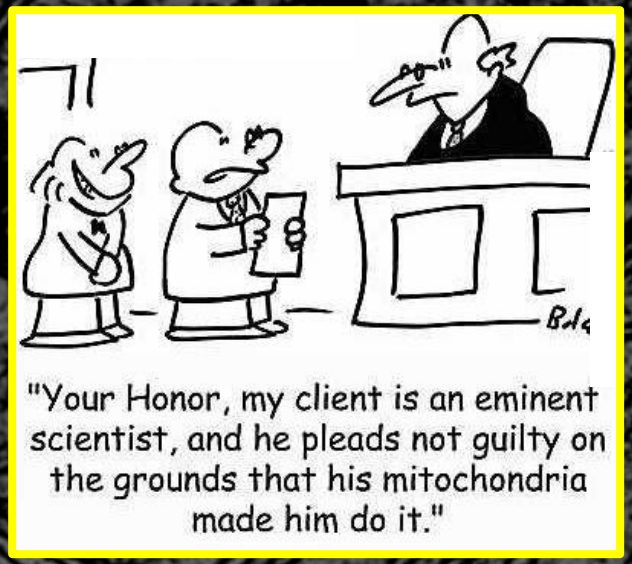
Mitochondrial Optic Neuropathies
Clinical Syndromes



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Financial Disclosures

- Consultant for GenSight Biologics
- Data Safety Monitoring Board Quark Study
- Medical-legal consultant

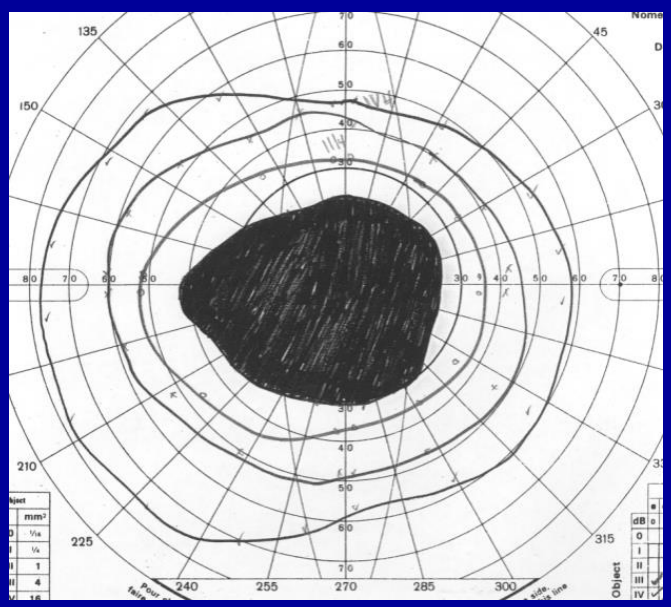
Learning Objectives

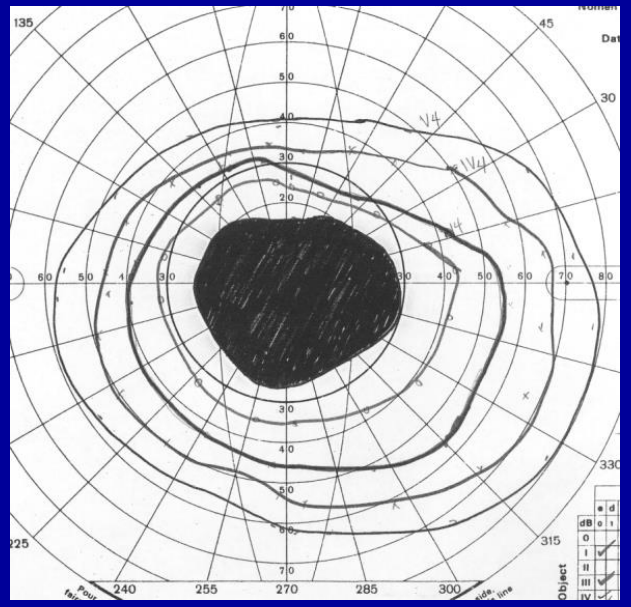
At the end of this session, participants will:

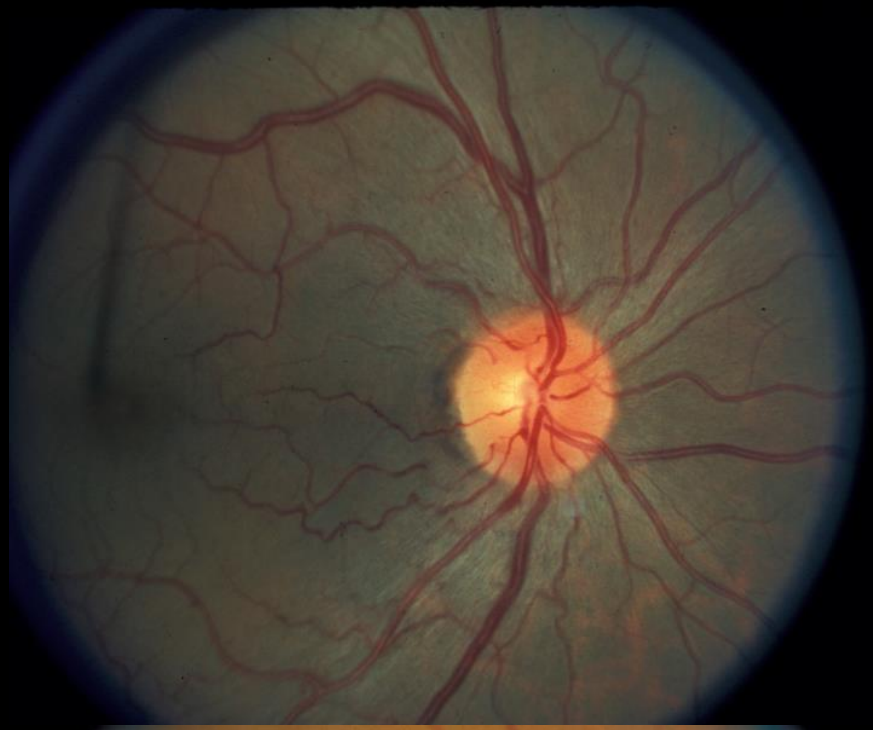
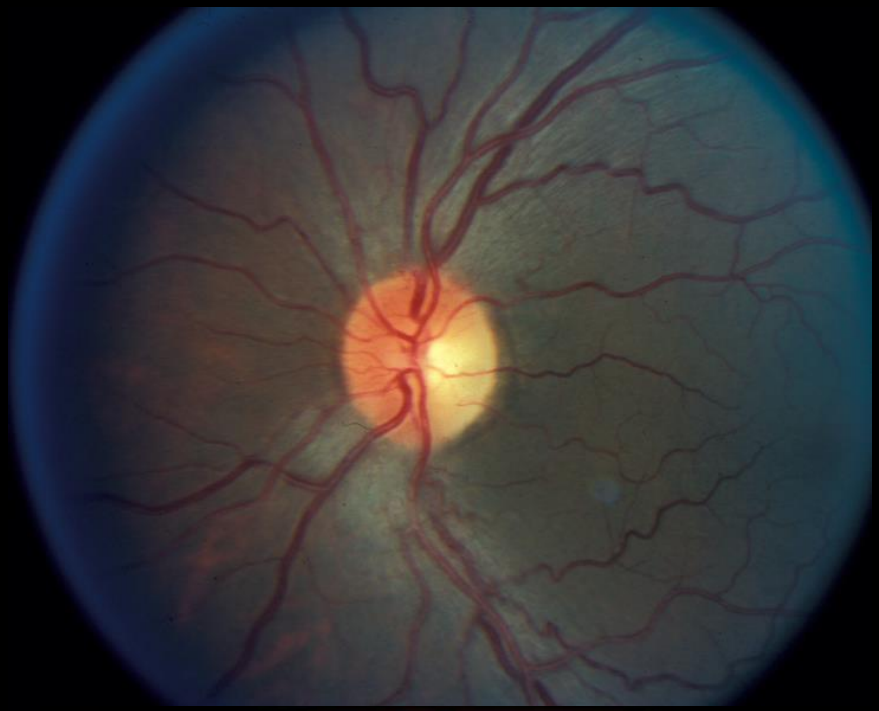
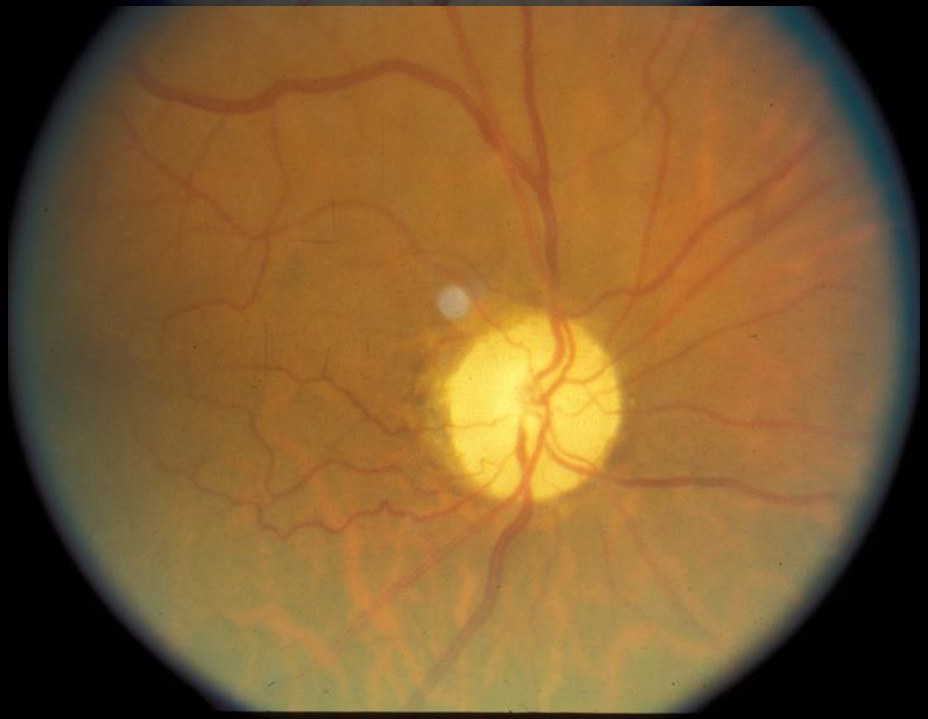
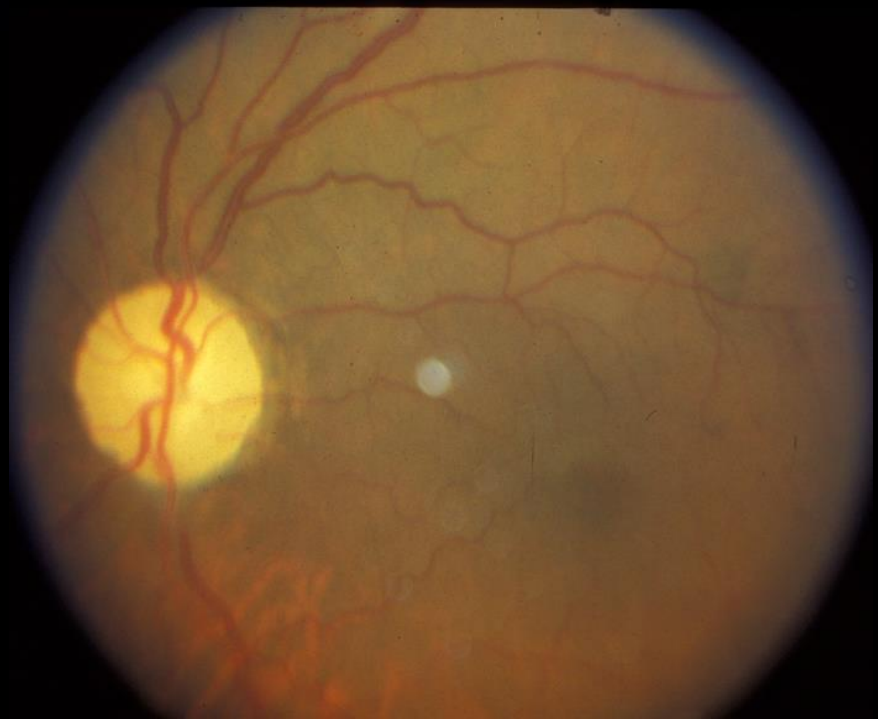
1. Recognize the clinical syndromes of the inherited mitochondrial optic neuropathies
2. Be aware that optic neuropathies occur not infrequently in syndromic disorders with a common final pathway of mitochondrial dysfunction

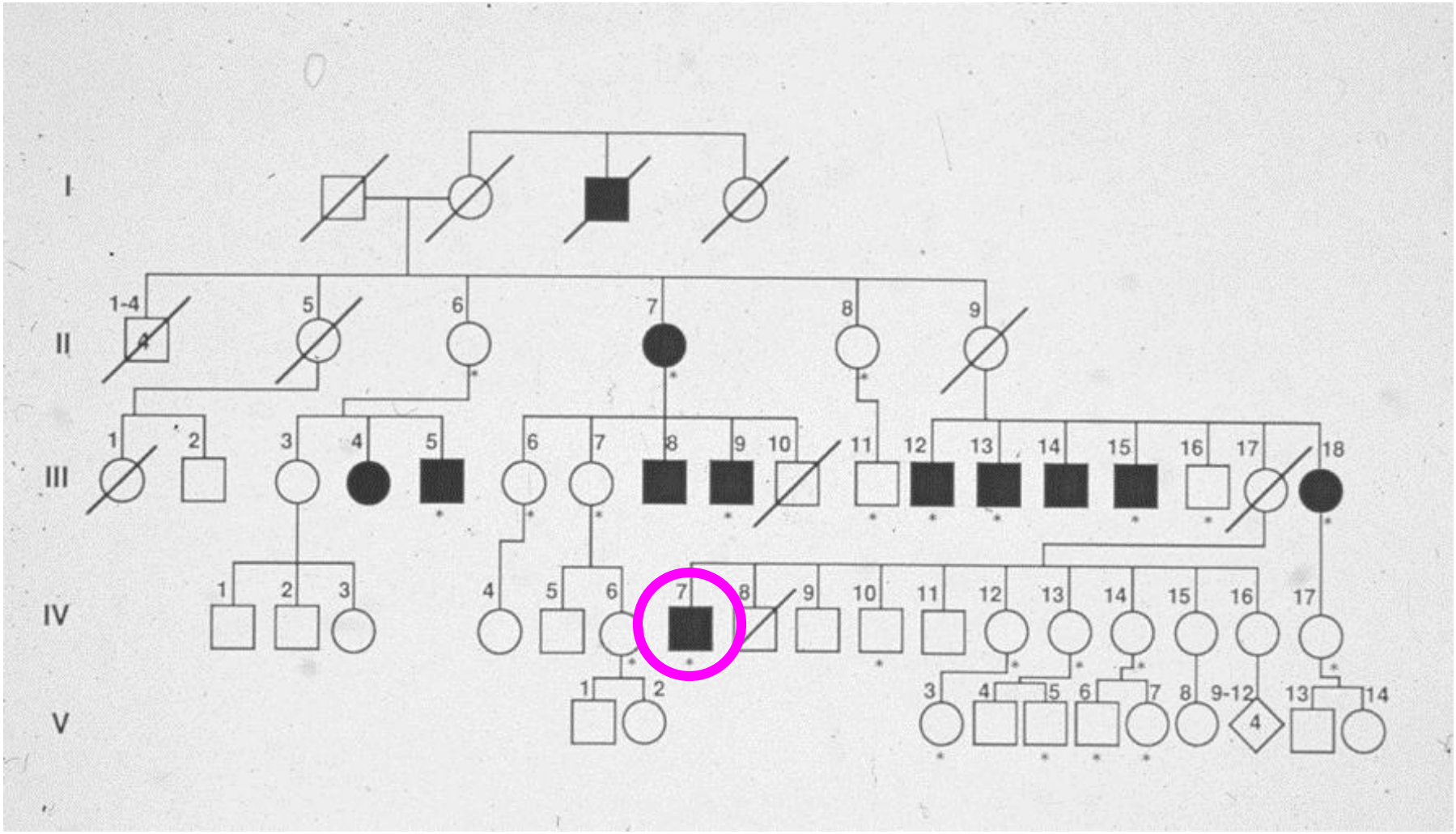
A 25 year old previously healthy man has painless loss of vision over 1 month in one eye and then 2 months later in the other

Vision is counting fingers in both eyes



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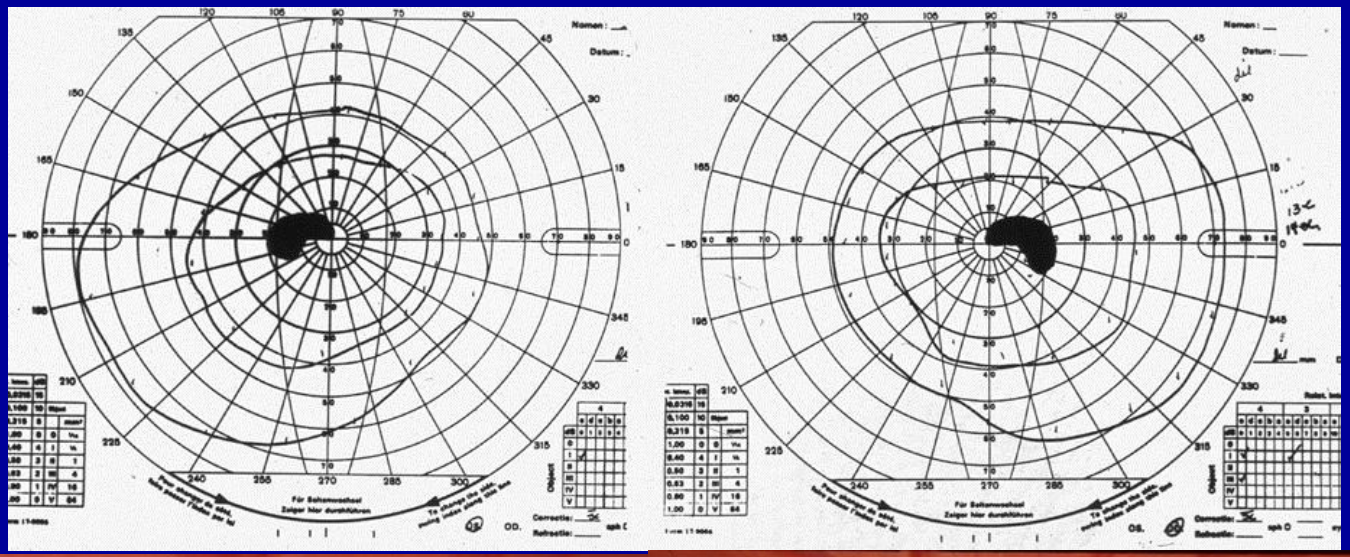
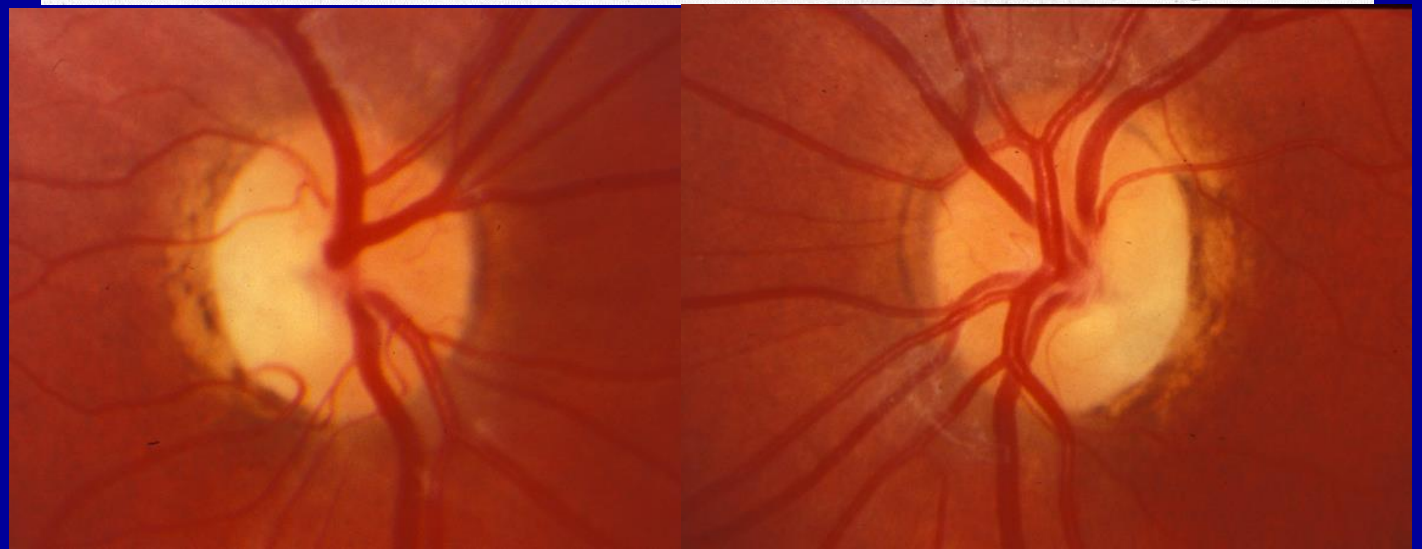
7 year old girl failed her school eye exam

Examination shows 20/50 vision both eyes



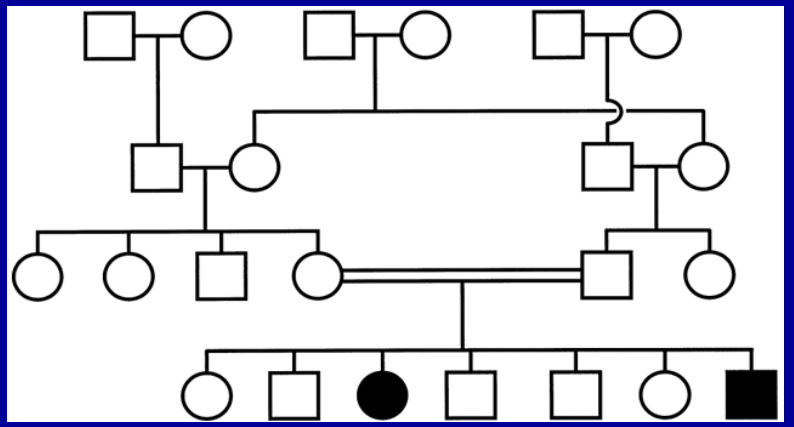


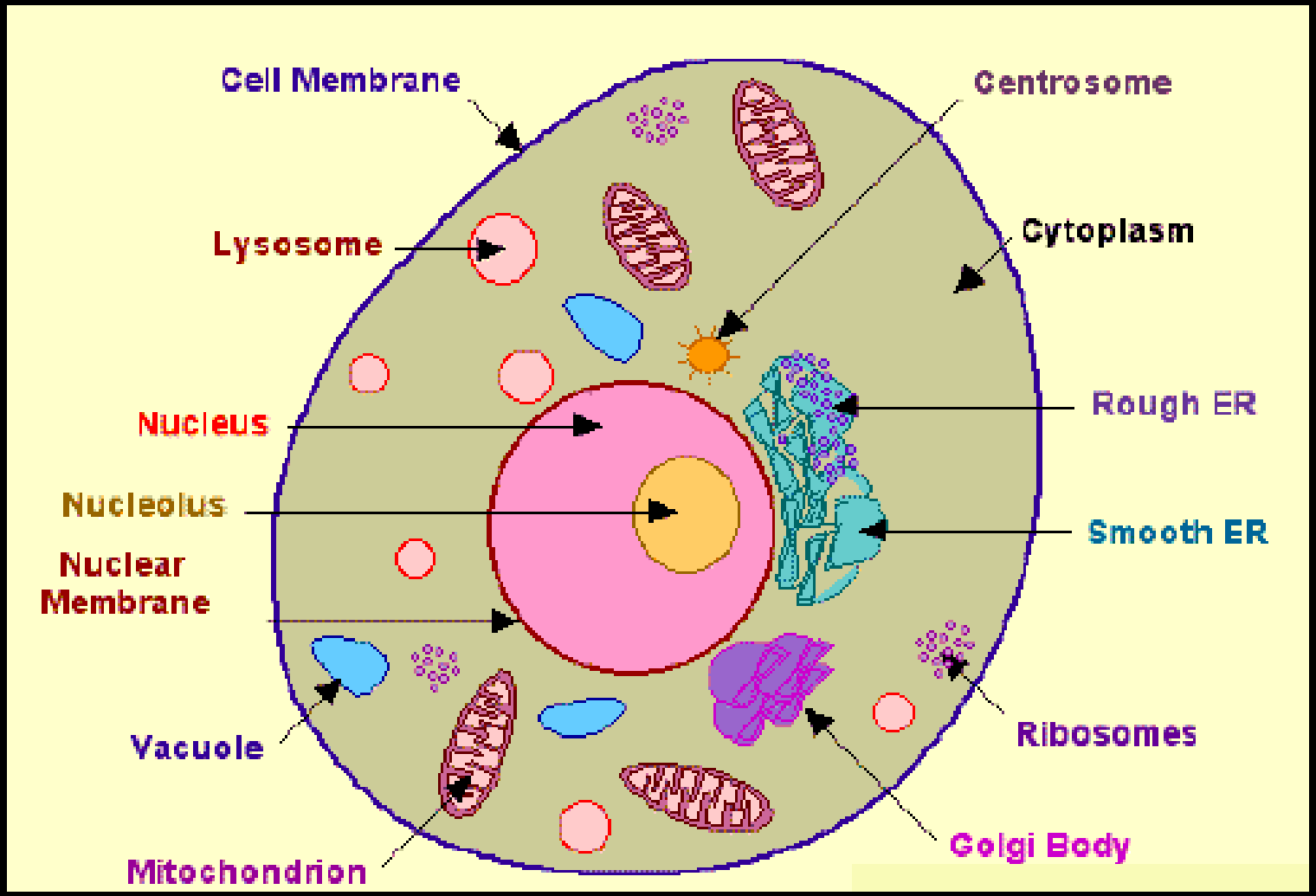
A 5 year old boy of Iraqi Jewish descent has developmental delay, spasticity, and severe visual loss with nystagmus and optic atrophy

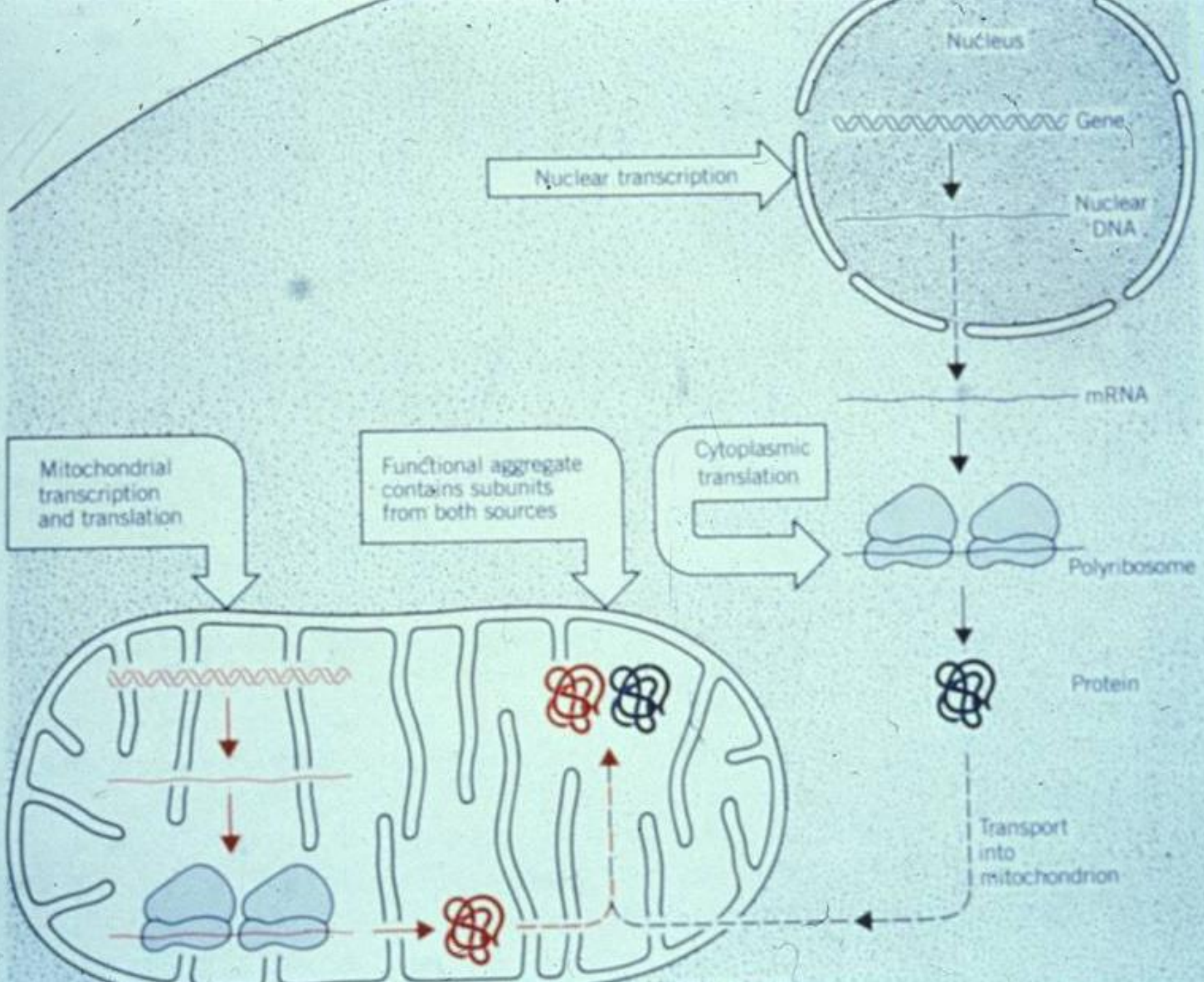
3-methylglutaconic acid levels are elevated in his urine

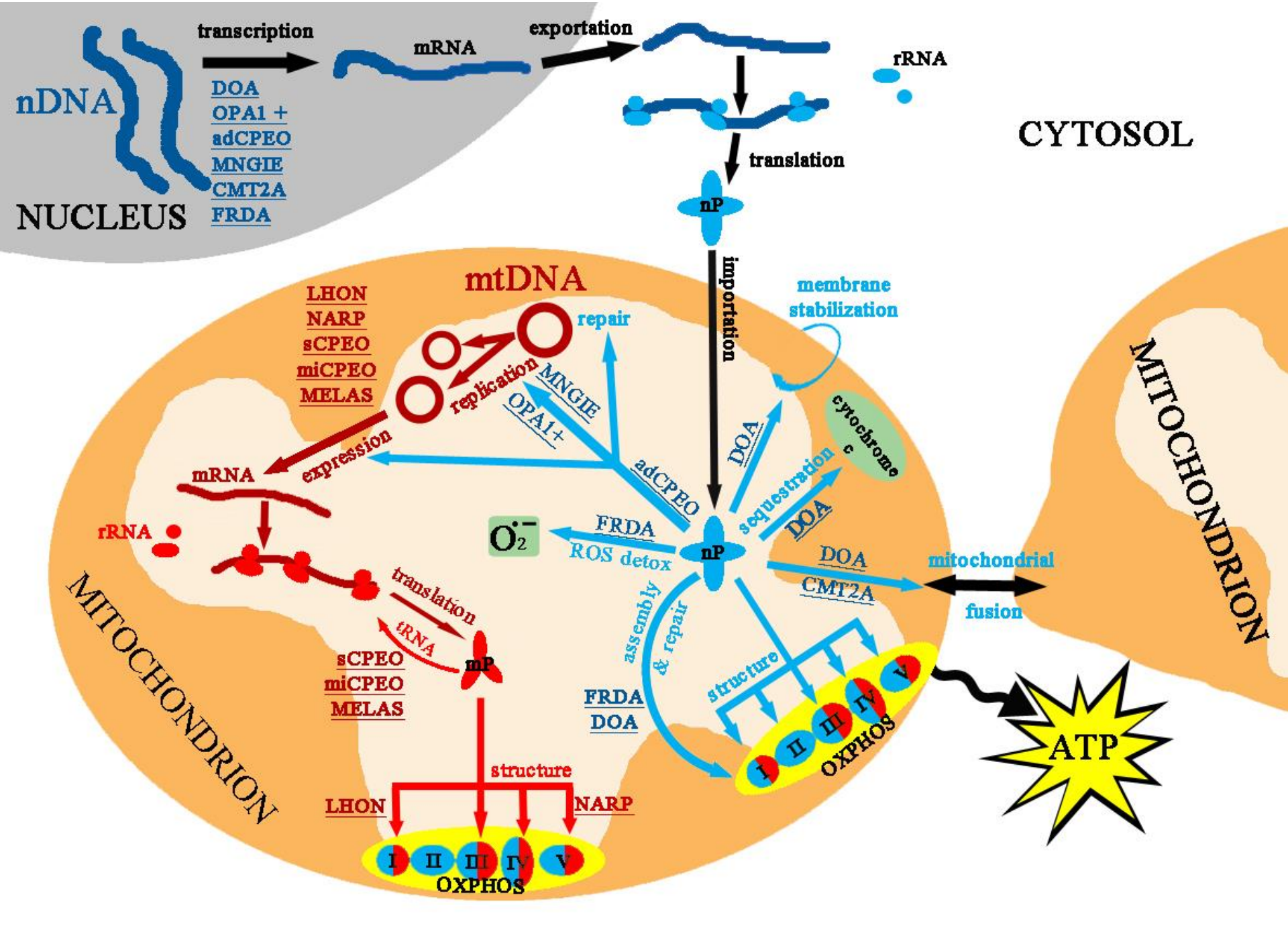
An older sister has a similar disorder, but not 5 other siblings

The parents are 1st cousins




Cell Membrane
Centrosome
Lysosome
Cytoplasm
Nucleus
Rough ER
Nucleolus
Smooth ER
Nuclear Membrane
Vacuole
Ribosomes
Mitochondrion
Golgi Body


Nucleus
Gene
Nuclear transcription
Nuclear DNA
mRNA
Mitochondrial transcription and translation
Functional aggregate contains subunits from both sources
Cytoplasmic translation
Polyribosome
Protein
Transport into mitochondrion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mRNA
exportation
rRNA
CYTOSOL
translation
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OPA1 +
adCPEO
MNGIE
CMT2A
FRDA
nP
importation
mtDNA
LHON
NARP
sCPEO
miCPEO
MELAS
repair
replication
MNGIE
OPA1+
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cytochrome
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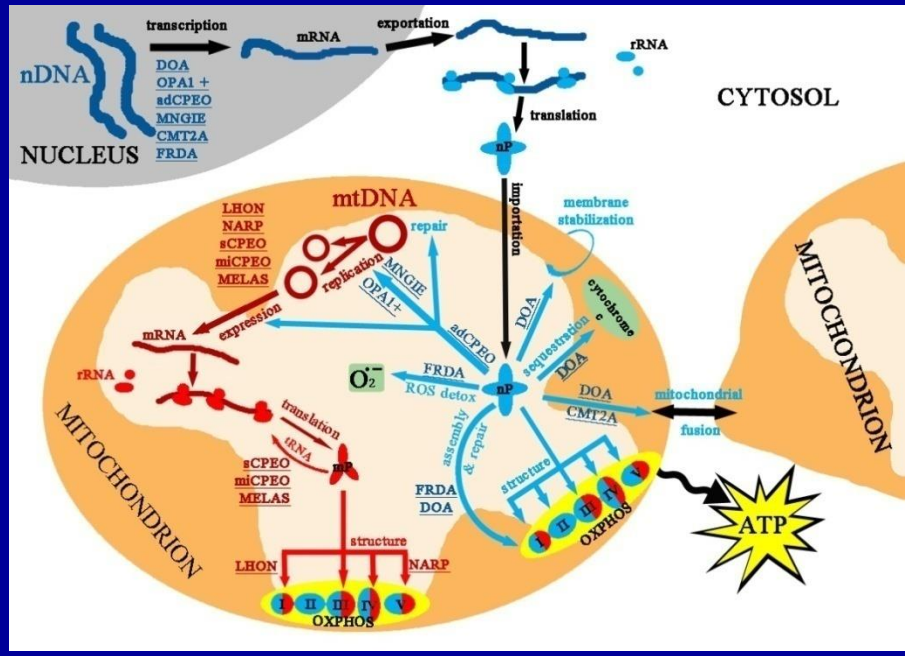
MITOCHONDRION

Mitochondrial Diseases

Potential Defect Sites:

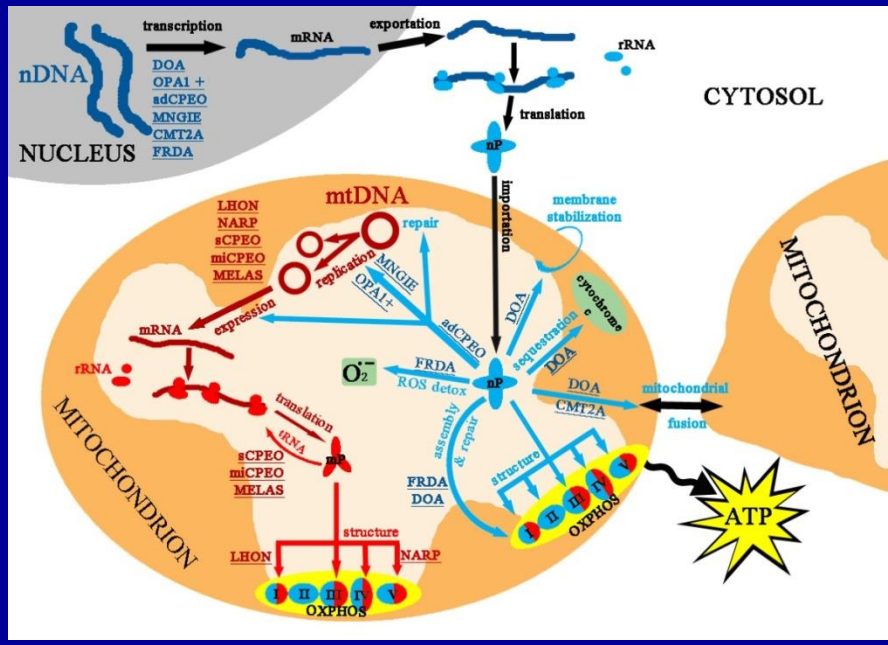


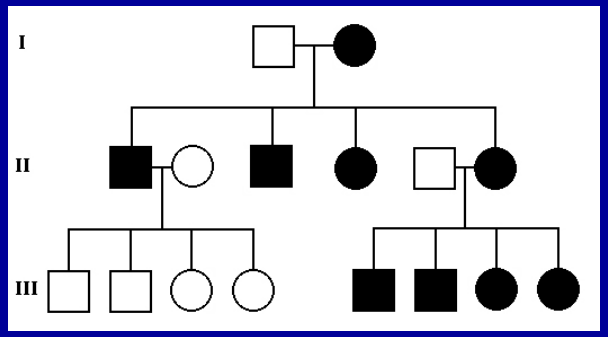
- Mitochondrial DNA
- Nuclear DNA
- Post-translational processing
- Nuclear-encoded control of mtDNA

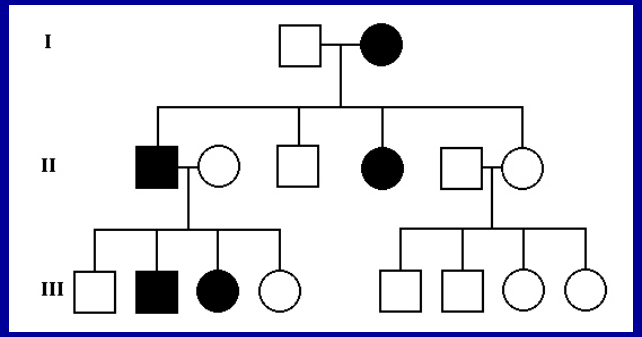
Mitochondrial Diseases

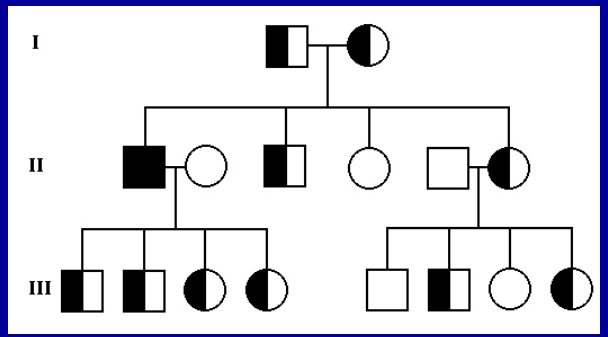
Inheritance

- Maternal (mtDNA)
- Autosomal Dominant
- Autosomal Recessive

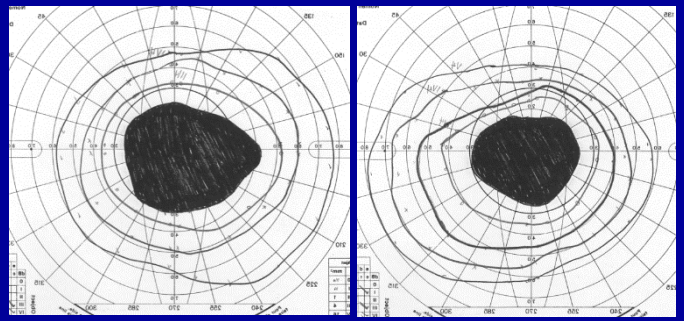


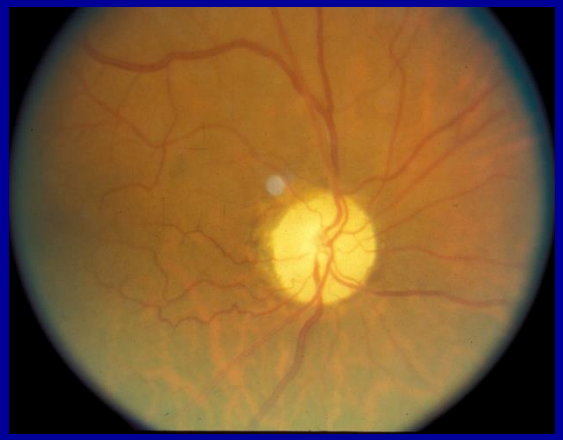


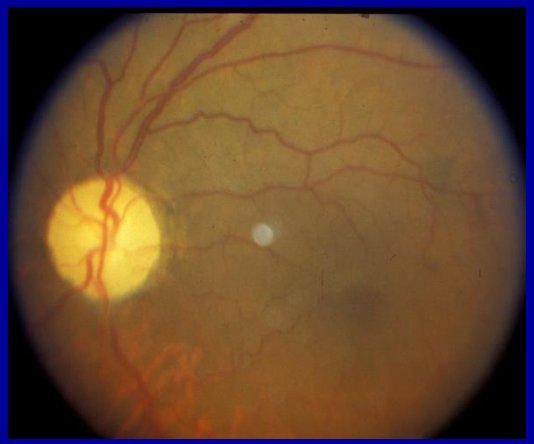




A 25 year old previously healthy man has painless loss of vision over 1 month in one eye and then 2 months later in the other





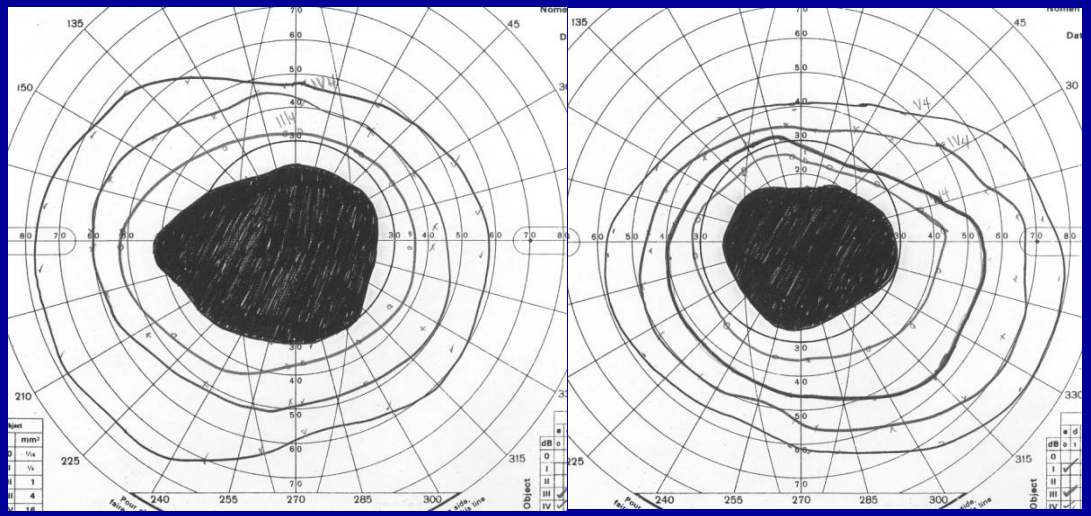


Leber's Hereditary Optic Neuropathy

- Subacute sequential bilateral central visual loss
- Age of onset typically 18-30 (range 1-87)
- Male predominance (80-90%)
- Progression in each eye over weeks to months
- Recognized interval between eyes in 50% (days to months)
- > 97% bilateral within 1 year

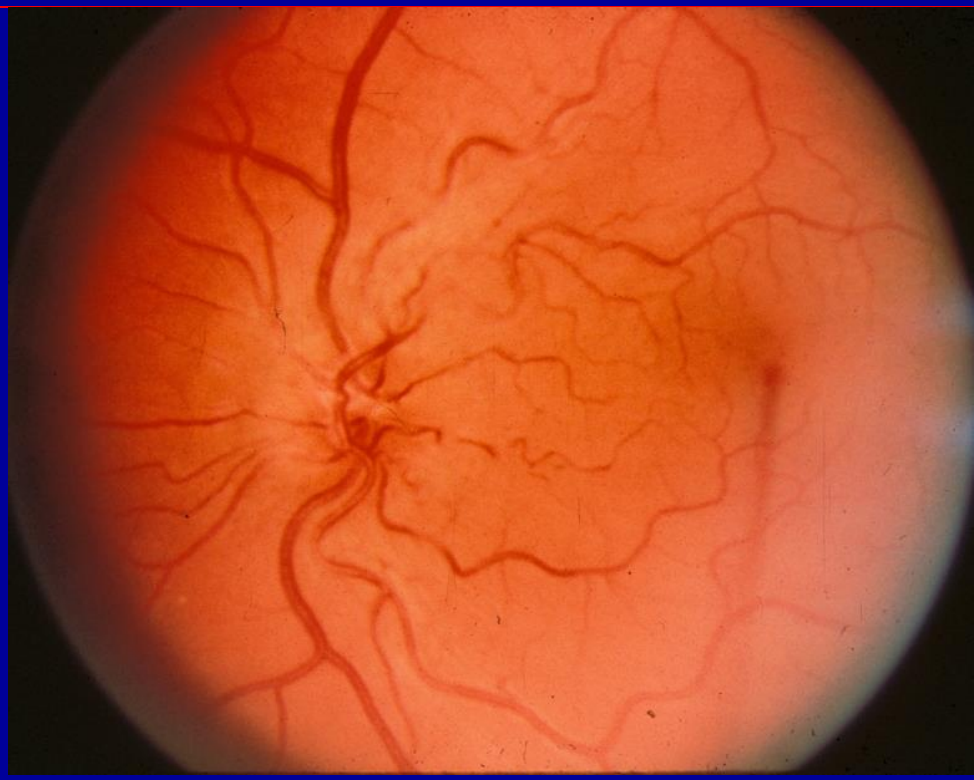
Leber's Hereditary Optic Neuropathy

- Acuity usually worse than 20/200
- Color vision affected early
- Central defects

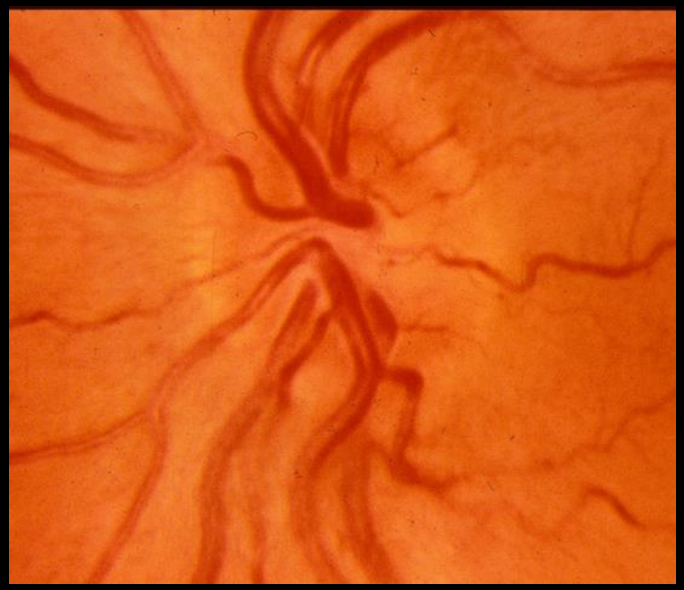
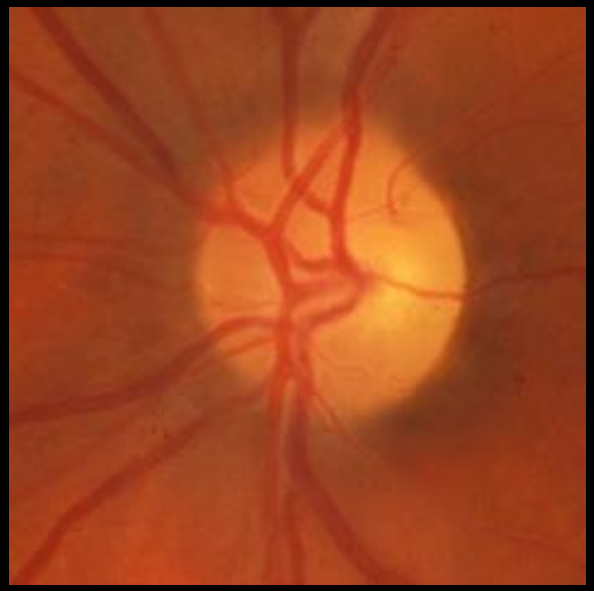
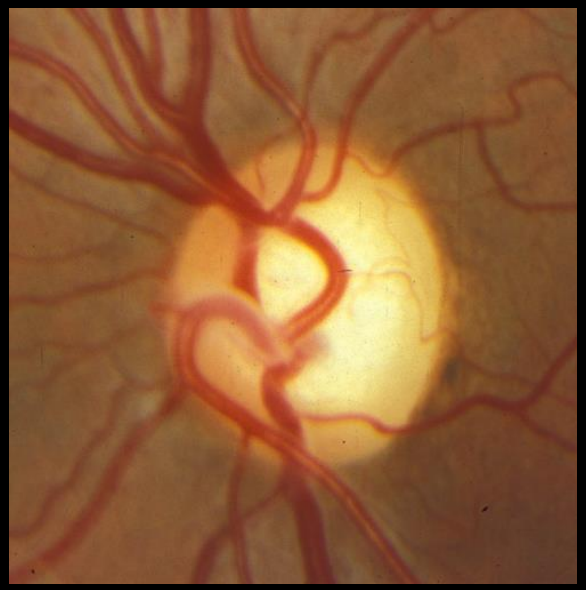


Leber's Hereditary Optic Neuropathy

Ocular Fundus



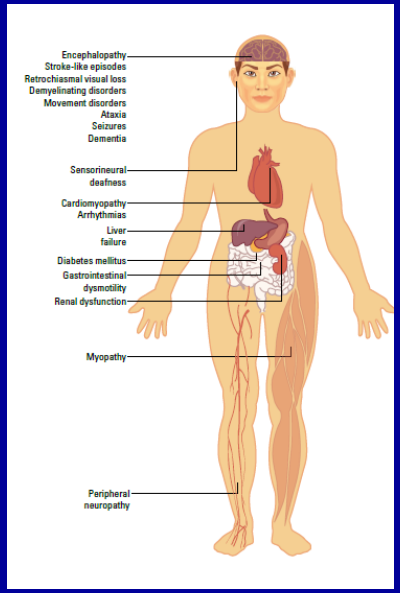
- Early ophthalmoscopy
  - Vascular tortuosity
  - Circumpapillary telangiectatic microangiopathy
  - Disk pseudoedema (no leakage on FA)

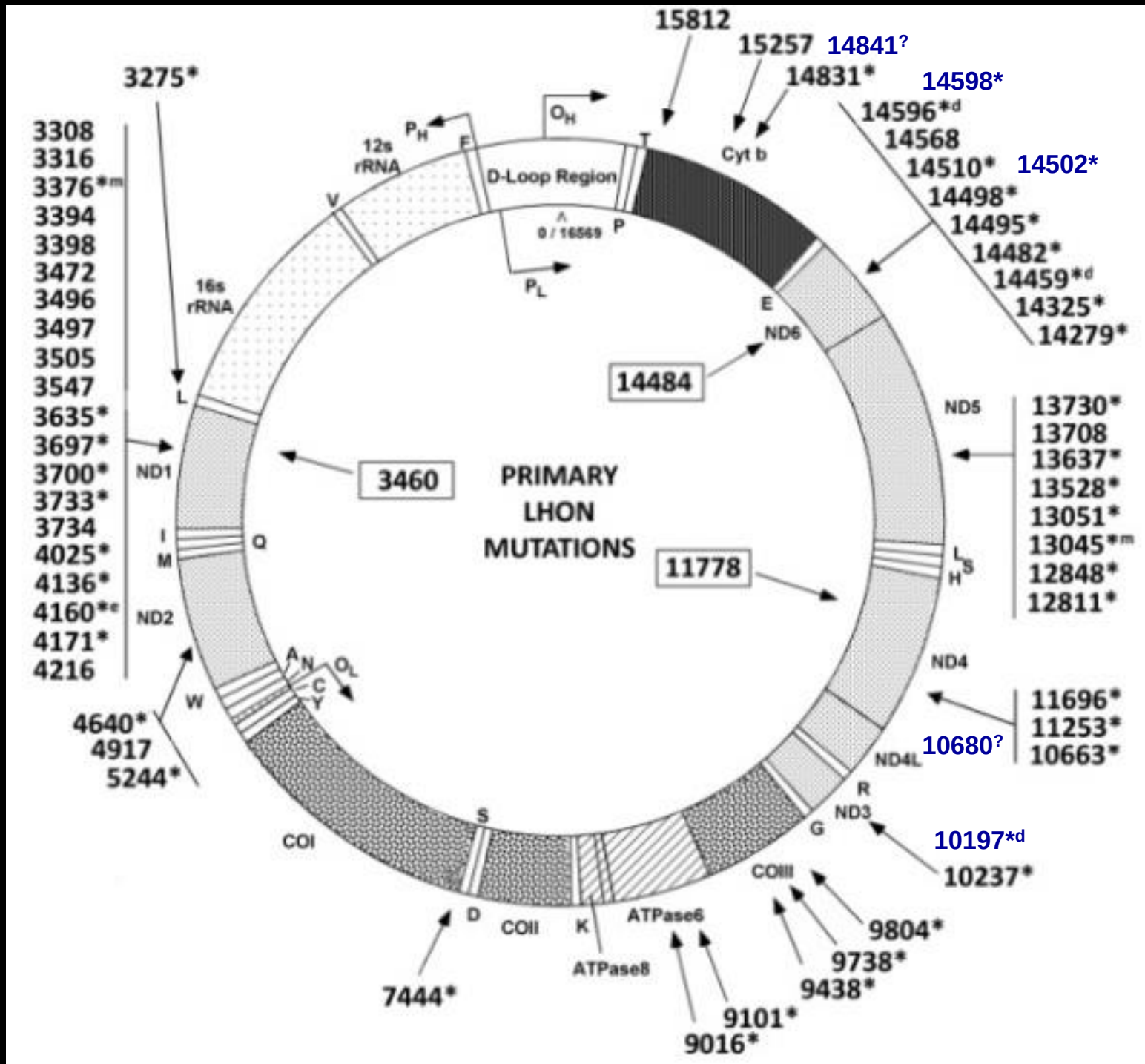




Leber's Hereditary Optic Neuropathy

Associated Findings

- Cardiac conduction defects
- Minor neurologic abnormalities
- Multiple sclerosis-like illness
- More severe neurologic syndromes

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ATPase6
COIII
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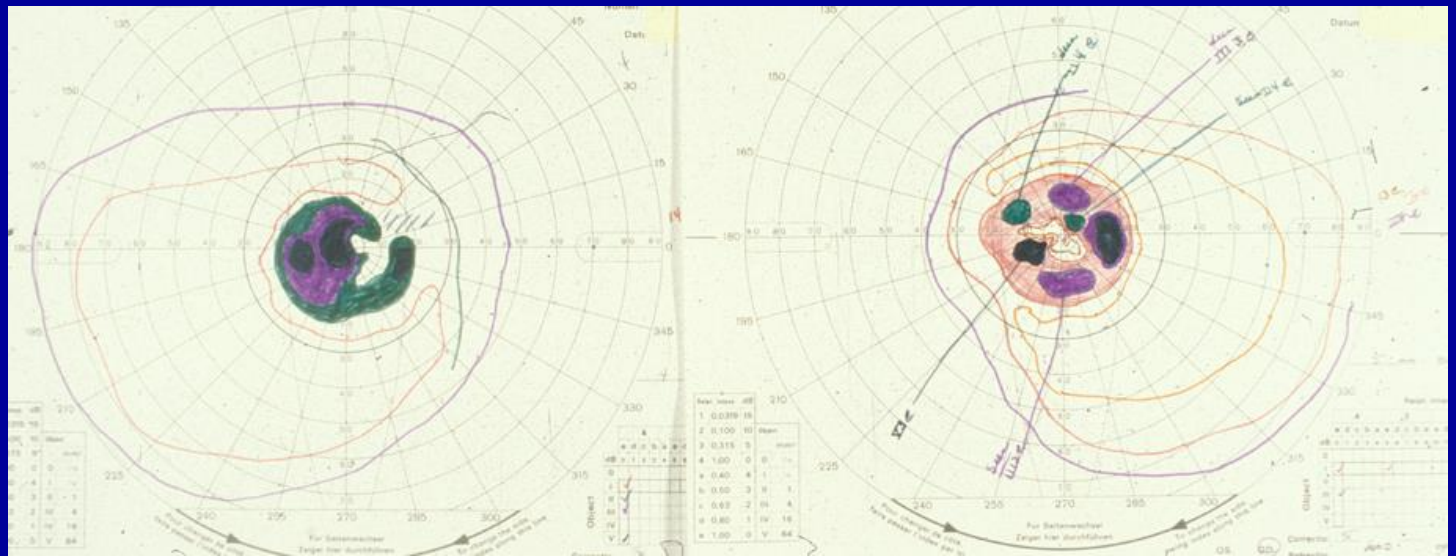
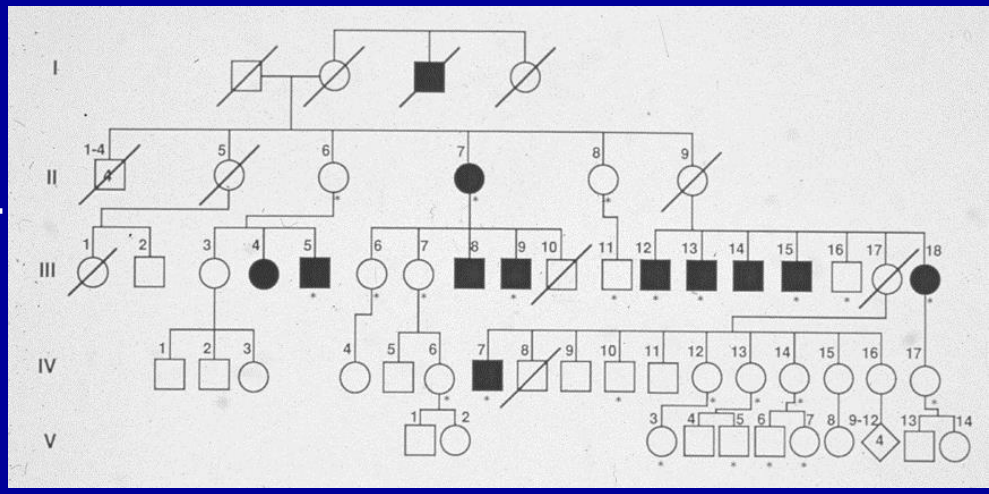
Leber's Hereditary Optic Neuropathy

Spontaneous Recovery

- May occur years later
- 4% - 71%
- Depends on the mtDNA mutation
- More likely if visual loss before age 20 (esp <10)
- ? More likely if thicker RNFL and larger discs



Leber Hereditary Optic Neuropathy



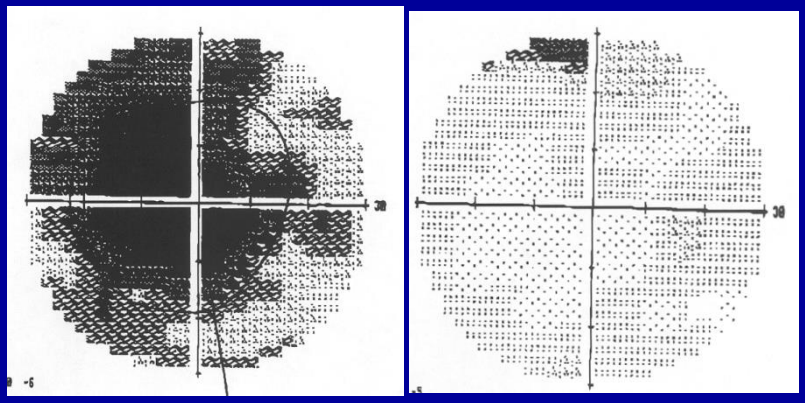
Determinants of Phenotype

- Genotype
  - –the mutation
  - –heteroplasmy
- MtDNA factors
- Nuclear factors
- Environmental factors

Leber Hereditary Optic Neuropathy

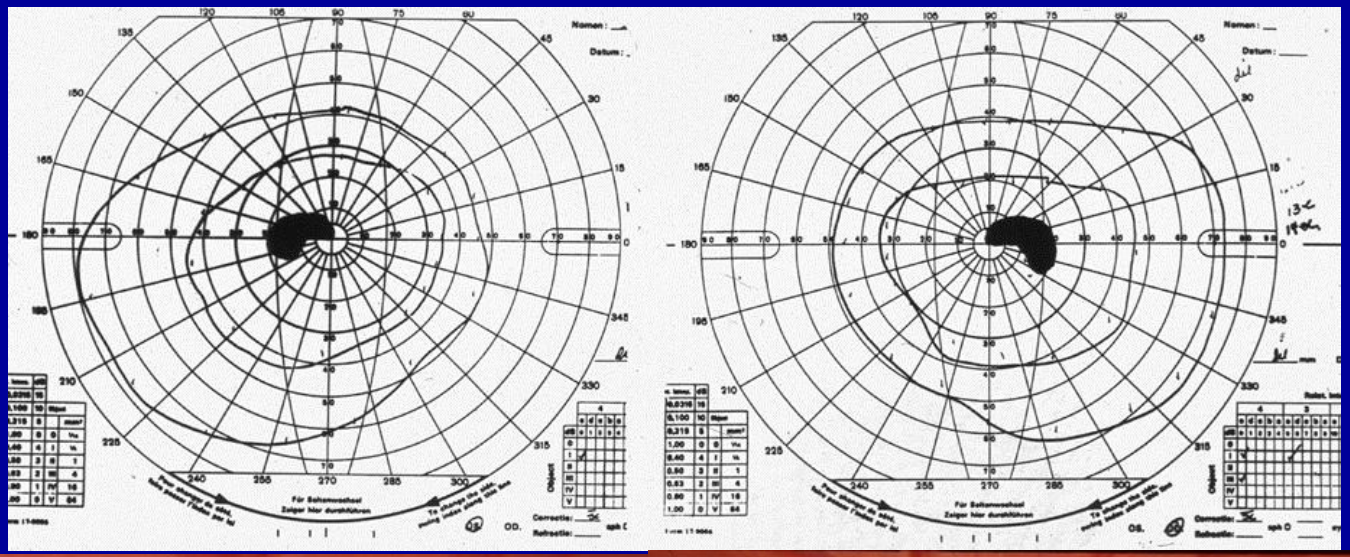
Treatment

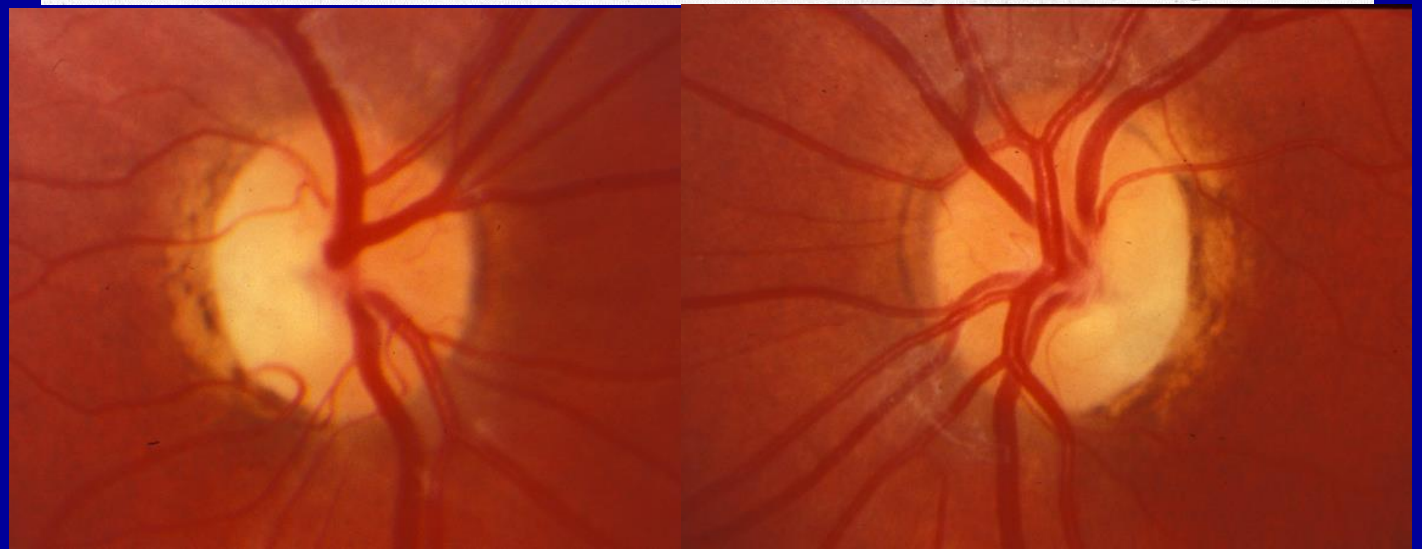
- Ideal “laboratory” for testing treatment efficacy
  - Sequential visual loss: therapeutic window
  - Accessibility via topical or intravitreal route
  - Implications for other optic neuropathies



7 year old girl failed her school eye exam

Examination shows 20/50 vision both eyes



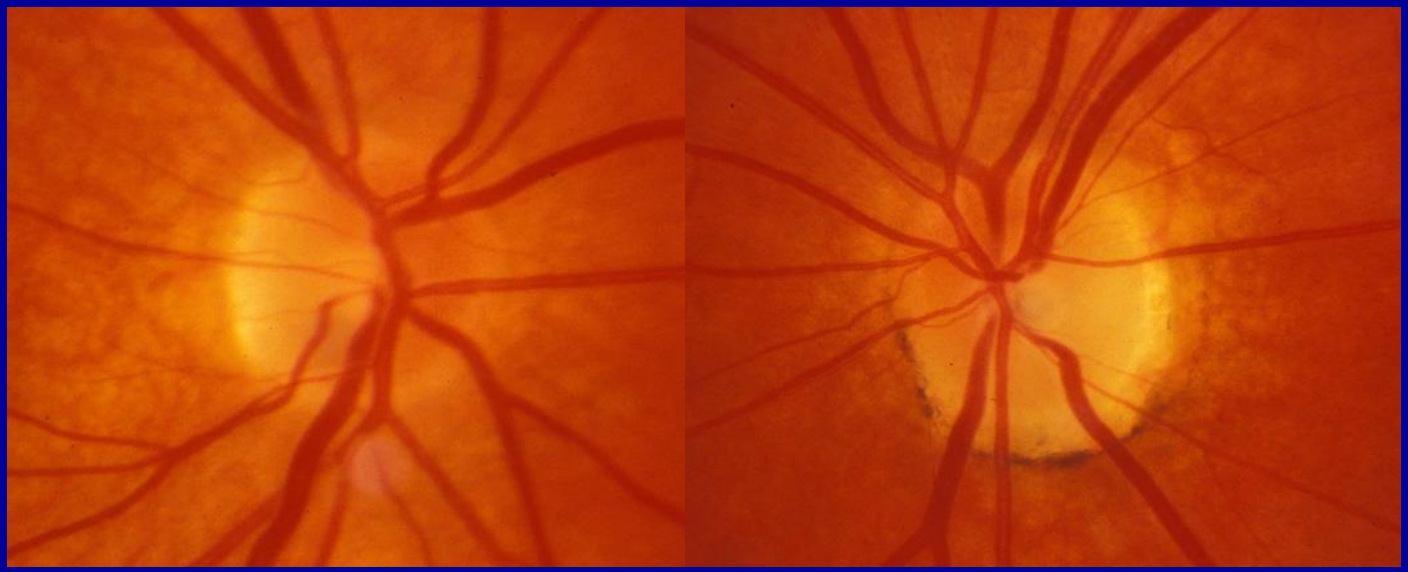


Examination of father:

Father: 20/25 OU

12/14 color OU

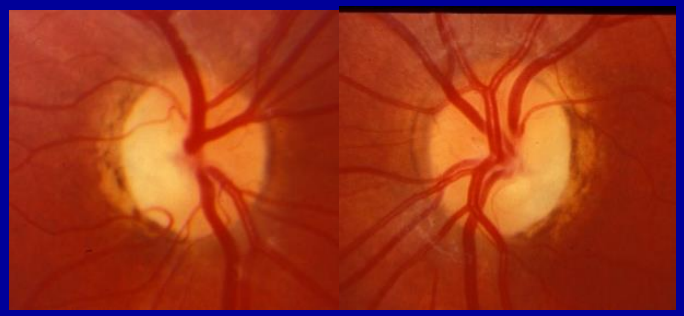
Optic nerves ? pale

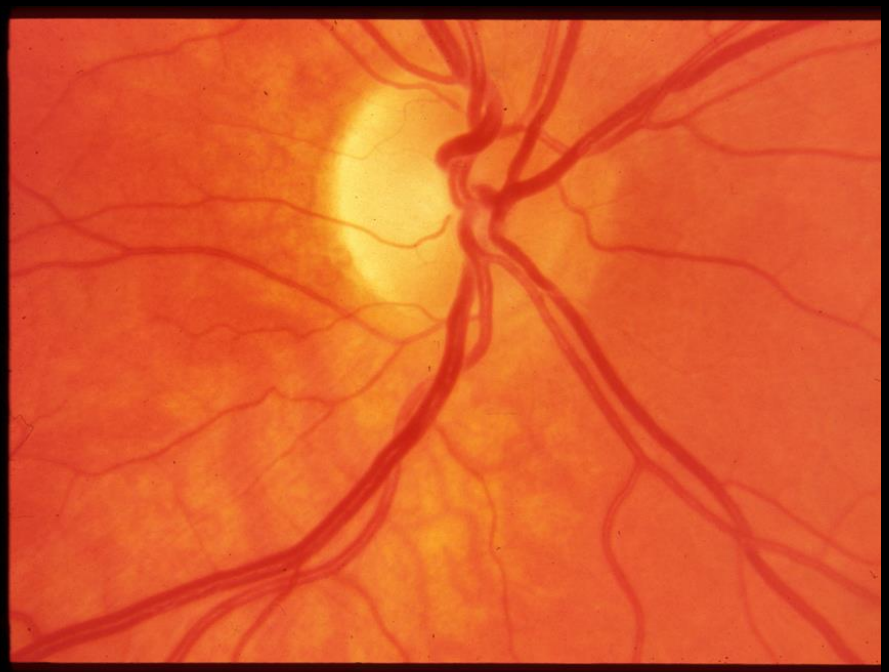
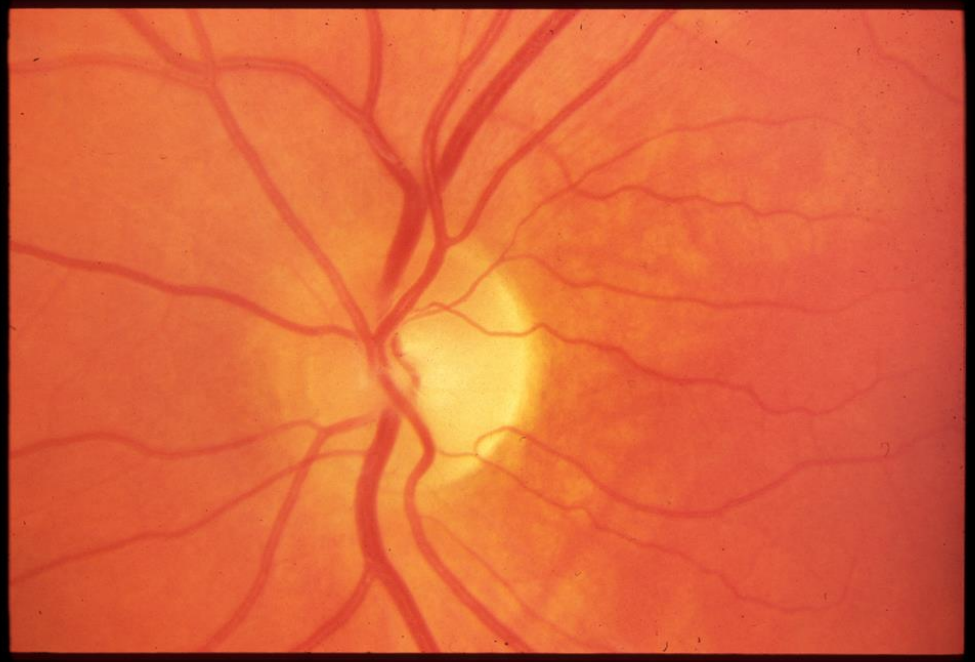


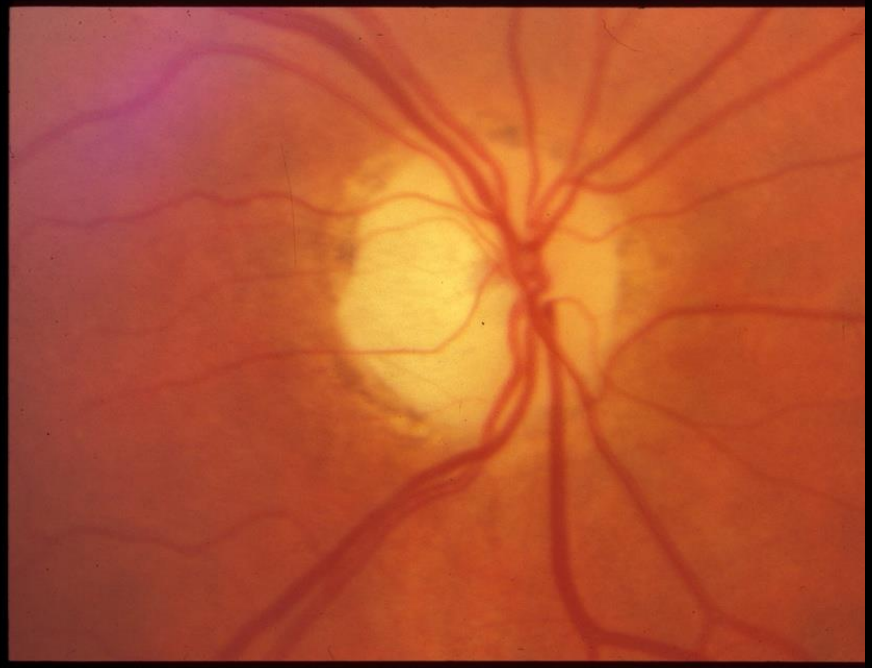
Dominant Optic Atrophy

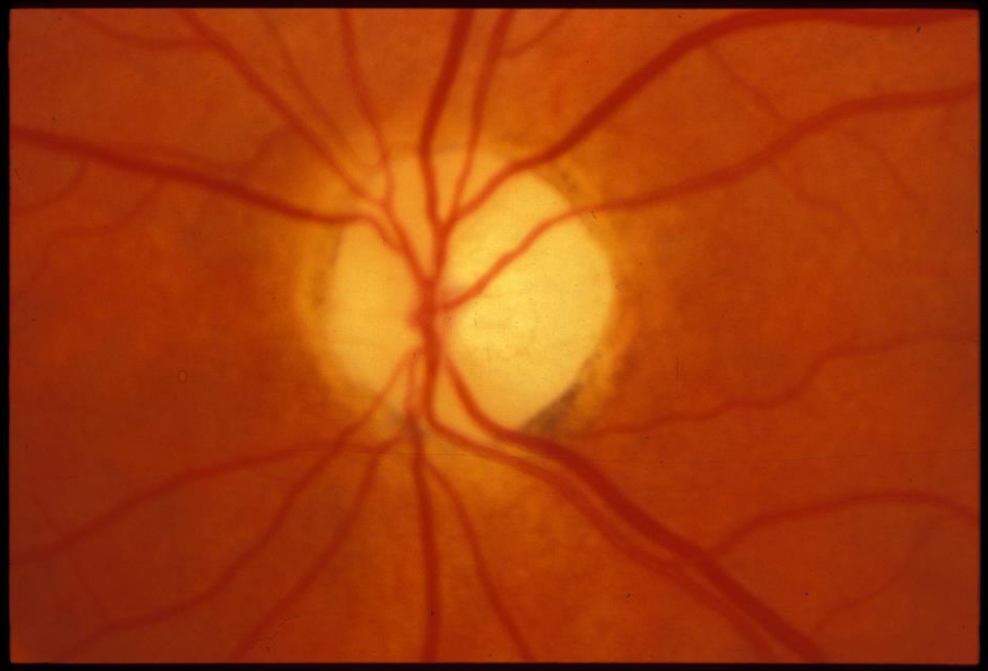
Kjer's

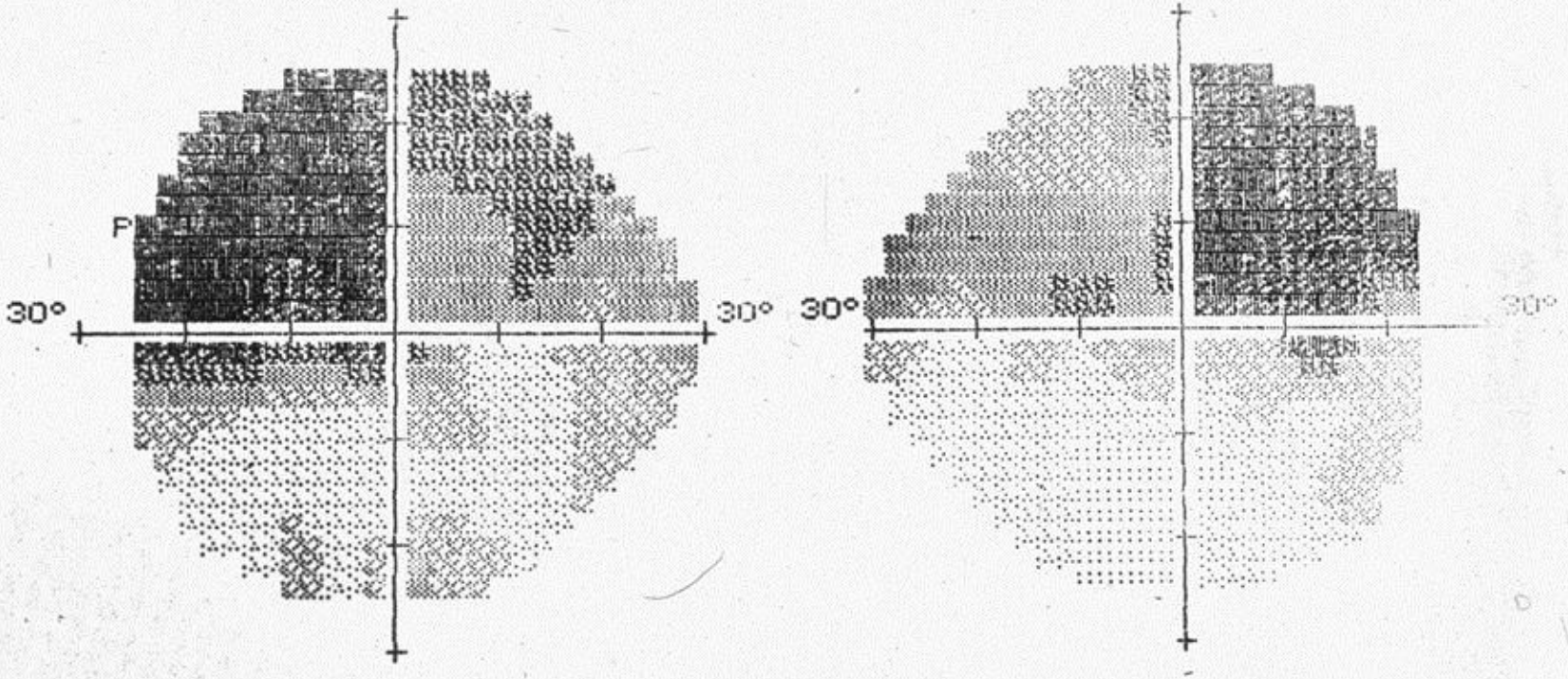
- Insidious onset age 4-8 (58-84% by age 11)
- Acuity 20/40 – 20/200 (mean 20/80-20/120)
- Mild progression (19-67%)
- Symmetric
- Tritanopia/mixed color deficit
- Excavated wedges of temporal pallor





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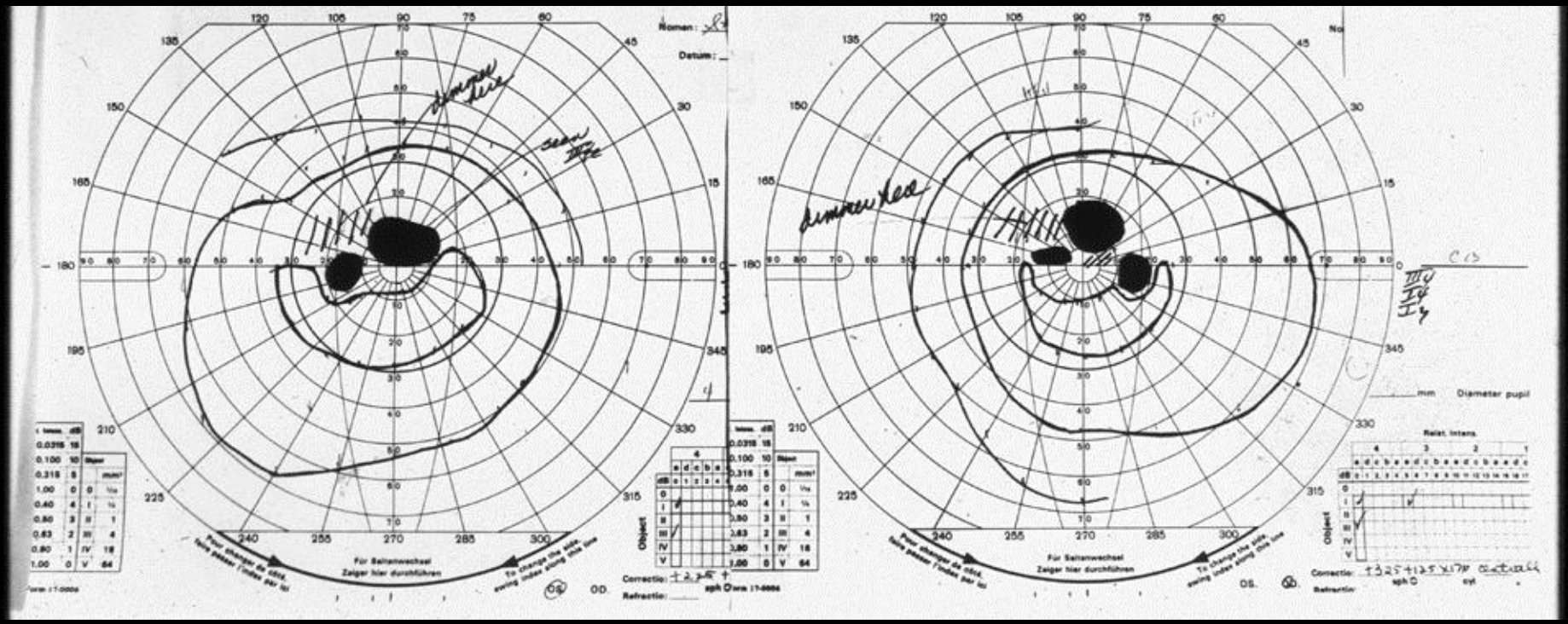
Für Seitenwechsel Zeiger hier durchführen
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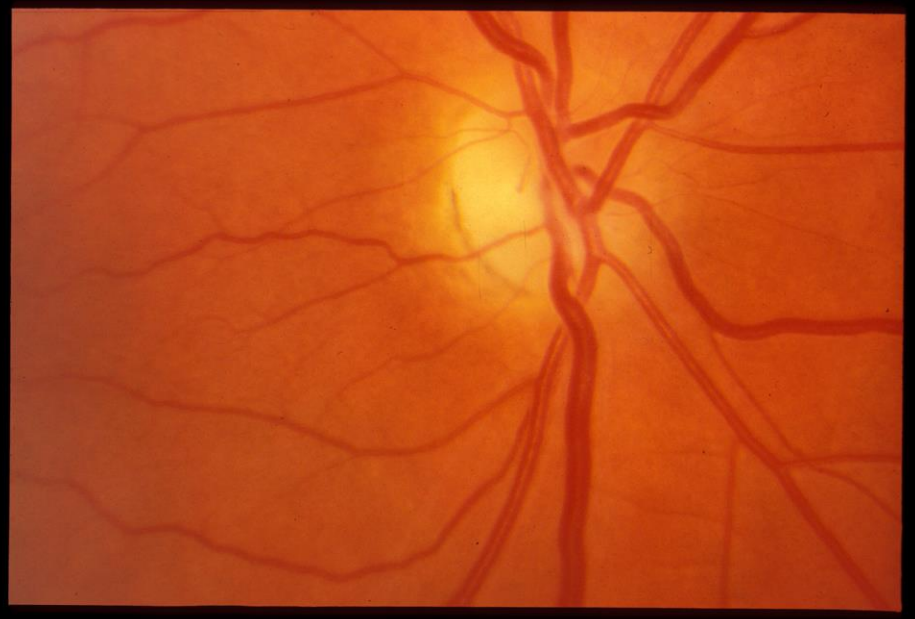

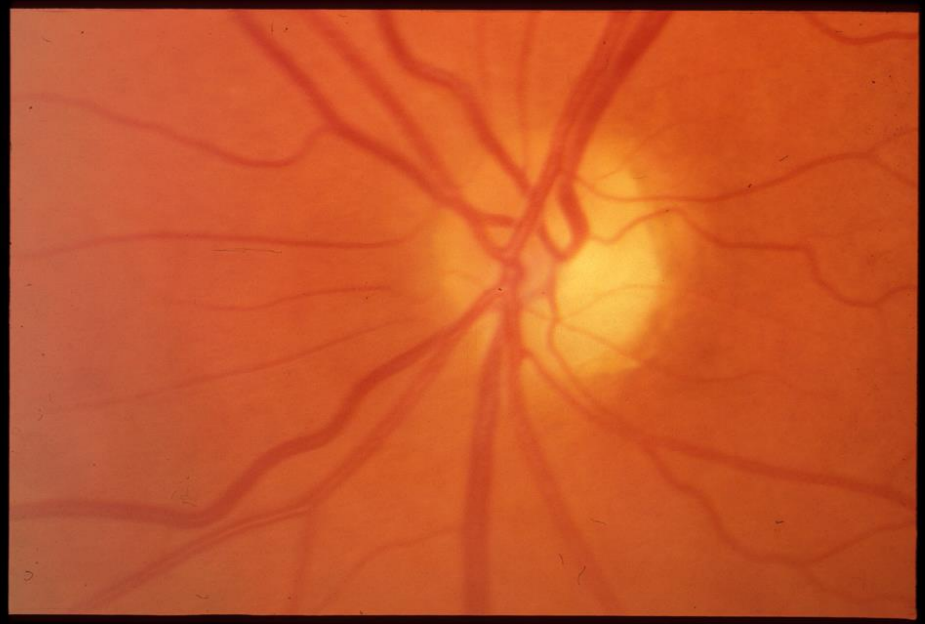

Dominant Optic Atrophy

Kjer's

- Variability of dysfunction
- Examination of family members

- Pedigrees with deafness
- Rare pedigrees with cataracts
- Individuals with CPEO and ragged red fibers on muscle biopsy

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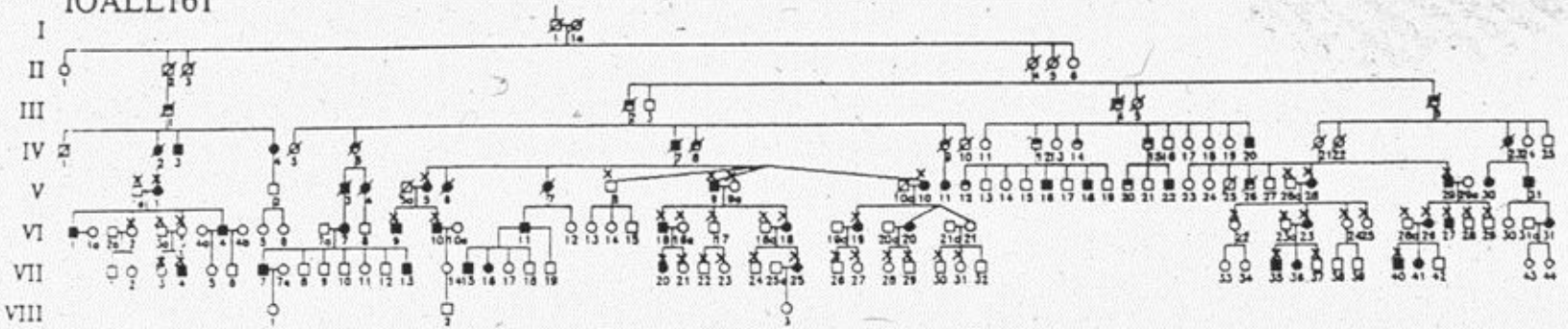

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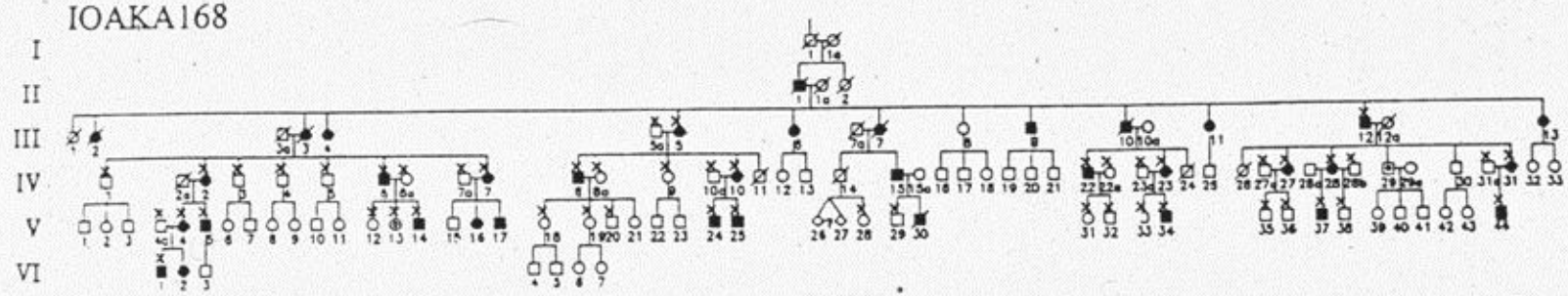

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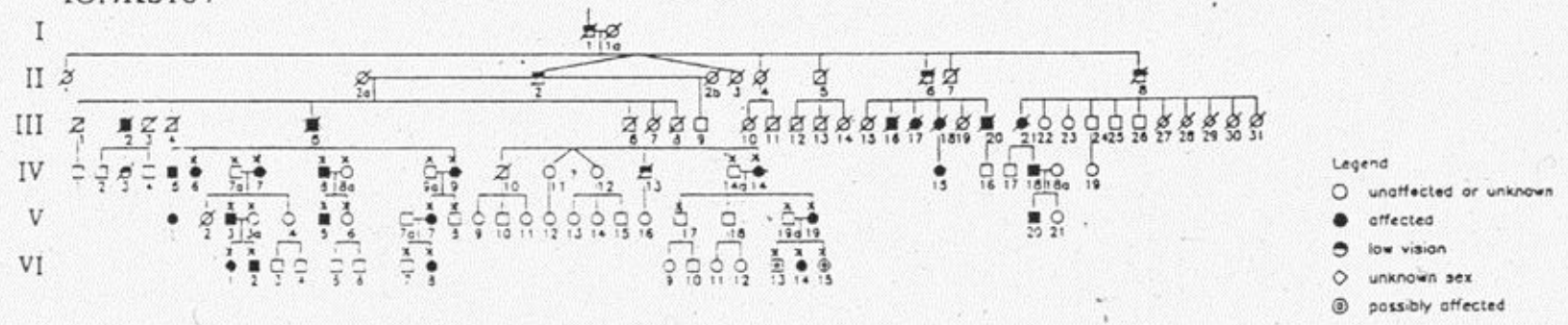


Dominant Optic Atrophy

Kjer's

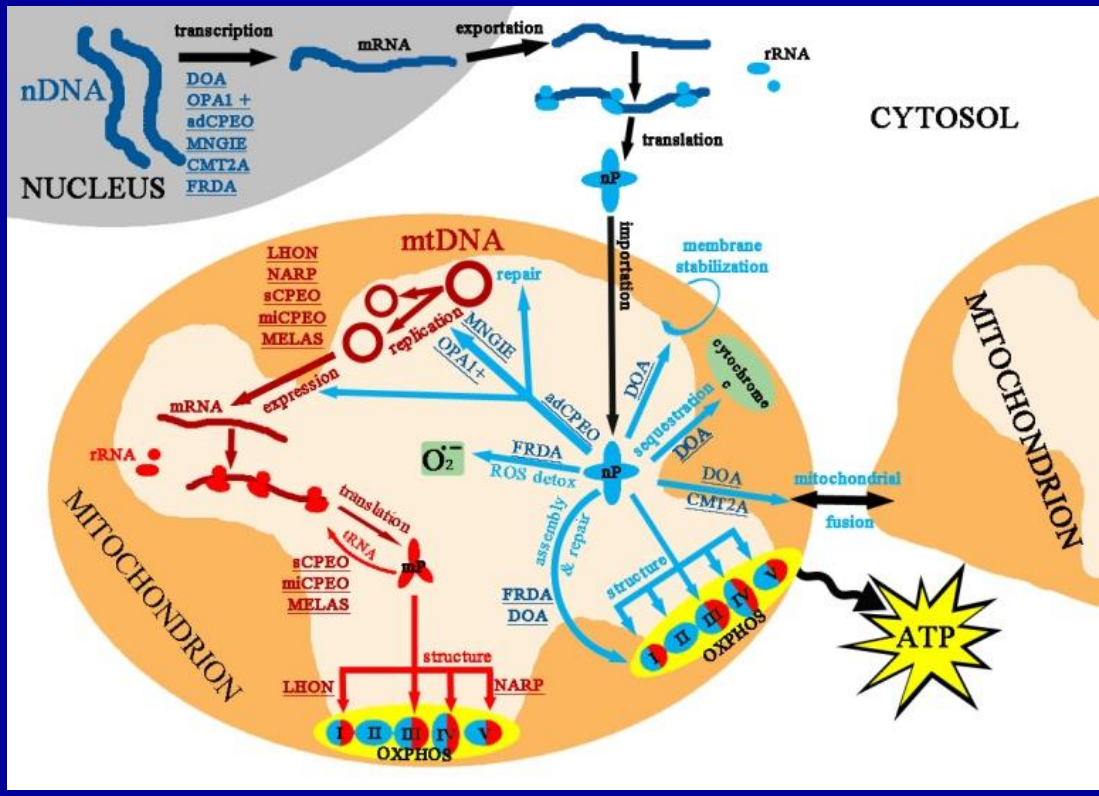
Linkage to:

- Chromosome 3 (3q28-29) (OPA1)
- Chromosome 19 (19q13.2-13.3) (OPA3)
- Chromosome 18 (18q12.2-12.3) (OPA4)

Dominant Optic Atrophy

Gene location:

- Chromosome 3 (3q28-29)



Gene product:

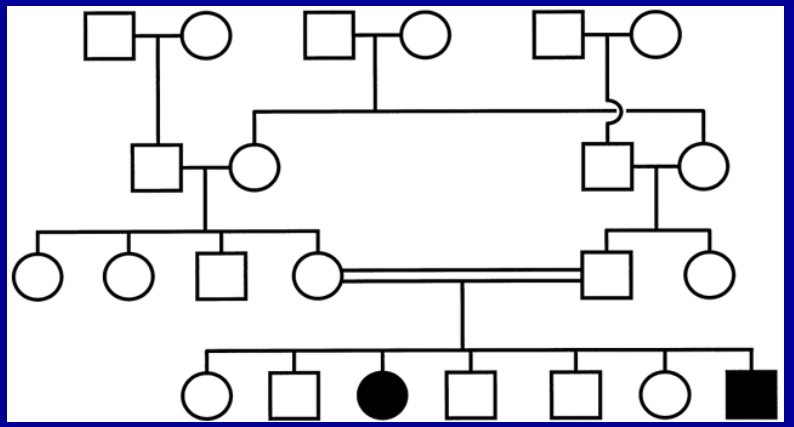
- Mitochondrial dynamin-related GTPase
- Mitochondrial biogenesis and membrane stabilization

A 5 year old boy of Iraqi Jewish descent has developmental delay, spasticity, and severe visual loss with nystagmus and optic atrophy

3-methylglutaconic acid levels are elevated in his urine

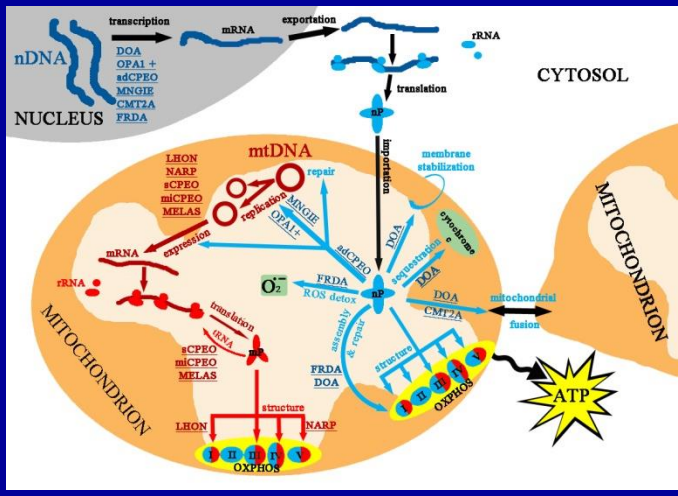
An older sister has a similar disorder, but not 5 other siblings

The parents are 1st cousins



Recessive Optic Neuropathies

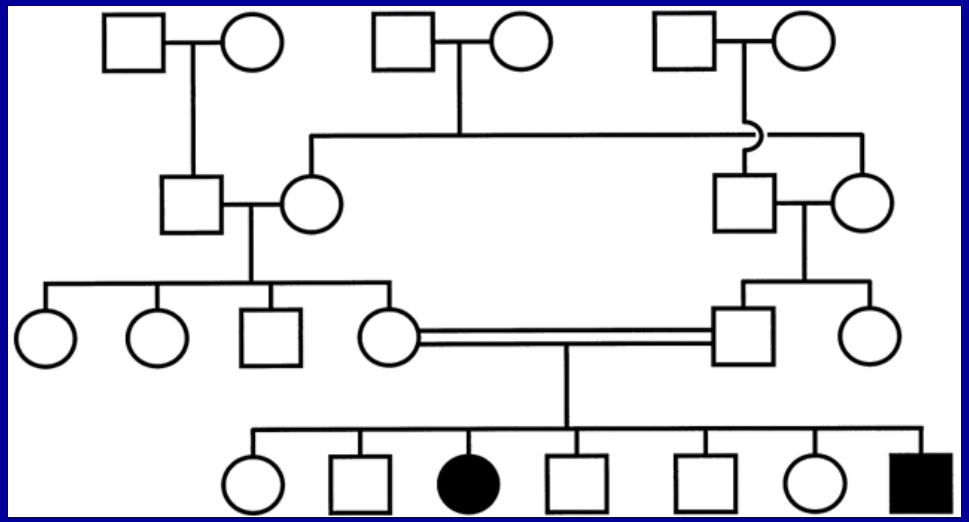
Costeff Syndrome



- Age less than 10
- Severe acuity loss
- Spasticity, extrapyramidal, cognitive signs
- Type III 3-methylglutaconic aciduria (MGA)
- Iraqi-Jewish population
- OPA3 gene – chromosome 19 (19q13.2-13.3)
  - Mitochondrial inner membrane protein

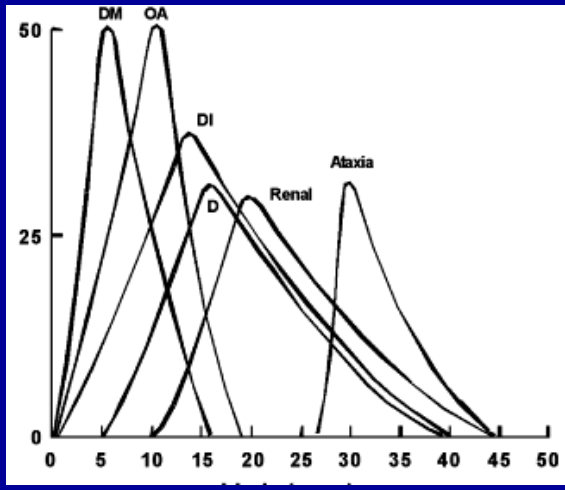
Recessive Optic Neuropathies

- Most heterogeneous groups
- Least common
- More severe visual dysfunction
- More neurologic/systemic findings
- Difficult to classify

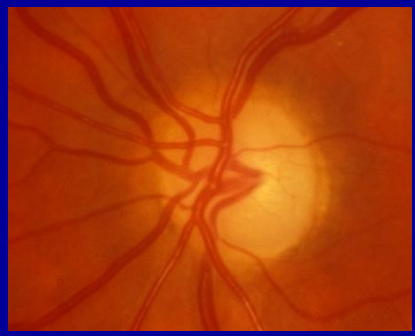


DIDMOAD/Wolfram's

- Juvenile-onset diabetes mellitus
- Sensorineural hearing loss
- Diabetes insipidus

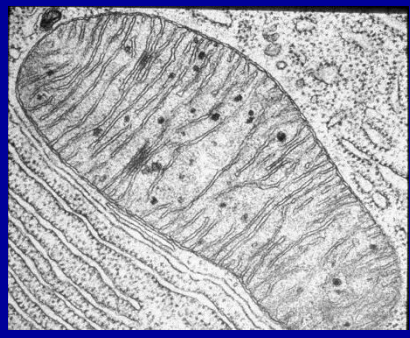


- Onset of visual loss 5-21
- Progressive acuity loss to worse than 20/400
- Severe dyschromatopsia
- Diffuse disc pallor



DIDMOAD/Wolfram's

Associated Findings

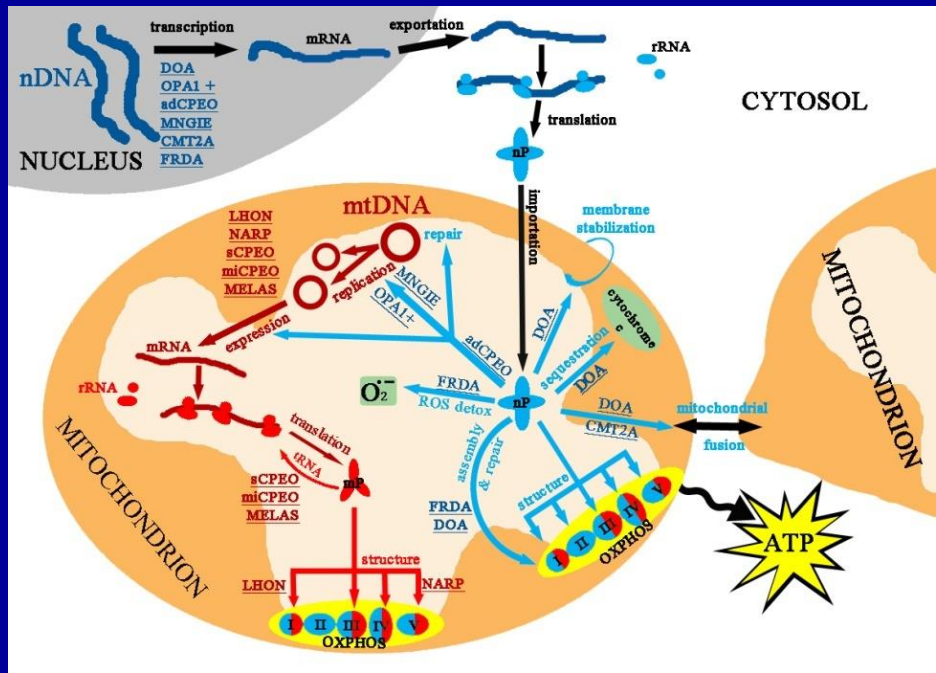


- Ataxia
- Seizures
- Mental retardation
- Nystagmus
- Ptosis
- Short stature
- Anosmia
- Urinary atonia
- Abnormal ERG
- Endocrine abnormalities
- Elevated CSF protein

DIDMOAD/Wolfram's

Linkage to:

- Chromosome 4 (4p16.1) (*WFS1*)
  - Wolframin (endoplasmic reticulum for calcium reg)
- Chromosome 4 (4q22-24) (*CISD2*)
- Definite heterogeneity



Mutations in the Wolframin Gene (*WFS1*)

- AR syndromic Wolfram syndrome
- AR isolated nonsyndromic optic atrophy

- AD progressive hearing loss with optic atrophy
- AD nonsyndromic low-frequency hearing loss
- AD nonsyndromic diabetes mellitus
- AD diabetes and congenital hearing loss
- AD congenital cataract

Hereditary Optic Neuropathies

Are they all mitochondrial?

- Other mitochondrial syndromic disorders
- Other syndromes with optic neuropathy as a defining feature
- Hereditary ataxias
- Hereditary polyneuropathies
- Hereditary spastic paraplegias

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Syndromic Optic Neuropathies

Primary Mitochondrial Disorders

- Leigh syndrome (subacute necrotizing encephalopathy)
- MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes)
- DCMA (dilated cardiomyopathy with ataxia)
- MERRF (myoclonic epilepsy and ragged red fibers)
- MNGIE (mitochondrial neurogastrointestinal encephalomyopathy)
- CPEO (chronic progressive external ophthalmoplegia)

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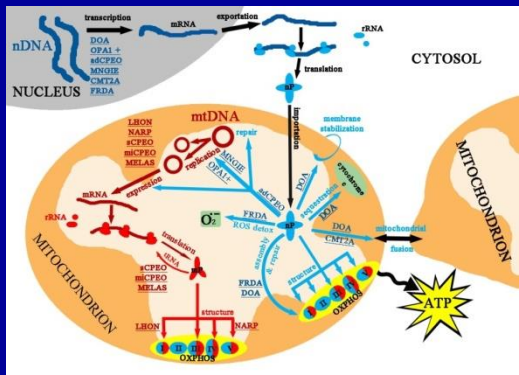
Mohr-Tranebjaerg/DDON

- Deafness, dystonia and optic neuropathy
- Ataxia, cognitive decline, psychiatric
- Optic atrophy by age 20, blind by 40

- X-linked recessive (Xq22) (*TIMM8A*)
- Mitochondrial intermembrane protein



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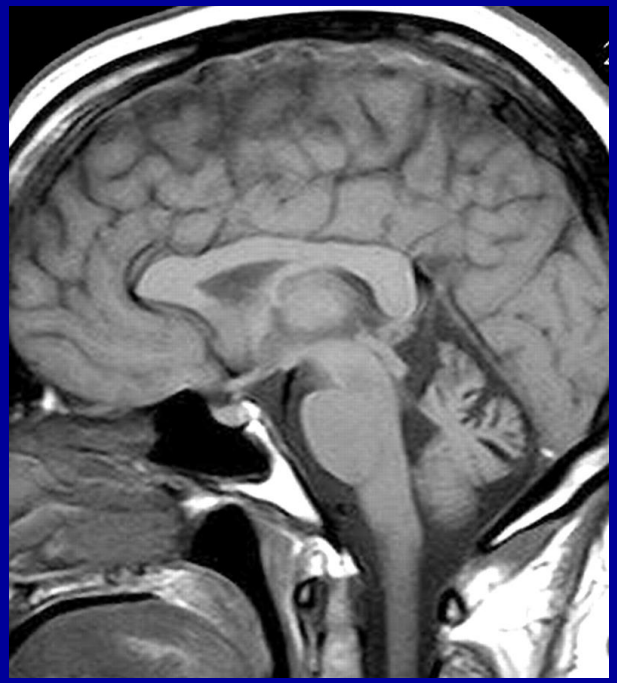
Syndromic Optic Neuropathies

Hereditary Ataxias

- Progressive degenerations of the cerebellum and its connections

- Friedreich ataxia
- Spinocerebellar ataxias



Syndromic Optic Neuropathies

Friedreich Ataxia

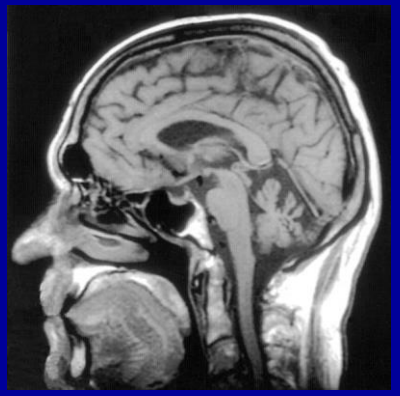
- Progressive ataxia, dysarthria, neuropathy
- Scoliosis, diabetes, cardiac disease
- Death by 4-5th decade
- Autosomal recessive
- 9q13-21 (*FRDA/X25*) (GAA repeats)
  - Frataxin regulates iron in mitochondria
- Optic neuropathy common
  - Usually asymptomatic but can be LHON-like

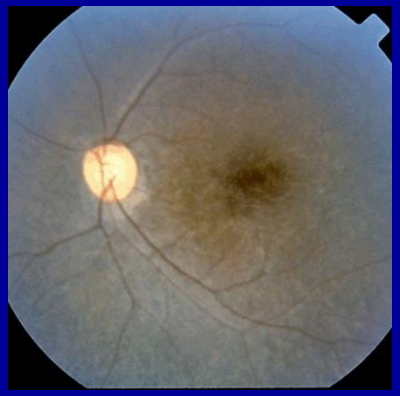
(Fortuna F, et al. Brain 2009;132:116-23)

Syndromic Optic Neuropathies

Spinocerebellar Ataxias

- Progressive cerebellar degenerations
- > 29 different genetic loci (*SCA 1-31*)
- Autosomal dominant (CAG repeats)
- SCA 1, 2, 3, 6, 7 account for 80%
- Retinopathy in SCA 7
- Optic neuropathy
  - Usually mild
  - SCA 1 and SCA 3





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Syndromic Optic Neuropathies

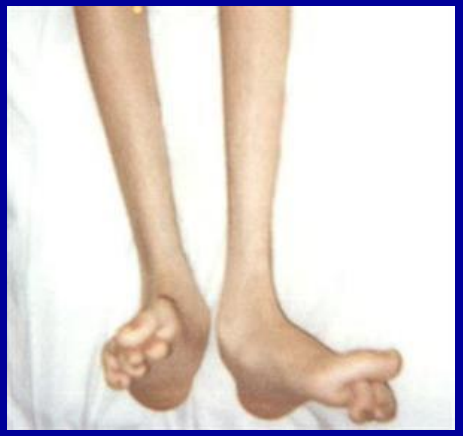
Hereditary Polyneuropathies

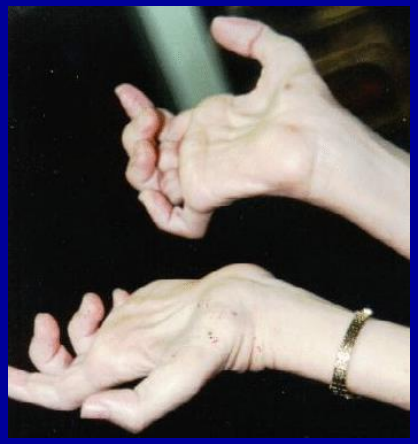
- Charcot-Marie-Tooth disease
- Riley-Day syndrome

Syndromic Optic Neuropathies

Charcot-Marie-Tooth

- Progressive motor neuropathy and atrophy
- Common polyneuropathy (1/2500)
- > 30 different genetic loci
- Autosomal dominant and recessive forms





Syndromic Optic Neuropathies

Charcot-Marie-Tooth

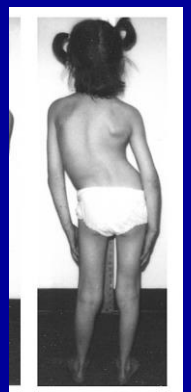
- Optic neuropathy
  - In up to 75% of cases, but usually subclinical
  - HMSN VI defined as CMT + optic atrophy
    - Autosomal dominant and recessive forms
    - Dominant HMSN VI = CMT2A
      - Mitofusin-2 gene (*MFN2*)
      - Vision loss onset 2nd decade
      - Progressive to 20/400
      - May have late recovery of vision

Syndromic Optic Neuropathies

Riley-Day Syndrome

- Familial dysautonomia (Ashkenazi Jews)
- Autosomal recessive
- Optic neuropathy very common (2nd decade)

  (Mendoza-Santiesteban CE et al. J Neuro-Ophthalmol)
- Early mortality probably precludes visual sxs



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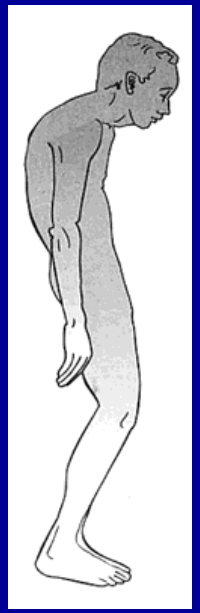
Syndromic Optic Neuropathies

Hereditary Spastic Paraplegias

(Strumpell-Lorrain disease)



- Progressive cortico-spinal degeneration
- > 41 genetic loci
- Optic atrophy associated with several loci
- 16q24.3 (*SPG7* gene)
  - Paraplegin – mitochondrial metalloproteinase
  - Autosomal recessive spastic paraplegia and optic atrophy in some patients

NEUROLOGY 2005;64:940–941

Editorial

HIGH LIGHT

Optic mitochondriopathies

Patrick F. Chinnery, PhD, MRCP; and Philip G. Griffiths, FRCOphth

Hereditary Optic Neuropathies: From the Mitochondria to the Optic Nerve

NANCY J. NEWMAN, MD

- PURPOSE: To review our current knowledge of inherited optic neuropathies.
- DESIGN: Perspective.
- METHODS: Literature review.
- RESULTS: The hereditary optic neuropathies consist of a group of disorders in which optic nerve dysfunction figures solely or prominently and direct inheritance is clinically or genetically proven. The most common of these disorders are autosomal dominant optic atrophy (Kjers' disease) and maternally-inherited Leber's hereditary optic neuropathy. Other inherited neurologic and systemic syndromic diseases will frequently manifest optic neuropathy. A selective vulnerability of the optic nerve to perturbations in mitochondrial function may underlie a final common pathway among these disorders.
- CONCLUSIONS: The ophthalmologist should be familiar with the clinical characteristics and diagnosis of the hereditary optic neuropathies. Recent advances in our understanding of the underlying pathophysiology of the inherited optic neuropathies may provide insight into their treatment and the treatment of acquired optic nerve disorders. (Am J Ophthalmol 2005;140:517–523.

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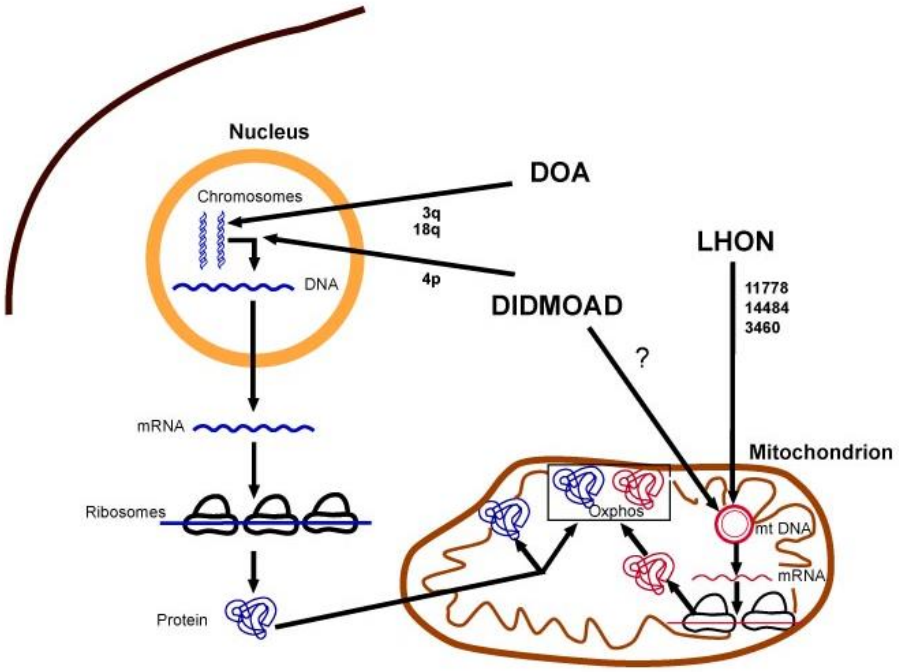

Mitochondrial Optic Neuropathies