5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 1

Mitochondrial diseases for beginners (Level 1)

Mitochondrial diseases of the brain

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ean congress Oslo 2019
5th Congress of the European Academy of Neurology
June 29 - July 2

TC Teaching Course 1 14:45 - 18:15

Mitochondrial diseases for beginners (Level 1)

Mitochondrial diseases of the brain

SyNergy Munich Cluster for Systems Neurology

Thomas Klopstock

DZNE German Center for Neurodegenerative Diseases within the Helmholtz Association

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
FRIEDRICH-BAUR-INSTITUT
AN DER NEUROLOGISCHEN KLINIK UND POLIKLINIK

1

Disclosures

Research support, speaker honoraria, travel costs and/or consulting fees from ApoPharma Inc., CoA Therapeutics, Retrophin Inc., GenSight Biologics and Santhera Pharmaceuticals

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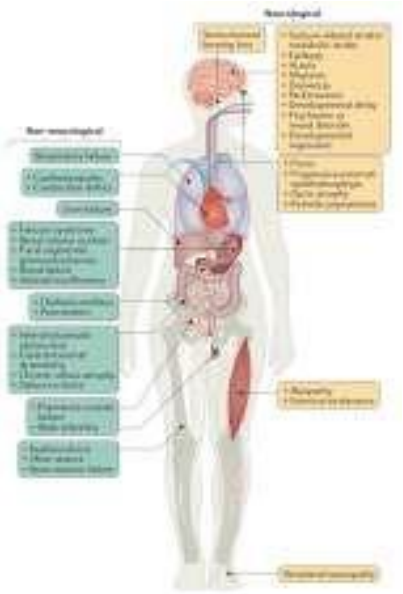
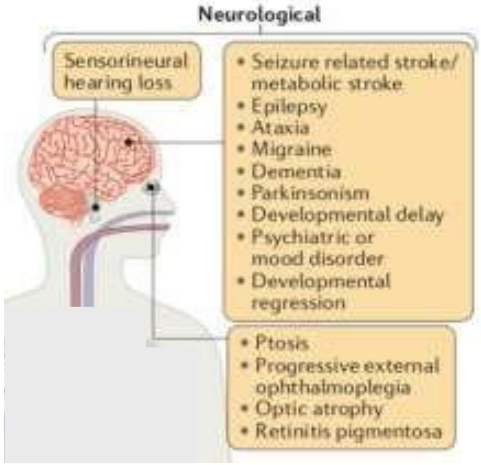
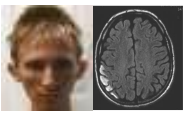
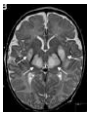
Mitochondrial diseases of the brain






MELAS


MERRF


Leigh sy.


LHON

Gorman et al, 2016

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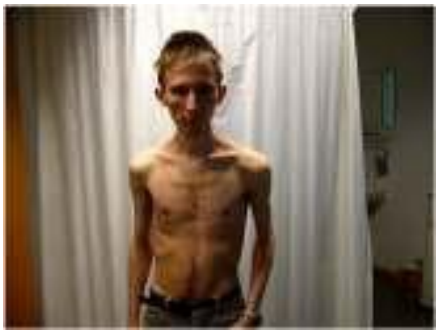
MELAS - Mitochondriale Enzephalomyopathy, Lactic Acidosis and stroke-like episodes



! Apraxia !

Frequency	Manifestations
≥90%	• Stroke-like episodes • Dementia • Epilepsy • Lactic acidemia • RRF on muscle biopsy
7%-89%	• Hemiparesis • Cortical vision loss • Recurrent headaches • Hearing impairment • Muscle weakness
50%-74%	• Peripheral neuropathy • Learning disability • Memory impairment • Recurrent vomiting • Short stature

Frequency	Manifestations
25%-49%	• Basal ganglia calcification • Myoclonus • Ataxia • Episodic altered consciousness • Gait disturbance • Depression • Anxiety • Psychotic disorders • Diabetes mellitus (type 1 or 2)
<25%	• Optic atrophy • Pigmentary retinopathy • PEO • Motor developmental delay • Cardiomyopathy • Cardiac conduction abnorm. • Nephropathy • Vitiligo

El-Hattab et al, 2018

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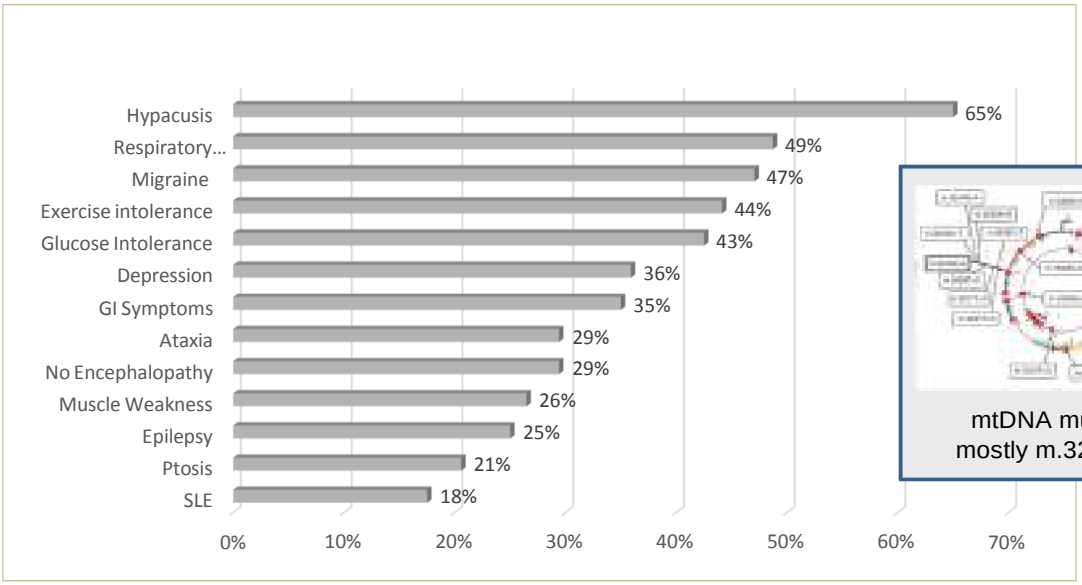
The phenotypical spectrum of the m.3243A>G mutation



Radelfahr et al, Poster X

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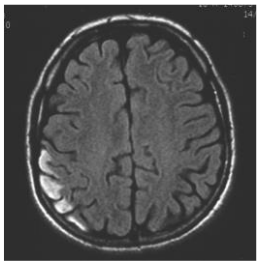
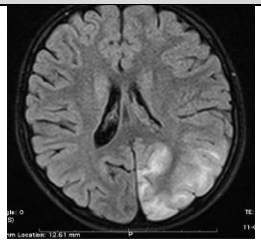
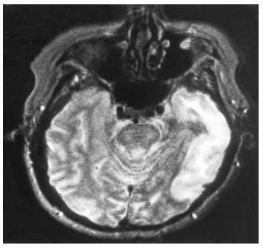
MELAS - Imaging



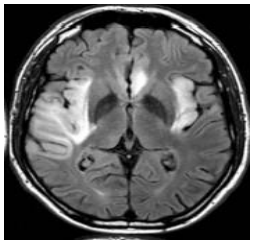
own patient, 29 yrs



Pauli et al, 2013



Sharfstein et al, 1999
„A herpes not so simplex"



Gieraerts et al, 2013

- cortical pattern
- independent of vascular territories
- occipital, temporal > parietal >> frontal

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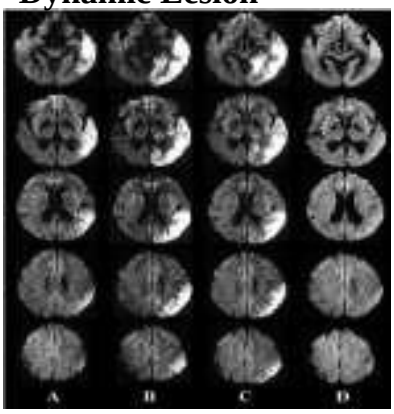
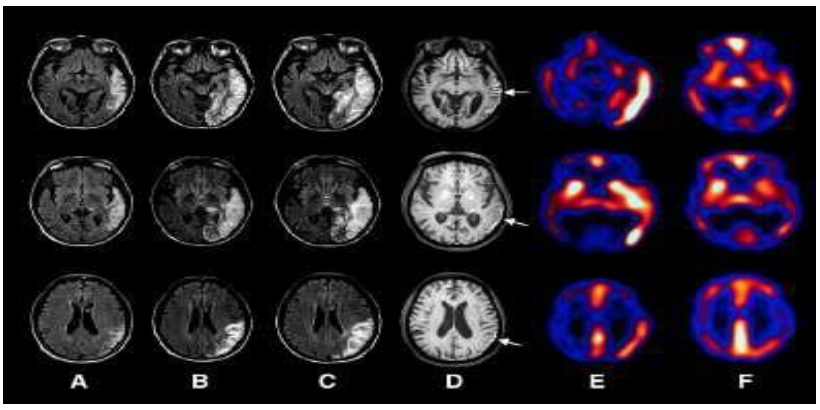
MELAS - Imaging

Dynamic Lesion



Day 4 9 14 29
MELAS 47 yof, DWI, expansion to posterior

Iizuka et al, 2003



Patient with MELAS (40 yrs)
A, B, C: FLAIR at days 4, 9, 14 expansion and edema
D: fettunterdrückte Bilder day 29
Cortical hyperintensity, cortical laminar necrosis

E, F: HMPAO-SPECT at days 5, 19: initial hyperperfusion left temporal Iizuka et al, 2007

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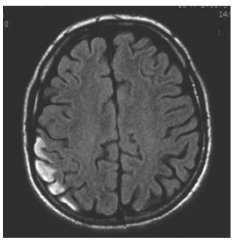
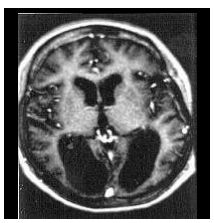
MELAS - Imaging



MELAS, 29 yrs
first stroke-like episode



MELAS, 39 yrs
After multiple stroke-like episodes; severe dementia

Stroke-like episodes and lesions
- may recover completely or incompletely
- but after multiple episodes predominantly occipital atrophy

Pathophysiological hypothesis

Neuronal energy deficiency
↓
Neuronale Hyperexcitability
↓
Epileptic Activity
↓
Cortical Edema
↓
Neuronal Loss

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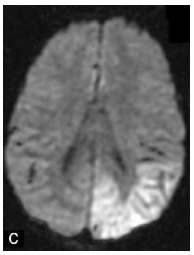
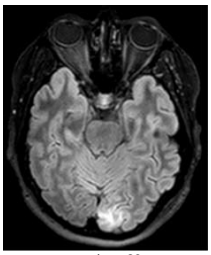
Stroke-like lesions beyond MELAS

- **Alpers-Syndrom**
  with mutations in the mitochondrial Polymerase gamma gene (POLG)



3 yrs old patient (Sofou et al, 2013)

- **SCAE (spinocerebellar ataxia and epilepsy)**
  with mutations in the mitochondrial Polymerase gamma gene (POLG)



own patient, 30 yrs

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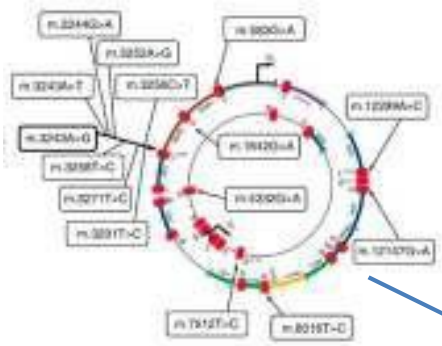
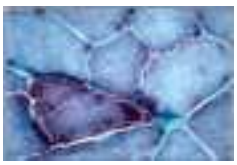
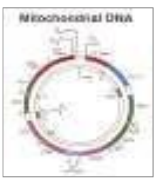
Diagnostics of MELAS resp. its associated mutations

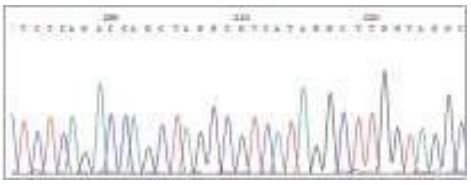




„ragged red fibers“
in muscle biopsy

Urine > Blood





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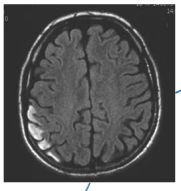
Therapy of MELAS



Ng et al, in preparation **Consensus-based Guidance for The Management of Mitochondrial Stroke-like Episodes**
We do not advocate the use of L-arginine in the treatment of stroke-like episodes. There is no robust scientific evidence. RCT needed.

Antiepileptic Tx
Acute i.v.:
- Levetiracetam
- Phenytoin
- Phenobarbital
- Lacosamide
- Midazolam

Later p.o.:
- Levetiracetam
- Topiramate
- Lamotrigine

Cave:
- Valproate

Autoren	Jahr	Medikament	Patienten	Design	Effekt
Tarnopolsky	1997	Kreatin	6 MELAS 1 MiMy	crossover 21-x-21	⇑ Laktat ⇒ klinisch
Glover	2010	Coenzym Q	15 MELAS 11 CPEO 1 LHON 3 diverse	crossover 60-67-60	⇑ Laktat ⇒ klinisch ⇒ MRS Gehirn
Kaufmann	2006	Dichloroacetat	30 MELAS	crossover 90-x-90	⇒ MRS Gehirn ⇒ Klinik !!! Abbruch wg. Neuropathie !!!

The KHENERGY Study: Safety and Efficacy of KH176 in Mitochondrial m.3243A>G Spectrum Disorders

Mirian C.H. Janssen[1,2], Saskia Koene[1], Paul de Laat[1], Pleun Hemelaar[3], Peter Pickkers[3], Edwin Spaans[4], Rypko Beukema[5], Julien Beyrath[1], Jan Groothuis[6], Chris Verhaak[7] and Jan Smeitink[1]

Phase IIa
↓
Phase IIb

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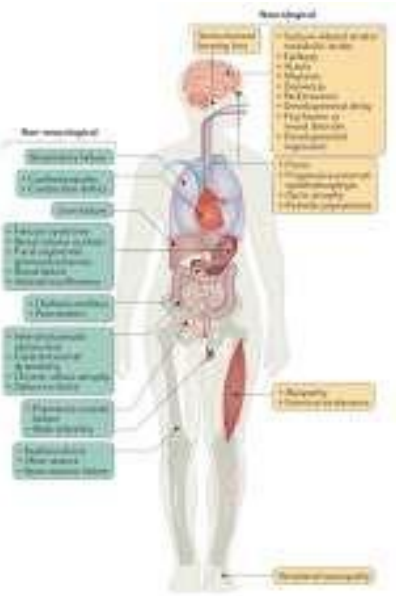
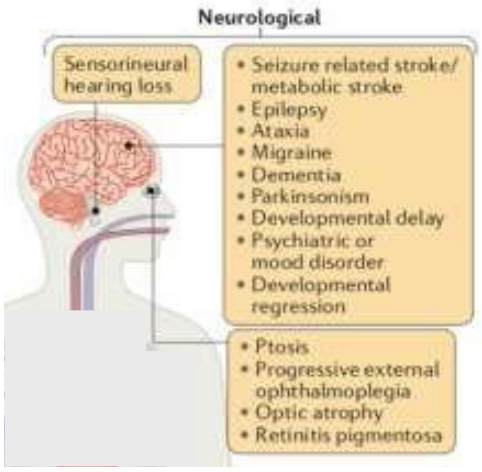
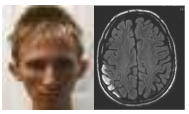
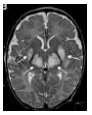
Mitochondrial diseases of the brain






MELAS


MERRF


Leigh sy.


LHON

Gorman et al, 2016

12

MERRF - myoclonic epilepsy and ragged-red fibres

- a multisystemic mitochondrial disease that is characterised by myoclonus, seizures, cerebellar ataxia, and mitochondrial myopathy with ragged-red fibres.
- 80–90 % of cases caused by the m.8344A>G mutation of the mtDNA

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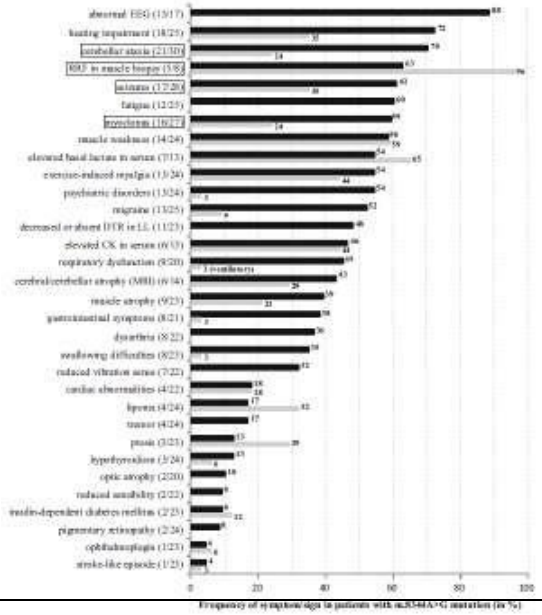
The phenotypical spectrum of the m.8344A>G mutation

German mitoNET cohort N = 34; black bars
Italian MITOCON cohort N= 34; grey bars



Mancuso et al, 2013; Altmann et al, 2016

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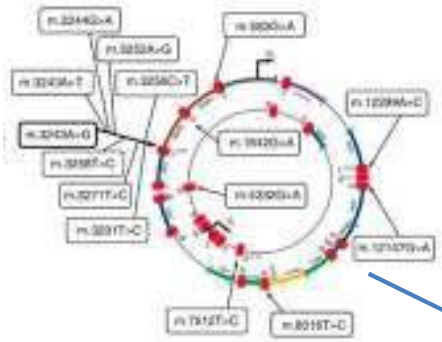
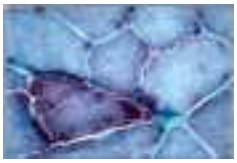
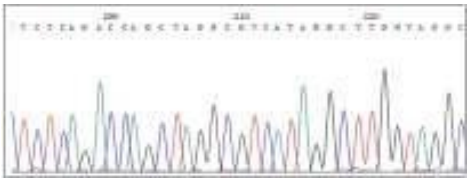
Diagnostics of MERRF resp. its associated mutations





„ragged red fibers“
in muscle biopsy



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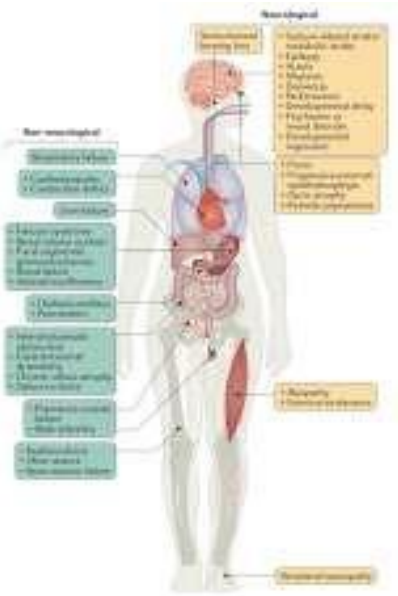
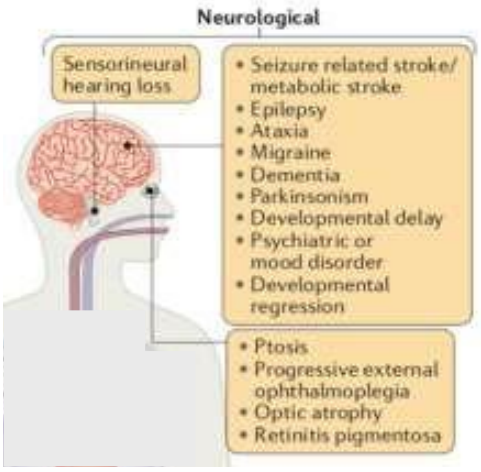
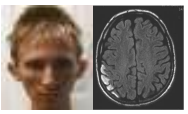
Mitochondrial diseases of the brain

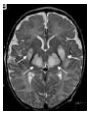






MELAS

MERRF



Leigh sy.

LHON

Gorman et al, 2016

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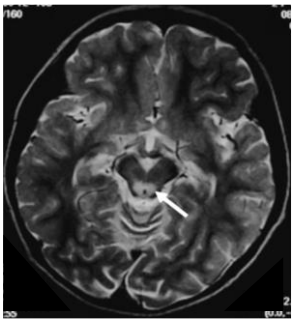
Leigh syndrome: infantile subacute necrotizing encephalomyelopathy

- fatal disorder of early childhood
- showing psychomotor regression, movement disorders and brain stem dysfunction
- symmetrical lesions in basal ganglia and brain stem in imaging and pathologically
- Caused by many different mitochondrial defects, both mtDNA- and nuclear-encoded

Biochemistry	Genetics
Complex I	nuclear and mtDNA subunits
Complex II	nuclear subunits *SDHA*
Complex III	nuclear assembly factor
Complex IV	nuclear assembly factors
Complex V	mtDNA
PDHC	X-chromosomal subunit



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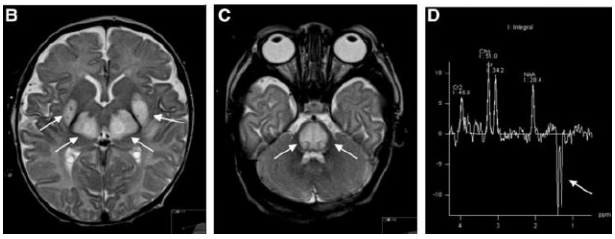
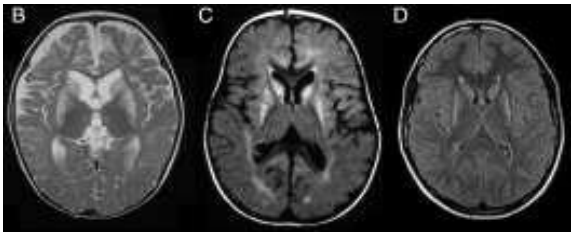
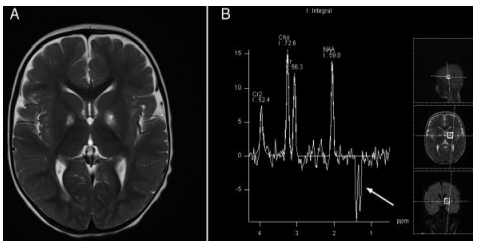
Leigh syndrome imaging



SLC19A3 mutation, neonatal onset, died at 2 months (Haack et al, 2014)



ECHS1 mutations, 3 patients aged 1, 2, and 15 yrs (Haack et al, 2015)



Complex III defect, 1 yof, dystonia (Baertling et al, 2014)

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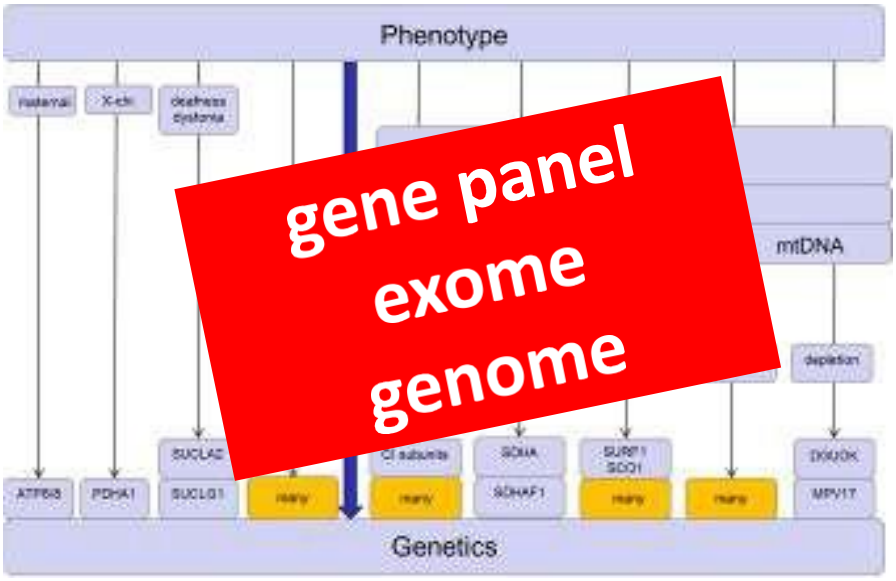
Leigh syndrome diagnostics



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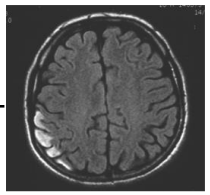
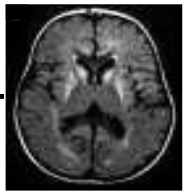
MRI imaging patterns in mitochondrial diseases

Two pathognomic patterns

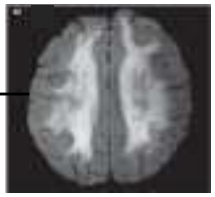
- **Cortical hyperintensity (stroke-like lesion)**
  eg in MELAS, POLG
- **Hyperintensity basal ganglia and brain stem**
  eg in Leigh syndrome

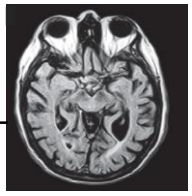




Two unspezific patterns

- **Leukenzephalopathie**
  eg in MNGIE, KSS
- **Cerebral atrophy**
  eg in CPEO, KSS





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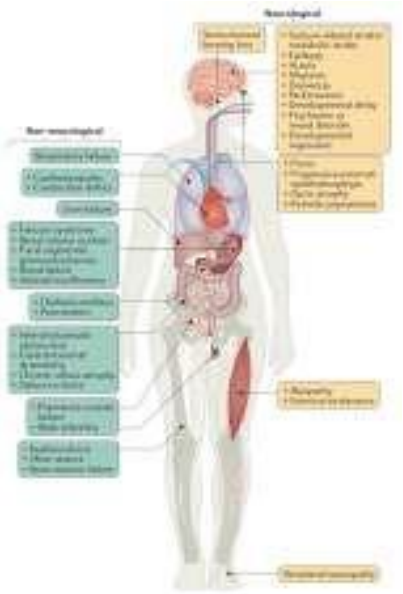
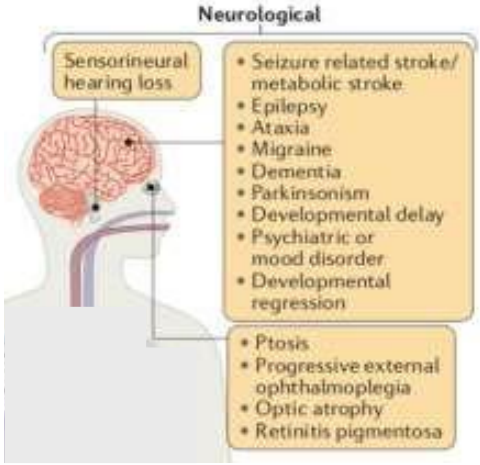
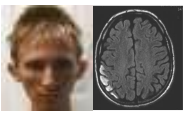
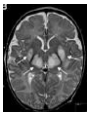
Mitochondrial diseases of the brain






MELAS


MERRF


Leigh sy.


LHON

Gorman et al, 2016

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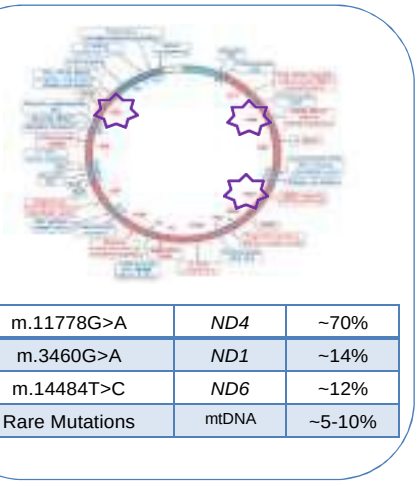
Leber`s Hereditary Optic Neuropathy (LHON)

- Estimated as the most frequent mitochondrial disease
- Minimum prevalence:
  - 1 in 31.000: North of the UK
  - 1 in 39.000: Netherlands
  - 1 in 50.000: Finland
- mtDNA mutation relative frequencies:
  - ~90% m.11778, m.3460, m.14484
  - Most frequent: ~70% m.11778G>A
    - Exception!!! ~90% m.14484T>C in patients of French-Canadian descent (due to founder event)



m.11778G>A	*ND4*	~70%
m.3460G>A	*ND1*	~14%
m.14484T>C	*ND6*	~12%
Rare Mutations	mtDNA	~5-10%

Fraser et al., 2010
Macmillan et al., 2000
Man et al., 2003
Spruijt et al., 2006
Puomila et al., 2007
Yu-Wai-Man et al., 2011

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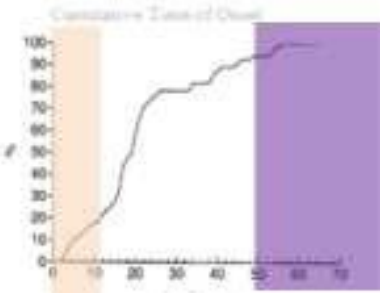
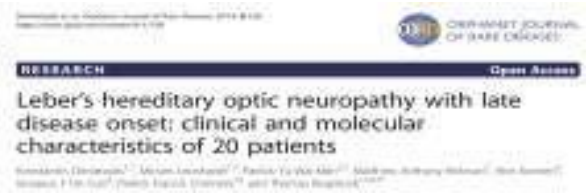
Leber`s Hereditary Optic Neuropathy (LHON)

- Predominantly affects young adult males
- M>F
- Age at onset: range 4 – 82 yrs
  - peak of onset: 2nd and 3rd decades
  - early-onset LHON (< 12yrs)
  - late-onset LHON (> 50 yrs)





RESEARCH Open Access

Leber's hereditary optic neuropathy with late disease onset: clinical and molecular characteristics of 20 patients

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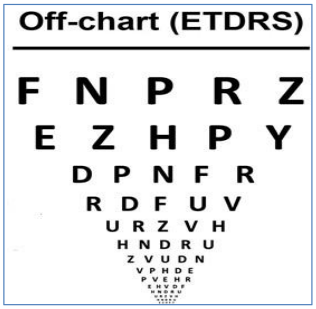
LHON: Clinical manifestations

- Painless acute/ subacute progressive vision loss
- Sequential affection of 1st and 2nd eye (after a median of 6-8 weeks) (~75%)

  or
- both eyes affected from onset (~25%)
- Progression in days/weeks/months, then stability



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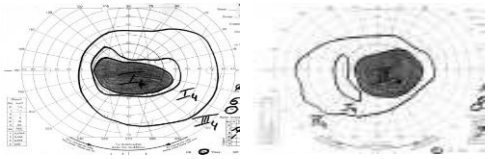
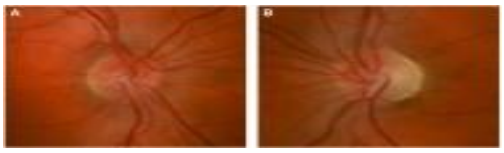
LHON: Clinical manifestations

- Fundoscopy: Papilledema in the acute phase, later optic atrophy, temporal predominant
- Visual fields: Bilateral central scotoma

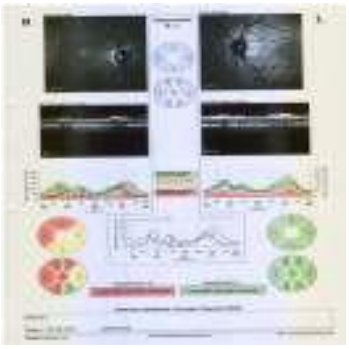


- OCT: Reduced temporal circumpapillary RNFL thickness



Mild hyperemia of the disc (acute vision loss of the second eye)

Prominent temporal optic nerve pallor (first eye affected 6 months before)



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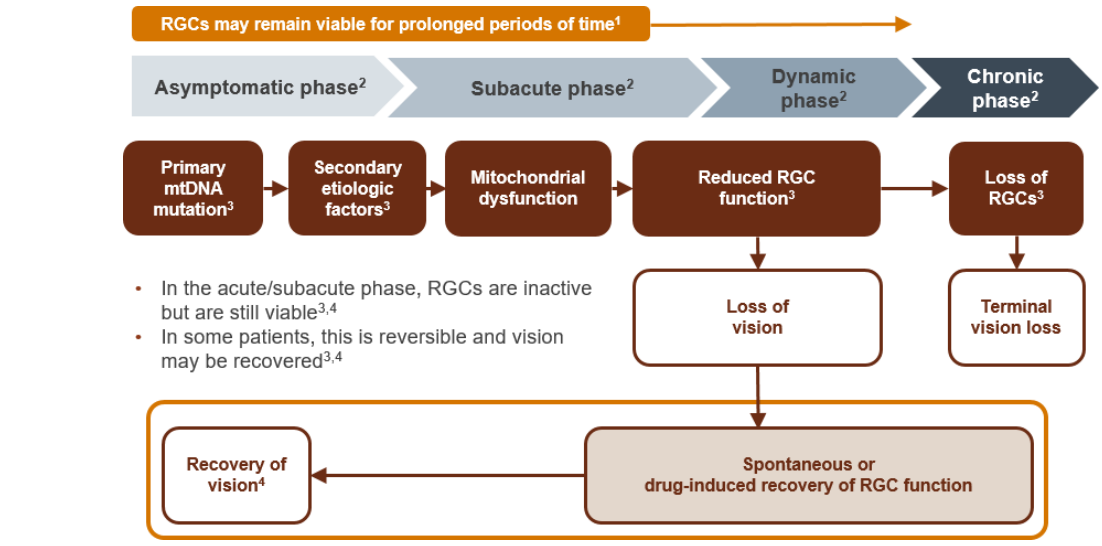
LHON: Pathogenesis & „window of opportunity“



1. Stone EM *et al. J Clin Neuroophthalmol.* 1992; 12:10–4; 2. Carelli V *et al. Acta Ophthalmologica.* 2016; 94:S256; 3. Howell N. *Vision Res.*1998; 38:1495–504; 4. Gueven N. *Biol Med.* 2014; 1:1–6.

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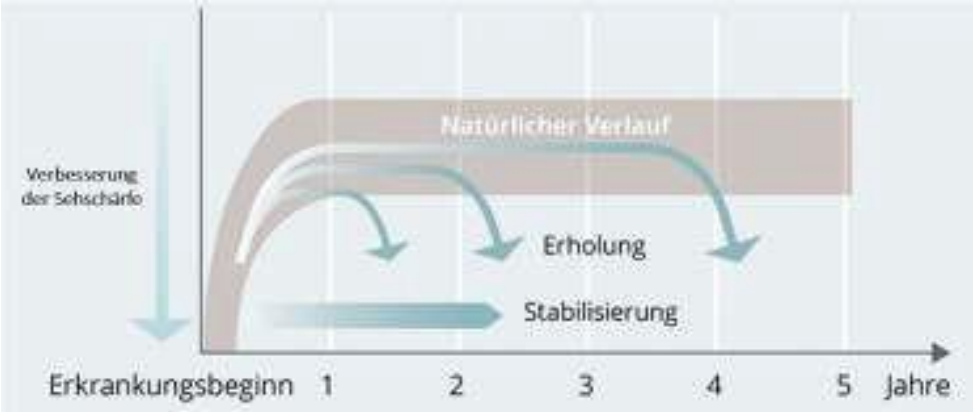
LHON: Natural history & goals of therapy



goals of therapy
Clinically Relevant Recovery (CRR)
Clinically Relevant Stabilization (CRS)

Quelle: 1. Hasham S et al. ARVO 2016, Seattle, USA. Poster 5085.; Bild: Santhera pharmaceuticals.

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RHODOS (Rescue Of Hereditary Optic Disease Outpatient Study)

doi:10.1093/brain/aar170 Brain 2011: 134; 2677–2686 | 2677

BRAIN
A JOURNAL OF NEUROLOGY

A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy

Thomas Klopstock,[1] Patrick Yu-Wai-Man,[2,3,4] Konstantinos Dimitriadis,[1] Jacinthe Rouleau,[5] Suzette Heck,[1] Maura Bailie,[2,3,4] Alaa Atawan,[2,3,4] Sandip Chattopadhyay,[2,3,4] Marion Schubert,[1] Aylin Garip,[6] Marcus Kernt,[6] Diana Petraki,[7] Christian Rummey,[7] Mika Leinonen,[8] Günther Metz,[7] Philip G. Griffiths,[2,3,4] Thomas Meier[7] and Patrick F. Chinnery[2,3,4]

- double-blind, randomized, placebo-controlled, parallel group trial
- 85 LHON patients in 3 centers (Munich, Newcastle, Montreal)
- largest trial to date in an mtDNA-associated disease

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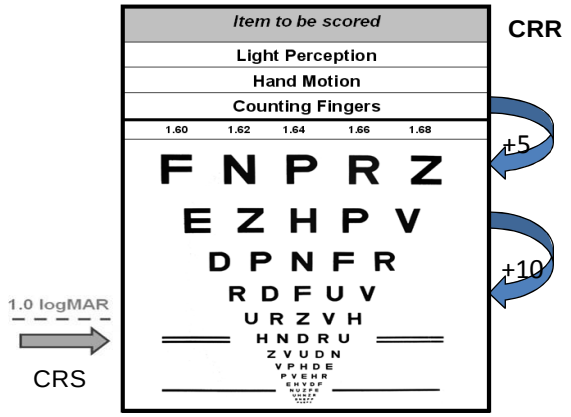
Expanded Access Program (EAP)

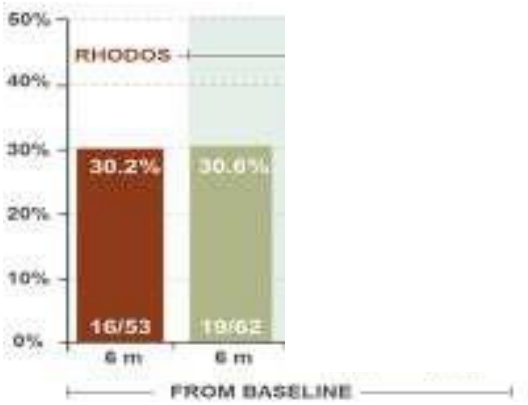
established in late 2011 following an increasing number of unsolicited requests from physicians for access to the drug

patients
n = 87[a]
(from 38

Idebenone 300 mg orally 3 times daily[b]

Month 0 — Month 60





Catarino et al, submitted

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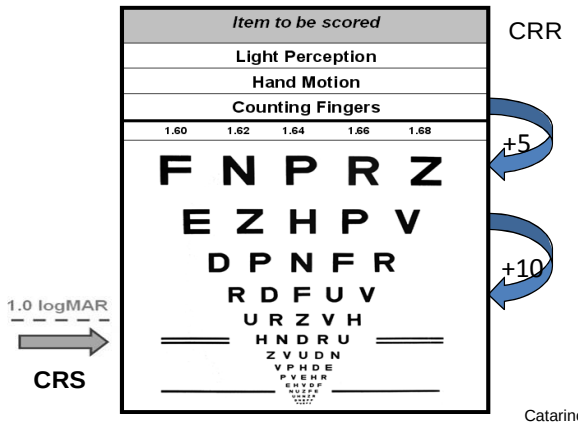
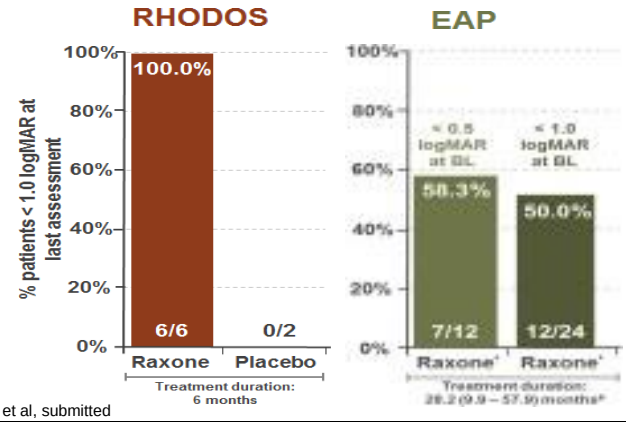
Expanded Access Program (EAP)

LHON patients
n = 87[a]
(from 38 sites)

Idebenone 300 mg orally 3 times daily[b]

Month 0 — Month 60





Catarino et al, submitted

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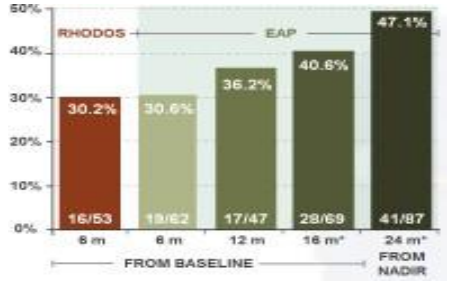
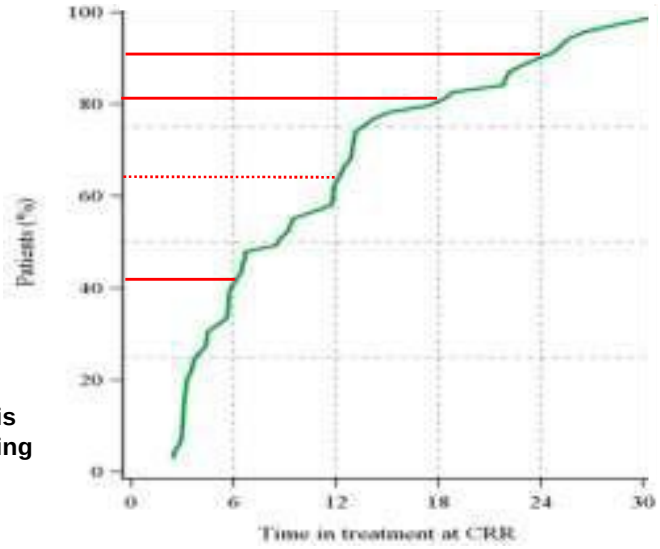
EAP-CRR: Time to first recovery





Total patients with CRR=41 patients (100%)

Treatment duration of at least 18-24 months is needed to maximize the probability of observing an initial CRR

Catarino et al, submitted

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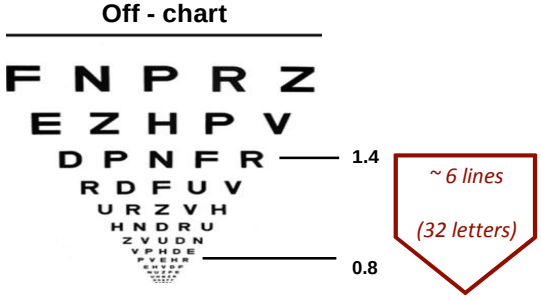
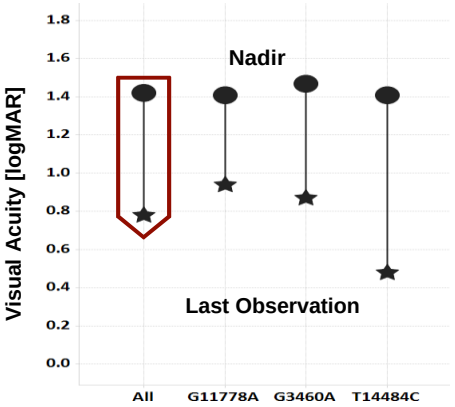
EAP: Average magnitude of VA recovery

Mean effect size of ~6 lines in responders after 16 month



n=34/69 responders with CRR at last assessment

Average visual acuity at nadir and last observation in patients CRR by mutation



In patients with recovery in both eyes, the eye with the best recovery is reported

Catarino et al, submitted

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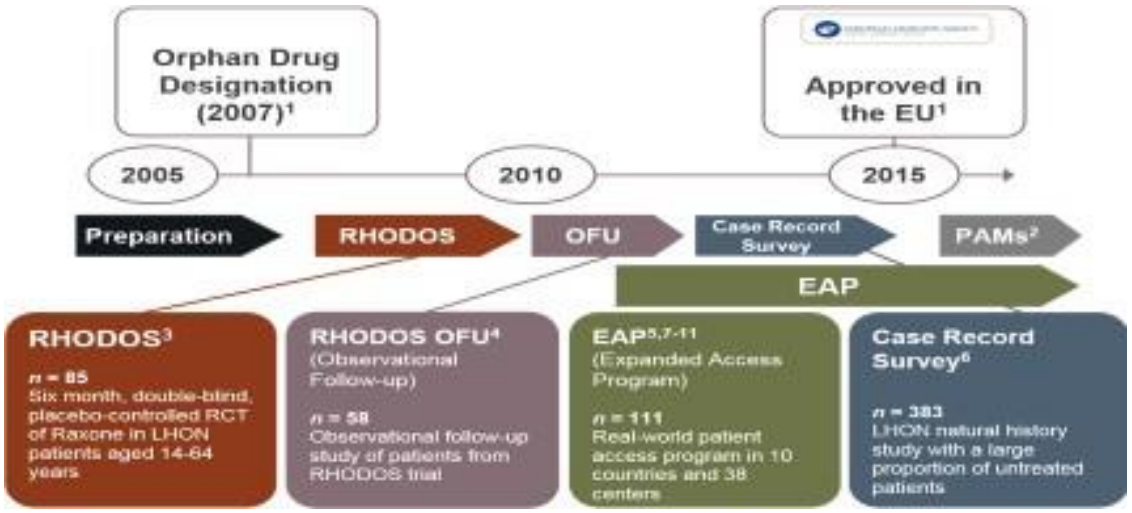
Idebenone development program in LHON



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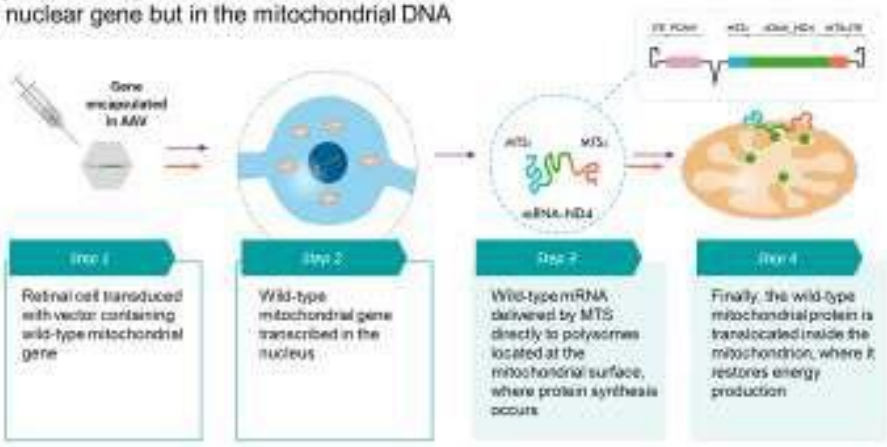
LHON – Gene therapy

- unmet need at least for idebenone non-responders
- the eye as an ideal organ for gene therapy
  - Immune-privileged, closed system
  - Intravitreal injections introduce genetic material close to target cells
  - Slow turnover of retinal cells support long-term expression of transduced genes
- AAV vector has proven safety and efficacy for transduction of retinal cells
- BUT: the mutation is not in a nuclear gene but in the mitochondrial DNA
  → allotopic expression



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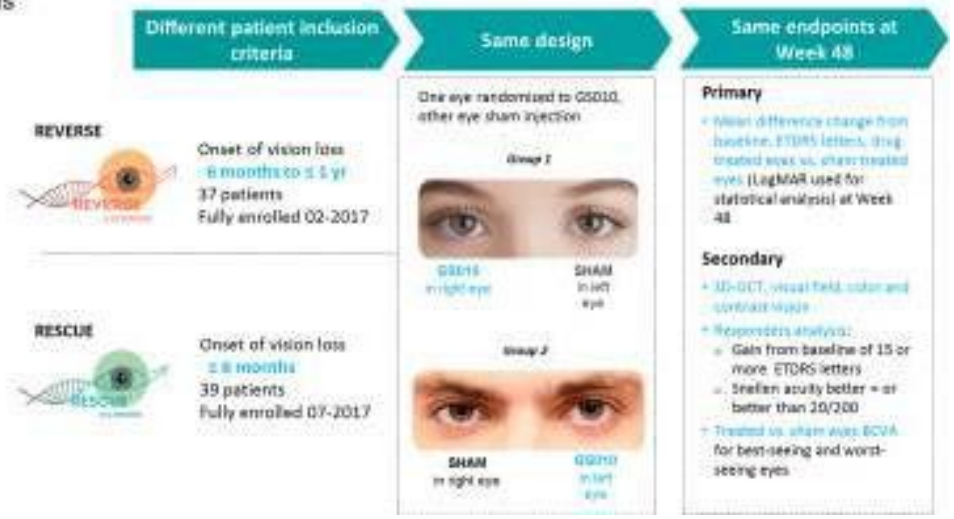
LHON – Gene therapy „from bench to bedside“

- GS010 restores respiratory chain complex I in patients fibroblasts
- GS010 prevents optic atrophy and visual loss in LHON rats
- Phase 1 trial demonstrates safety, tolerability and trends of efficacy
- Phase 3 trials



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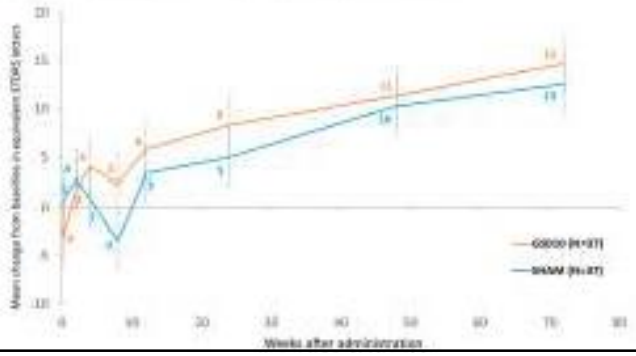
LHON – Gene therapy - Results

- well tolerated, frequent intraocular inflammation responsive to conventional treatment and without sequelae
- change in retinal ganglion cell macular volume from baseline to week 72
  - Treated eyes: no loss
  - Untreated eyes: -0.044mm³ p=0.0080 (ANCOVA analysis)
- change in thickness of the papillo-macular bundle from baseline to week 72
  - Treated eyes: -1.6 µm
  - Untreated eyes: -3.6 µm p=0.0362 (ANCOVA analysis)
- clinically meaningful improvement of +15 ETDRS letters in treated eyes but similar in untreated eyes



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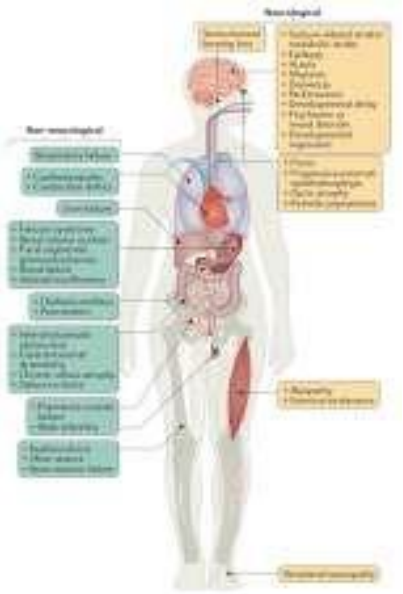
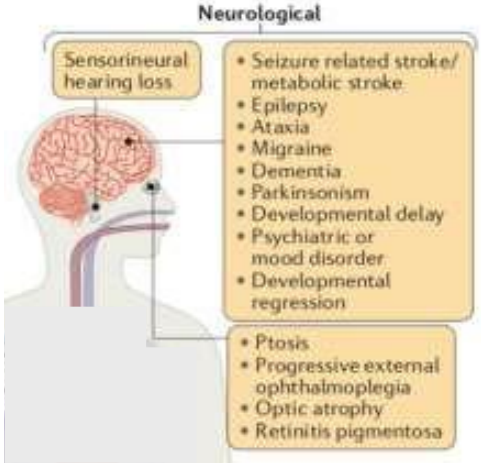
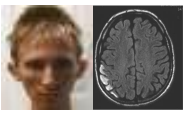
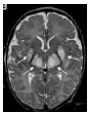
Mitochondrial diseases of the brain






MELAS


MERRF


Leigh sy.


LHON

Gorman et al, 2016

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Networks

Antragstellung für die Fördermaßnahme
Translationsorientierte Verbundvorhaben im Bereich der seltenen Erkrankungen

Federal Ministry of Education and Research

mitoNET
German Network for mitochondrial disorders

No.	Principal investigator	Institution	Title of Subproject	Function in the consortium
1	Dr. Klopstock Dr. Prokisch Dr. Komblum	LMU München TU München Univ. of Bonn	Coordination of the consortium	Coordination, Monitoring, Processing of results
2*1	Dr. Prokisch Dr. Freisinger	TU München Children Hospital Reutlingen	mitoGENE	Molecular diagnostics by whole genome and RNA sequencing
2*2	Dr. Kremer Dr. Prokisch	TU München TU München	mitoVALID	Validation platform for variants of uncertain significance by functional complementation
2*3	Dr. Pietzner Dr. Kastenmüller	Univ. Greifswald TU München	mitoMETABO	Biomarker discovery for disease, progression and treatment by metabolomics
2*4	Dr. Wittig Dr. Meierhofer	Univ. of Frankfurt MPI Berlin	mitoPROT	Investigate molecular pathomechanisms and treatment effects by proteomics and complexomics
4*1	Dr. Klopstock Dr. Büchner Dr. Gagneur	LMU München LMU München TU München	mitoREGISTRY	Clinical registry (cross-sectional and longitudinal)
4*2	Dr. Steinmetz Dr. Komblum Dr. Klopstock	EMBL Heidelberg Univ. of Bonn LMU München	mitoWEAR	eHealth project to evaluate utility of wearable activity monitors as possible new endpoints for future clinical trials
5	Dr. Meitinger	TU München	mitoSAMPLE	To collect biological materials and make them available for mitochondrial research

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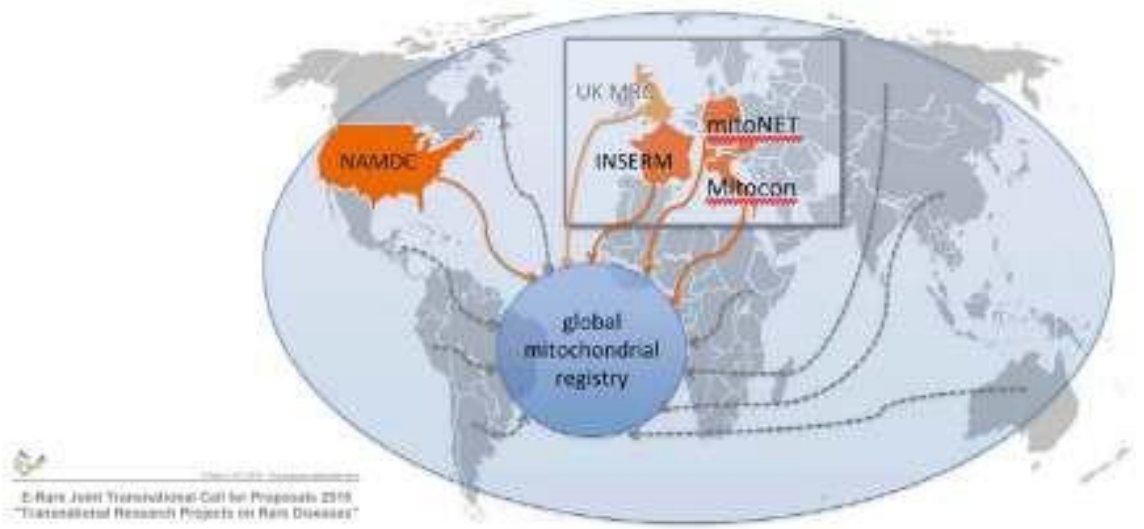
Global Networks

GENOMIT

Mitochondrial Disorders:
from a world-wide registry to medical genomics, toward molecular mechanisms and new therapies



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Ludwig-Maximilians-Universität München
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Friedrich-Baur-Institute
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Anna Baur-Ulatowska
Almut Bischoff
Ira Brandstetter
Boriana Büchner
Claudia Catarino
Ivan Karin
Florentine Radelfahr
Claudia Stendel
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mitoNET
German Network for mitochondrial disorders

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