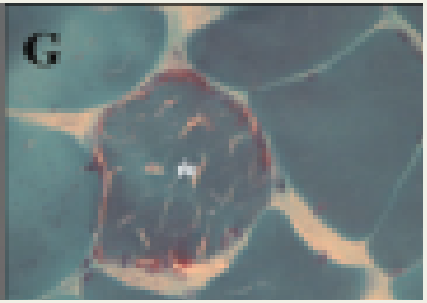
doi:10.1093/brain/awm298 *Brain* (2008), 131, 338–351

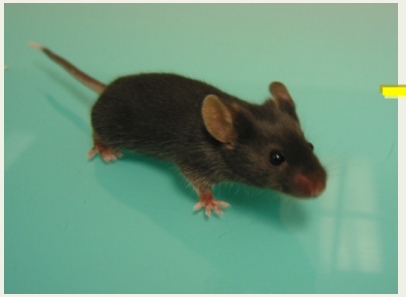
OPA1 mutations induce mitochondrial DNA instability and optic atrophy 'plus' phenotypes

Patrizia Amati-Bonneau,[1,2,*] Maria Lucia Valentino,[3,*] Pascal Reynier,[1,2] Maria Esther Gallardo,[4] Belén Bornstein,[4] Anne Boissière,[5] Yolanda Campos,[6] Henry Rivera,[6] Jesús González de la Aleja,[6] Rosanna Carroccia,[3] Luisa Iommarini,[3] Pierre Labauge,[7] Dominique Figarella-Branger,[8] Pascale Marcorelles,[9] Alain Furby,[10] Katell Beauvais,[10] Franck Letournel,[11] Rocco Liguori,[3] Chiara La Morgia,[3] Pasquale Montagna,[3] Maria Liguori,[12] Claudia Zanna,[13] Michela Rugolo,[13] Andrea Cossarizza,[14] Bernd Wissinger,[15] Christophe Verny,[16] Robert Schwarzenbacher,[17] Miguel Ángel Martín,[6] Joaquín Arenas,[6] Carmen Ayuso,[18] Rafael Garesse,[4] Guy Lenaers,[5] Dominique Bonneau[1,2] and Valerio Carelli[3]









Mitochondrial Fusion Is Required for mtDNA Stability in Skeletal Muscle and Tolerance of mtDNA Mutations

Hsiuchen Chen,[1,5] Marc Vermulst,[1,5,6] Yun E. Wang,[1] Anne Chomyn,[1,2] Tomas A. Prolla,[3] J. Michael McCaffery,[4] and David C. Chan[1,2,*]
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California Institute of Technology, Pasadena, CA 91125, USA
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[4]Integrated Imaging Center, Department of Biology, Johns Hopkins University, Baltimore, MD 21218, USA
[5]These authors contributed equally to this work
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*Correspondence: dchan@caltech.edu
DOI 10.1016/j.cell.2010.02.026

2010
Cell

Early-onset Behr syndrome

The second mutations is frequently p.Ile382Met

Table 1 Clinical features and genotypes of cases with proven compound heterozygosity for OPA1 mutations

Patients (gender, age)	Age of onset	Optic atrophy (age at diagnosis)	Ataxia	Peripheral neuropathy	Deafness	Digestive symptoms	Brain MRI	Mutations in *OPA1*	Domain	Reference
Case 1 (M, 14 years)	18 months	+ (18 months)	+	+	+	-	Cerebellar atrophy	p.Ile382Met p.Arg824*	GTPase Truncative	This study
Case 2 (F, 11 years)	1 year	+ (3 years)	+	+	-	Vomiting episodes	Cerebellar atrophy	p.Val402Met Val903Glyfs*	GTPase Truncative	This study
Case 3 (F, 4 years)	14 months	+	+	+	-	Chronic constipation	Normal at 4 years	p.Ile382Met p.Arg557*	GTPase Truncative	This study
Case 4 (M, 15 years)	3 year	+	+	+	-	-	Vermian atrophy; atrophy of optic nerves and chiasm	p.Ile382Met p.Glu487Lys	GTPase GTPase	This study
Schaaf *et al.* Case 1 (M, 8 years)	1 year	+ (1 year)	+	?	?	Dysphagia, vomiting episodes, intestinal dysmotility with severe constipation	Mild periventricular leukomalacia	p.Ile382Met p.Val903Glyfs*	GTPase Truncative	Schaaf *et al.*, 2011
Schaaf *et al.* Case 2 (F, 3 years)	6 months	+ (6 months)	+	?	?	Dysphagia, constipation	?	p.Ile382Met p.Val903Glyfs*	GTPase / Truncative	Schaaf *et al.*, 2011

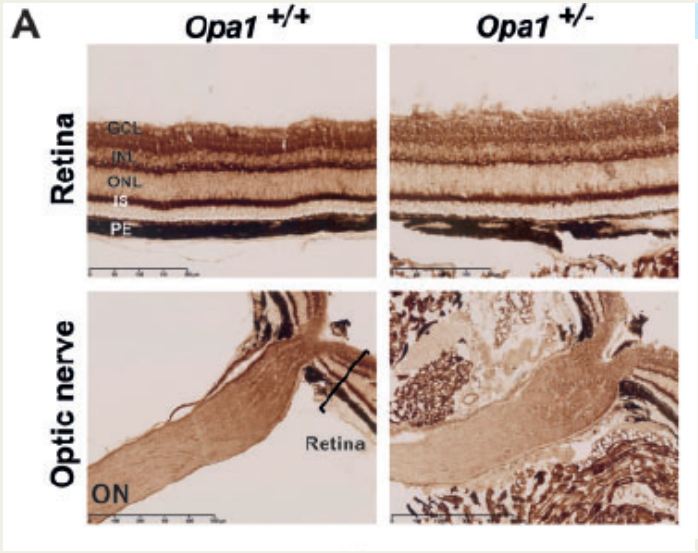
M = male; F = female.

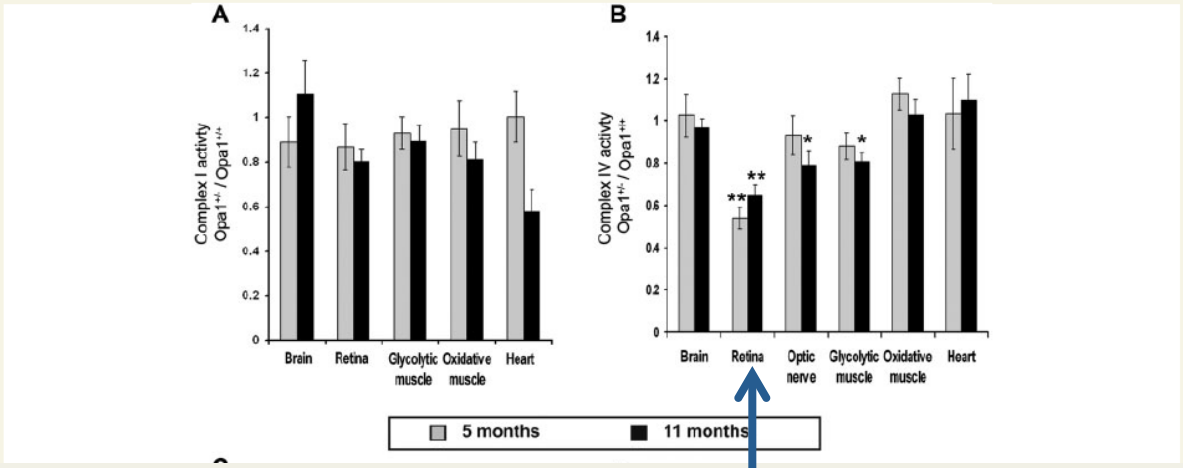
As shown in the 3 OPA1 mouse models , homozygous mutations are letal in early embryogenesis

→ The p.I382M could be a « mild mutation » allowing a second mutated allele ?

...Multiple energetic defects

Mouse model OPA1$^{+/-}$: **Cx IV**





RETINA and OPTIC NERVE
Reduced Cox staining

Precoce 46% decrease of Cox activity (p=0.0007)

…Multiple pathophysiological mechanisms

Altered mt structures
mt network
mt dynamics
cristae

Altered mt functions
OXPHOS
mtDNA instability
ROS
Calcium
Apoptosis
Quality control
Mitophagy

Neurodegeneration
Dendropathy
Axonal transport
Synaptic alteration
Demyelinization

?

Clinical expression

Typical of…

Biological alterations

Mt fusion defect

quality control defect

MtDNA instability

…OXPHOS defects

Premature age-related neurodegeneration

Importance des bases de données

The knowledge of OPA1 gene

→ Completely **refined the clinical spectrum** of DOA

→ Allowed to describe **new clinical entities**

→ Showed strong **genotype/phenotype correlations**

→ To further progress, eOPA1 → **advanced clinical data (2014)**

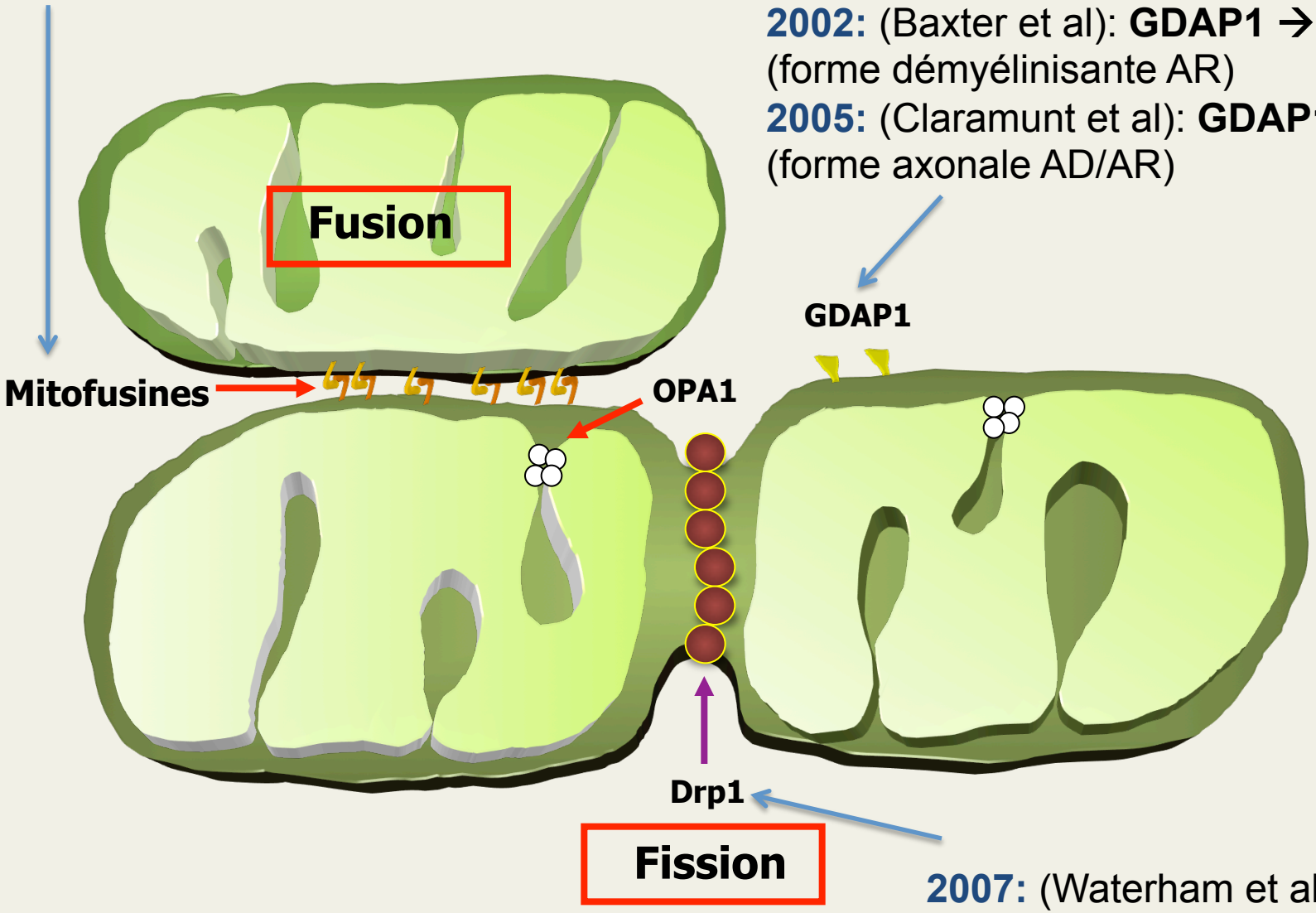
Variant data	
Allele	Unknown
Reported pathogenicity	Pathogenic
Concluded pathogenicity	Unknown
DB-ID	OPA1_00207
DNA change (cDNA)	c.2635C>T (View in UCSC Genome Browser, Ensembl)
Type	Substitution
Location	Exon
Exon	26
Affected domain	Dynamin Central (exons 18-26)
RNA change	-
Protein	p.(Arg879*)
Reference	Ferre et al. (2009)
Technique	SEQ
Template	DNA
Tissue	Blood
Re-site	-
DNA change/variant 1	NM_015560.1:c.2470C>T
Exon/variant 1	24
Protein/isoform 1	NP_056375.1:p.(Arg824*)
DNA published	-
Variant remarks	eOPA1 identifier (obsolete):OA_00216; Nucleotide change: C to T at 2470 (reference: OPA1 transcript variant 1, NM_015560.1)
Frequency	-

Patient data (#0000522)	
Gender	Male
Disease	ADOA
Age of onset	11-20 years
Age at last examination	23 years
Duration of disease	< 11 years
Affected relatives	Yes
Additional features	-
Visual acuity	OD: Moderately impaired vision (Log MAR: 0.2-0.1), OS: Severely impaired vision (Log MAR: 0.9-0.3)
Evolution of vision loss	Unknown
Optic disc	OD: Temporal pallor, OS: Temporal pallor
Cupping	OD: [0-0.4], OS: [0-0.4]
Color vision	OD: Normal, OS: Normal
Visual field	OD: Type: Humphrey/Octopus automated perimetry, OD: MD: [0 to -4], OD: Result: Central scotoma, OS: Type: Humphrey/Octopus automated perimetry, OS: MD: [0 to -4], OS: Result: Central scotoma
OCT	OD: Mean RNFL: Thinning in 2 or more quadrants, OD: Mean GCL: Mean average GCL thickness thinner, OS: Mean RNFL: Thinning in 2 or more quadrants, OS: Mean GCL: Mean average GCL thickness thinner, Device: Cirrus
Visual handicap	D: Able to drive, F: Able to eat, cook and buy food without help, SL: No difficulty at all
Hearing loss	No
Pure tone audiometry	-
Auditory brainstem responses	-
Otoacoustic emission	-
Functional disability	-
Clinical score	-
Electroneuromyography	-
Histology	Muscle biopsy: Not performed, Nerve biopsy: Not performed
Brain imaging	-
Habits	Tobacco: Occasionally, Alcohol: Occasionally
Geographic origin	France
Reference	France:Angers
Remarks	-
# Reported	1
Submitter	Angelique Caignard

Les autres pathologies de la dynamique mitochondriale

2004: (Züchner et al)**: Mfn2 → CMT2A (forme axonale AD)**
2006: (Züchner et al): **Mfn2 → HMSN VI** (CMT + AO)

2002: (Baxter et al): **GDAP1 → CMT4A** (forme démyélinisante AR)
2005: (Claramunt et al): **GDAP1 → CMT2K** (forme axonale AD/AR)



2007: (Waterham et al): **DRP1 → Encéphalopathie néonat. + AO**

The *MFN2* gene is responsible for mitochondrial DNA instability and optic atrophy 'plus' phenotype

Cécile Rouzier,[1,2] Sylvie Bannwarth,[1,2] Annabelle Chaussenot,[1] Arnaud Chevrollier,[3,4] Annie Verschueren,[5] Nathalie Bonello-Palot,[6] Konstantina Fragaki,[1,2] Aline Cano,[7] Jean Pouget,[5] Jean-François Pellissier,[8] Vincent Procaccio,[3,4] Brigitte Chabrol[7] and Véronique Paquis-Flucklinger[1,2]

Brain 2012: 135; 23–34

Maladies neurodégénératives « communes »

EXPRESSION NEUROLOGIQUE

→ Axones

→les plus long

→transport axonal

→à forte demande énergétique

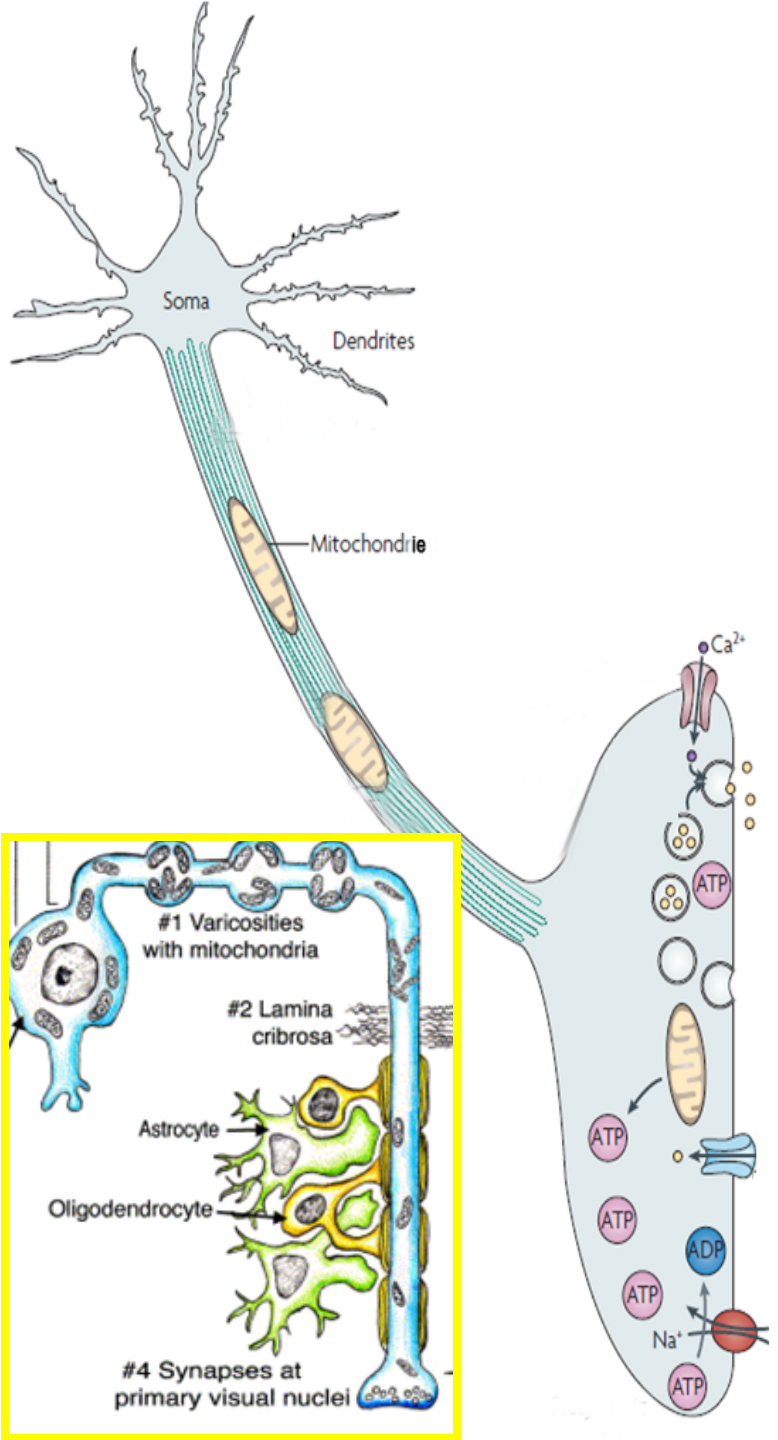
→Parties non myélinisées

3 SURPRISES

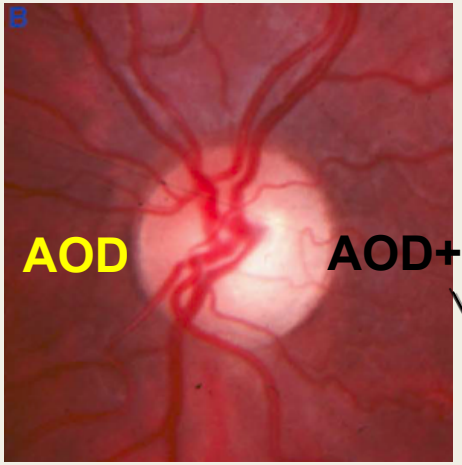
→ **Diversité des phénotypes**

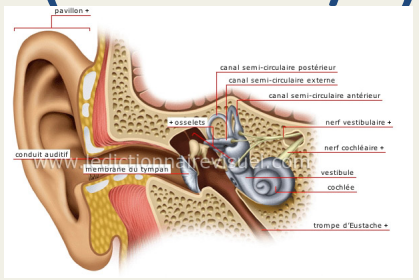
→ **Instabilité de l'ADNmt**

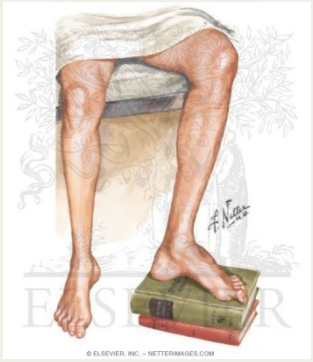
→ **Maladies neurodégénératives communes**

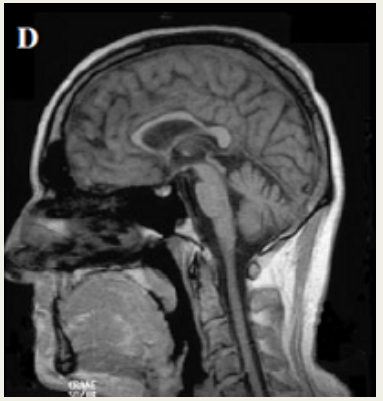


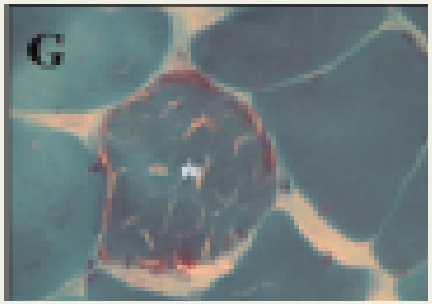
Diversité des phénotypes cliniques (OPA1+/-)











+ Sd de Behr (Marelli et al. 2010)
+ Formes multi-systémiques pédiatriques…

2009: Altération de la plasticité mitochondriale dans les maladies neurodégénératives communes

Published in final edited form as:
J Neurosci. 2009 July 15; 29(28): 9090–9103. doi:10.1523/JNEUROSCI.1357-09.2009.

Impaired Balance of Mitochondria Fission and Fusion in Alzheimer Disease

Xinglong Wang[1], **Bo Su**[1], **Hyoung-gon Lee**[1], **Xinyi Li**[1], **George Perry**[1,2], **Mark A. Smith**[1], and **Xiongwei Zhu**[1]

[1]Department of Pathology, Case Western Reserve University, Cleveland, Ohio USA

[2]College of Sciences, University of Texas at San Antonio, San Antonio, Texas USA

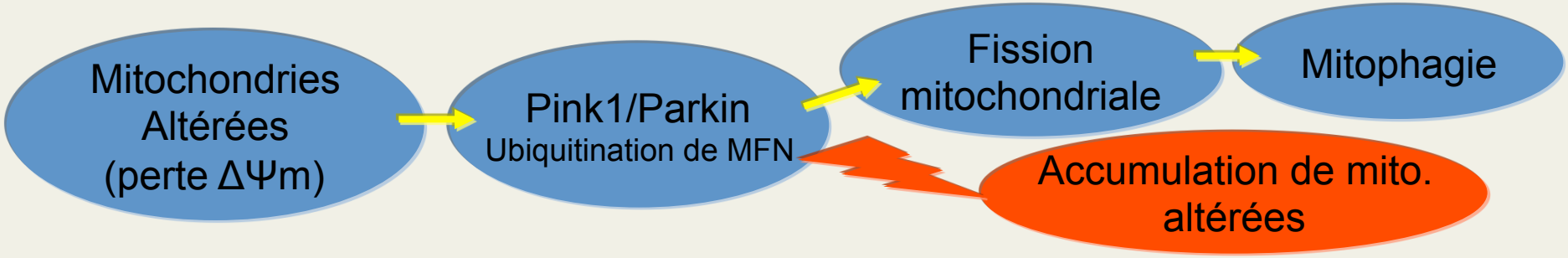
Published in final edited form as:
Brain Res Rev. 2009 June ; 61(1): 33–48. doi:10.1016/j.brainresrev.2009.04.001.

Mitochondrial Structural and Functional Dynamics in Huntington's Disease

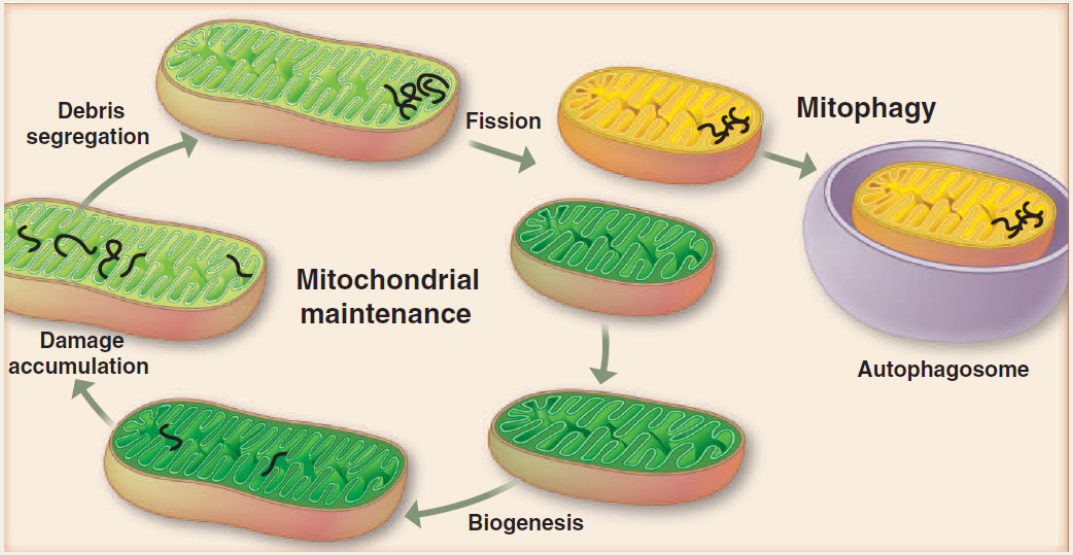
P. Hemachandra Reddy[a,b], **Peizhong Mao**[a], and **Maria Manczak**[a]

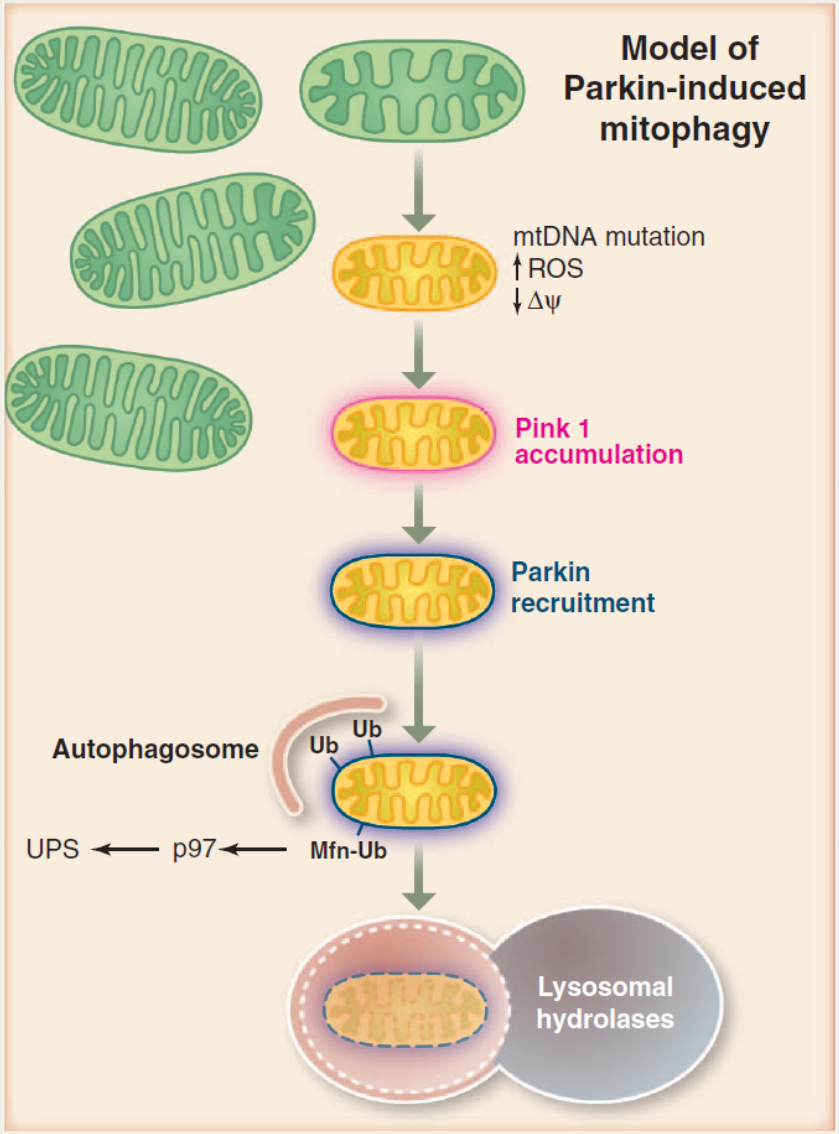
[a] Neurogenetics Laboratory, Neuroscience Division, Oregon National Primate Research Center, West Campus, Oregon Health & Science University, 505 NW 185th Avenue, Beaverton, OR 97006

[b] Department of Physiology and Pharmacology, Oregon Health and Science University, Portland,



Mitophagie et contrôle de qualité des mitochondries

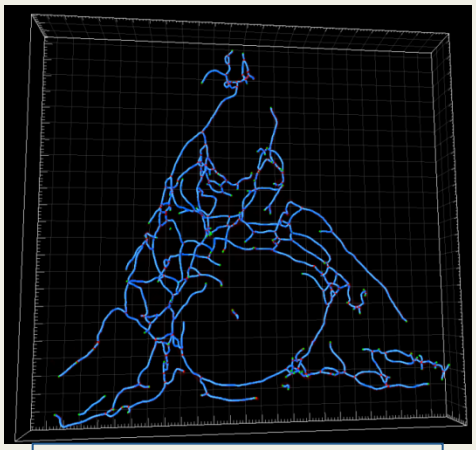




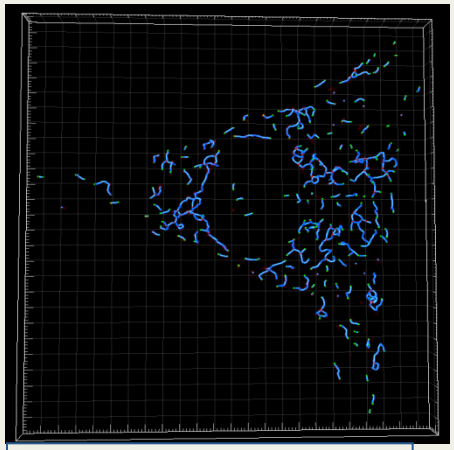
Youle et al Science, 2012

Renouveler/remplacer les mitochondries altérées ?

Stimuler une séquence destructions/sélection/ amplification

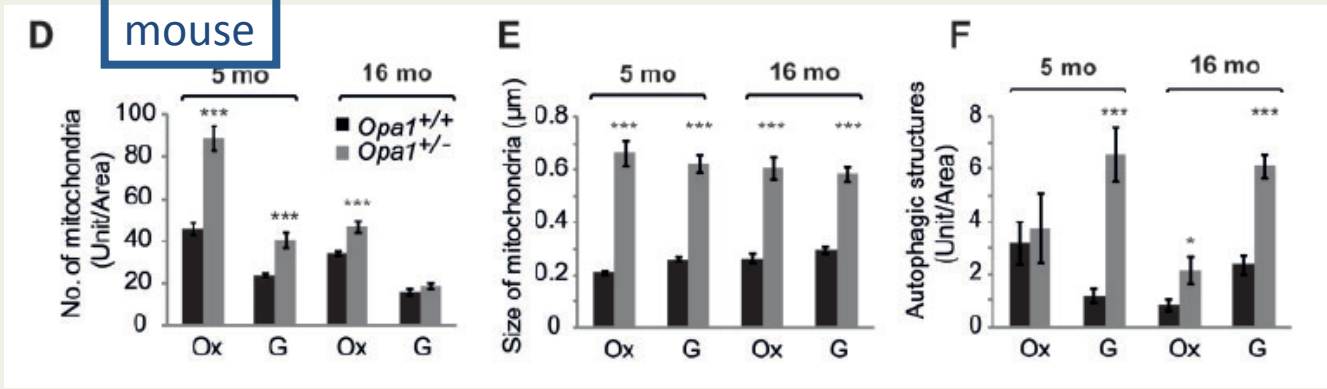


Control fibroblasts

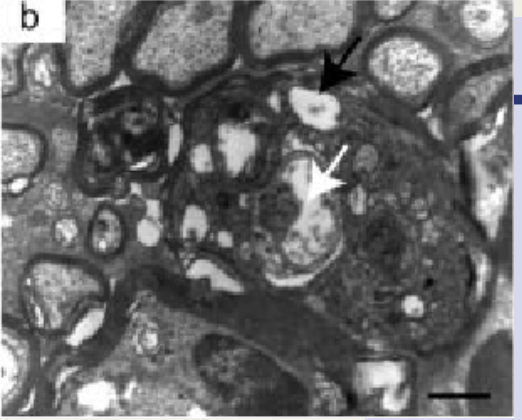


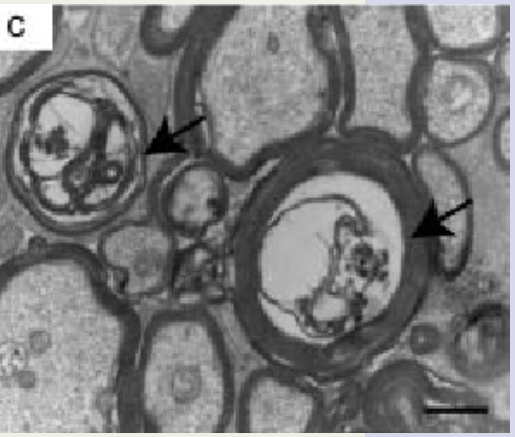
Patient fibroblasts

mouse



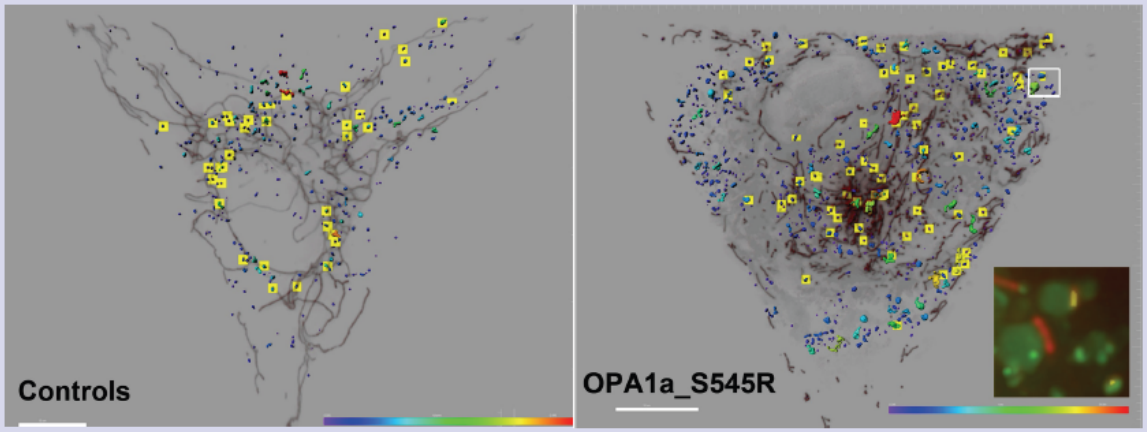
Autophagy is activated in OPA1-mutated fibroblasts

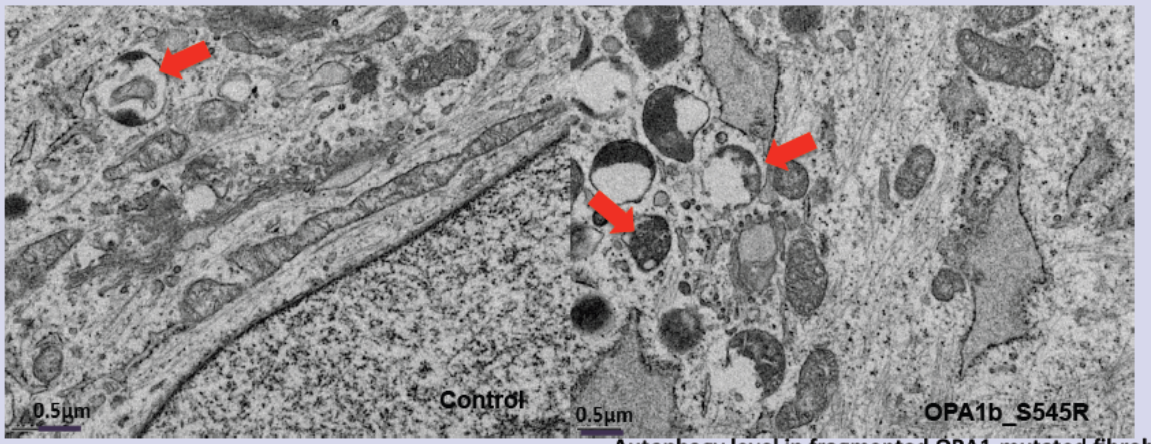




Souris OPA1$^{+/-}$

Découplant





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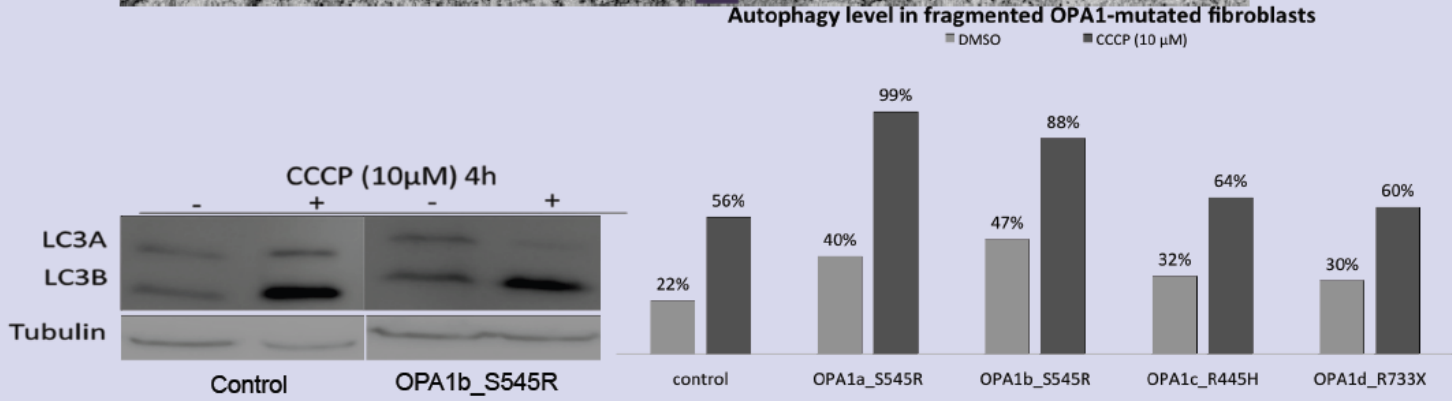
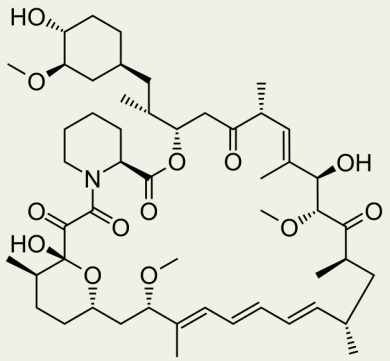


Figure 4 : Autophagy level (LC3 expression) in OPA1-mutated fibroblasts

Renouveler les mitochondries



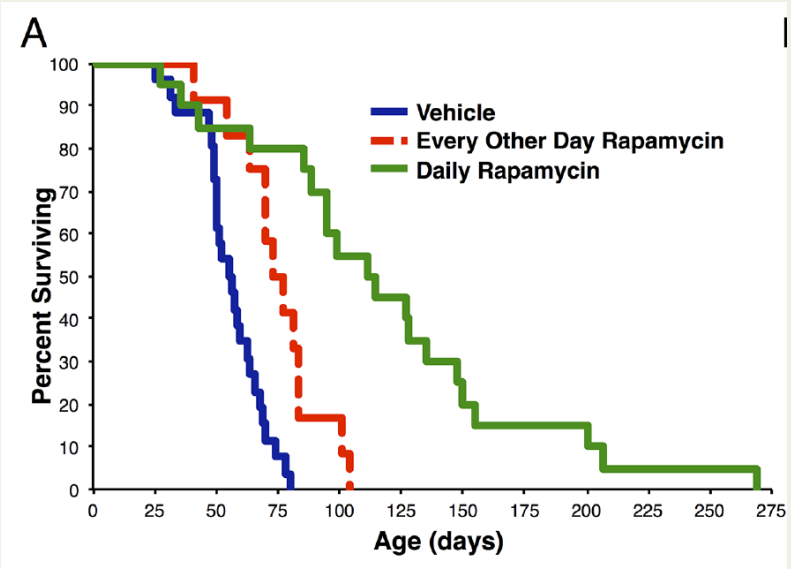
Sciencexpress

mTOR Inhibition Alleviates Mitochondrial Disease in a Mouse Model of Leigh Syndrome

Simon C. Johnson,[1] Melana E. Yanos,[1,2] Ernst-Bernhard Kayser,[3] Albert Quintana,[4] Maya Sangesland,[1] Anthony Castanza,[1] Lauren Uhde,[1] Jessica Hui,[1] Valerie Z. Wall,[1] Arni Gagnidze,[1] Kelly Oh,[1] Brian M. Wasko,[1] Fresnida J. Ramos,[1] Richard D. Palmiter,[4] Peter S. Rabinovitch,[1] Philip G. Morgan,[3] Margaret M. Sedensky,[3] Matt Kaeberlein[1]*

[1]Department of Pathology, University of Washington, Seattle, WA 98195, USA. [2]Department of Psychology, University of Washington, Seattle, WA 98195, USA. [3]Anesthesiology and Pain Medicine, Seattle Children's Hospital, Seattle, WA 98105, USA. [4]Howard Hughes Medical Institute and Department of Biochemistry, University of Washington, Seattle, WA 98195, USA.

*Corresponding author. E-mail: kaeber@uw.edu



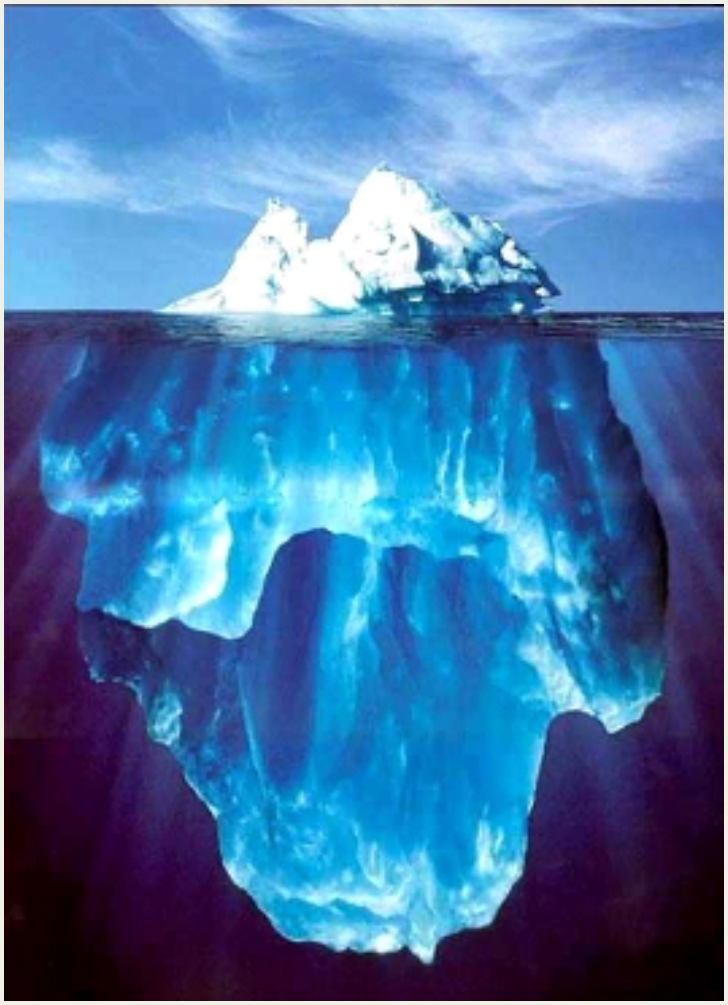
Souris déficientes en CI
Meurent à 50 jour par encéphalopathie

Rapamycine (Sirolimus, immunosuppresseur, 8 mg/Kg /J en IP)
inhibiteur de la voie mTOR (mammalian Target Of Rapamycin)
Inducteur mitophagie

Renouveler les mitochondries ? Conclusion

- **Contrôle de qualité des mitochondries:**
  - Sélection des mitochondries déficientes (pot de mb)
  - → mitophagie
  - → amplification des mito fonctionnelles
- **Voies activables pharmacologiquement** (rapamycine/ polyphénols)
- **Opportunité pour les maladies neurodégénératives ?**
  - Accumulations de mitochondries anormales (instabilité ADNmt)
  - Renouvellement mitochondrial actif même si neurones ne se divisent plus

Dysfonctions mitochondriales dans la plupart des pathologies communes



~1/5000 hab
~ 80,000 in EU

1/200
mtDNA mutation
At birth ?

Mitochondrial cytopathies

Other rare diseases
CMT, SCA,…

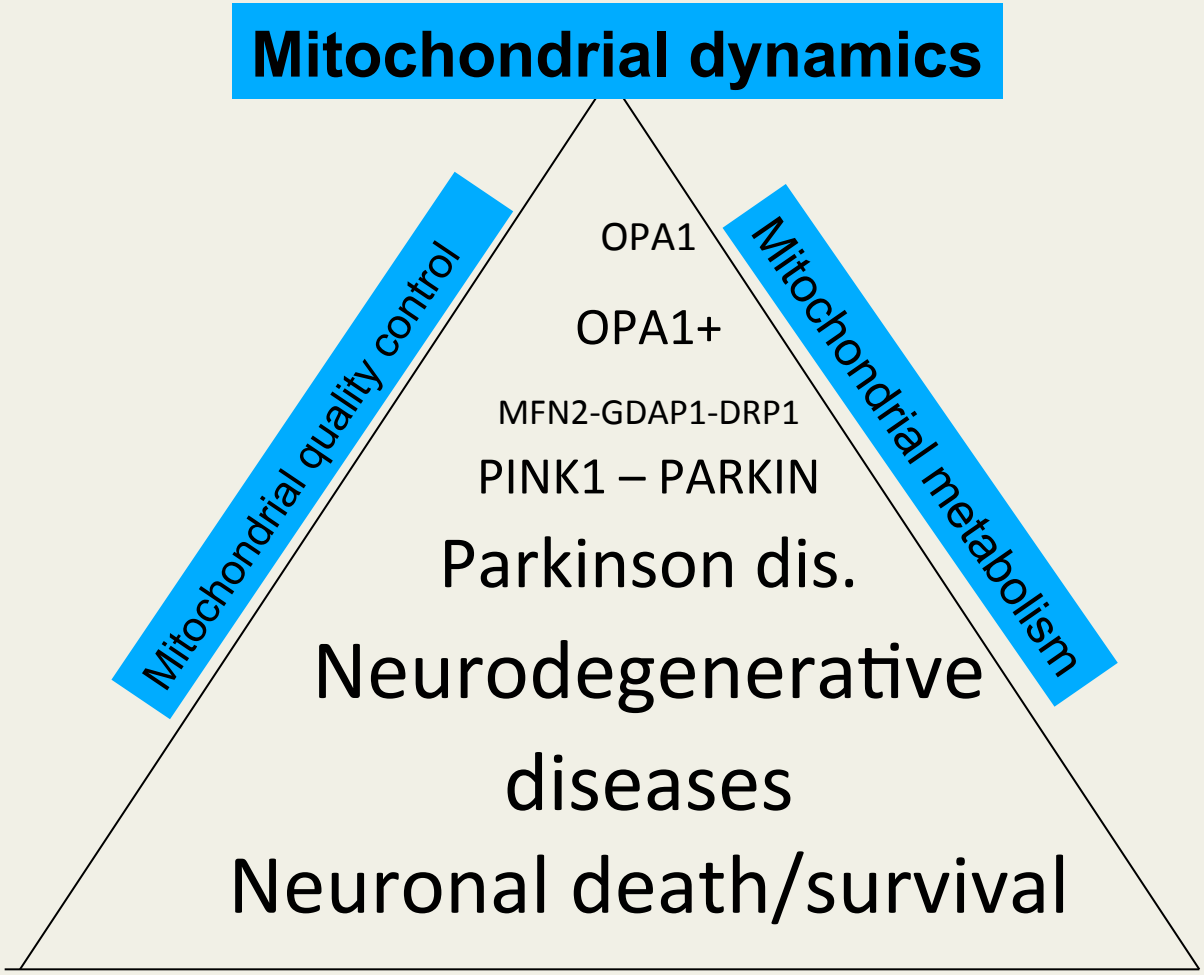
Cancer
PG, Leiomyoma

Diabetes / Obesity

Neurodegenerative diseases
AD, PD, HD, ASL

Ageing

Mitochondrial dynamics disorders



Pistes thérapeutiques mitochondriales en Neurologie

Neurotoxicity of mitochondrial damages

Energetic deficiency

Mitochondrial accumulation and toxicity of protein aggregates

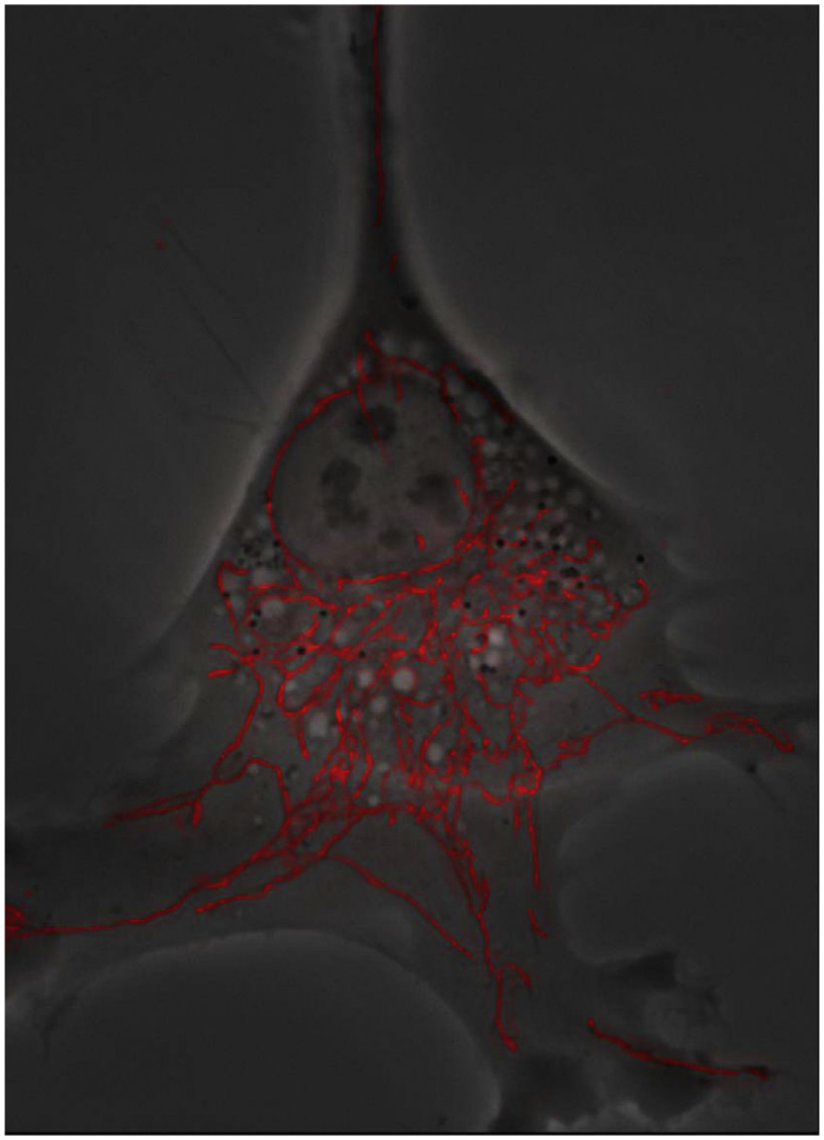
Accumulation of mtDNA mutations

Toxicity of oxidative Stress

Mitochondrial toxicity of xenobiotics

Impairment of mitochondrial dynamics

Compromised axonal transport



Optimizing mitochondrial neuroprotection

Favour mitochondrial quality controls

Stimulate mitophagy of damaged mitochondria

Increase mitochondrial biogenesis

Enhance mitochondrial dynamics

Regulate metabolic flows by nutritional supply

Fight against oxidative stress

NEUROLOGIE

C VERNY
J CASSEREAU
V GUILLET

OPHTALMOLOGIE

D MILEA
S LERUEZ

GENETIQUE

D BONNEAU
V PROCACCIO

BIOCHIMIE

P AMATI-BONNEAU
A CHEVROLLIER
M FERRE
N GUEGUEN
V DESQUIRET-DUMAS

MONTPELLIER

G LENAERS
E SARZI

mitolab