Late onset neurometabolic diseases: phenotypic presentations and guidelines for the diagnosis

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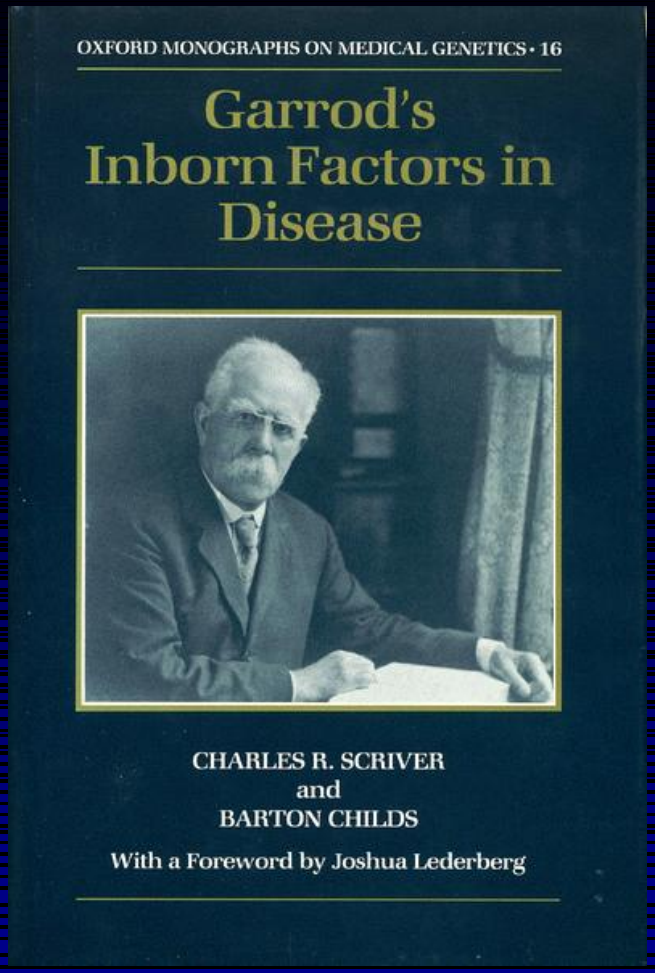
OXFORD MONOGRAPHS ON MEDICAL GENETICS • 16
Garrod's Inborn Factors in Disease
CHARLES R. SCRIVER
and
BARTON CHILDS
With a Foreword by Joshua Lederberg


THE METABOLIC BASIS OF INHERITED DISEASE
the metabolic basis of inherited disease
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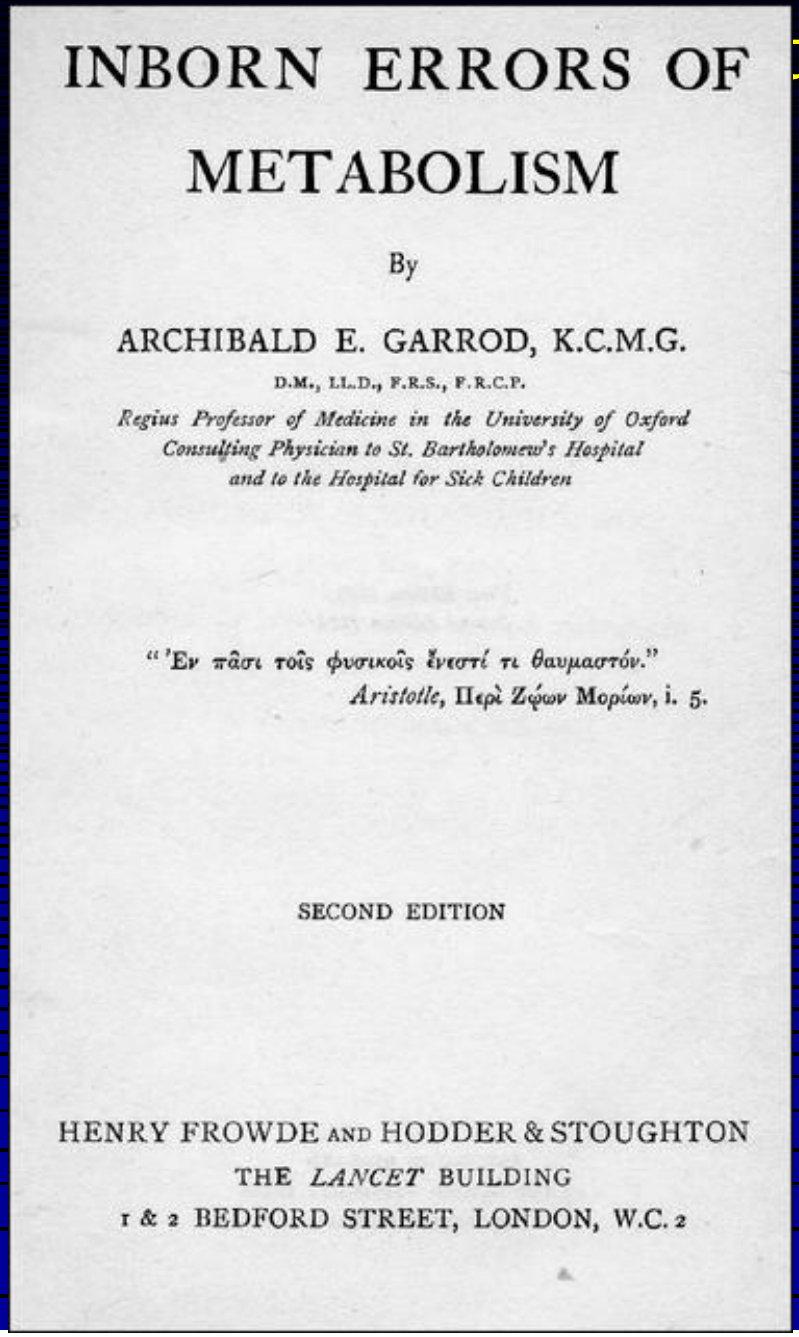
Garrod AE: Inborn errors of metabolism (Croonian Lectures). Lancet 2:1, 1908



INBORN ERRORS OF METABOLISM

By

ARCHIBALD E. GARROD, K.C.M.G.

D.M., LL.D., F.R.S., F.R.C.P.

Regius Professor of Medicine in the University of Oxford
Consulting Physician to St. Bartholomew's Hospital
and to the Hospital for Sick Children

"Ἐν πᾶσι τοῖς φυσικοῖς ἔνεστί τι θαυμαστόν."
Aristotle, Περὶ Ζῴων Μορίων, i. 5.

SECOND EDITION

HENRY FROWDE AND HODDER & STOUGHTON
THE *LANCET* BUILDING
1 & 2 BEDFORD STREET, LONDON, W.C. 2

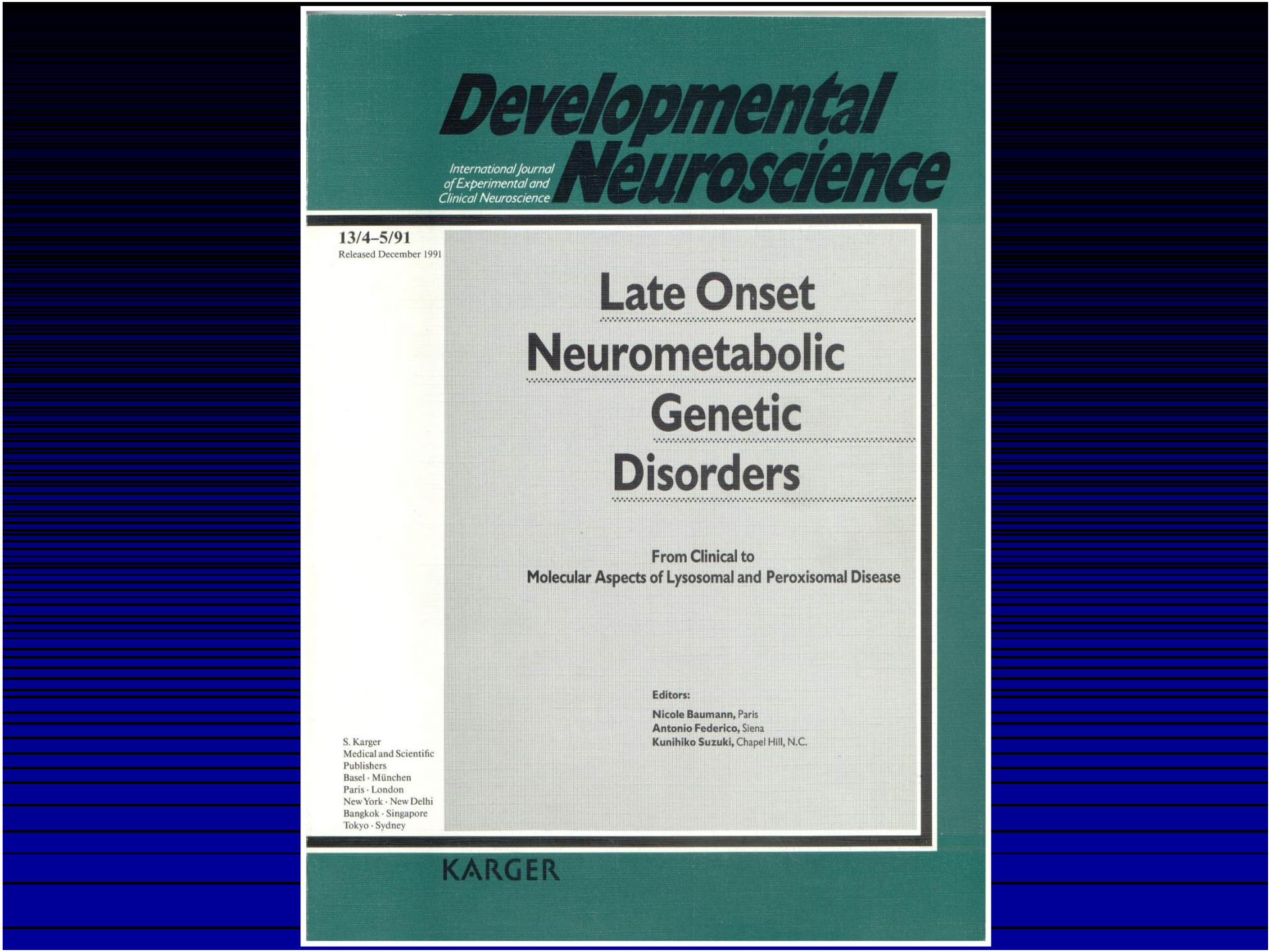
….The factors which confer upon us our predispositions to and immunities from the various mishaps which are spoken of as diseases, are inherent in our very chemical structure; and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang.

Late onset neurometabolic diseases

- The biochemical pathogenesis of many hereditary diseases of the nervous system and muscle has in the recent years been very much investigated: for many diseases an enzyme defect and metabolic substances accumulating in the tissues or in biological fluids have been identified facilitating the diagnosis of a large number of genetic metabolic encephaloneuromyopathies.

Late onset neurometabolic diseases

- **Beside the well known infantile- and juvenile-onset diseases, an increasing number of cases with a slowly progressive disease and adult onset have been described, the pathogenesis of which is linked to the same congenital defect of lysosomal, mitochondrial or peroxysomal metabolism as the early onset forms, but in which the onset of the clinical manifestations is delayed in adult age.**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Late Onset Neurometabolic Genetic Disorders
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In children, the phenotype of inborn errors of metabolism has well known and the strategy of investigation have been developed from many years

Every known condition presenting in childhood may have a less severe clinical presentation leading to signs only in later ages

Late onset neurometabolic diseases

- In these diseases an early diagnosis and therapy can prevent the very severe clinical manifestations in certain cases (es CTX).
- In all cases, however, an early diagnosis will prevent the birth of other affected cases, through the identification of healthy carriers and through the prenatal counselling for at risk pregnancies.

Late onset neurometabolic diseases

- The clinical approach
- The pathogenesis of a hereditary disease in adult age
- Some clinical presentations

Late onset neurometabolic diseases

- The correct definition of the neurometabolic pathogenesis of a syndrome requires multidisciplinary diagnostic procedures.
- The role of clinical neurologists is essential to correctly direct these investigations on the basis of a correct evaluation of the clinical symptoms in order to obtaining the morphological and biochemical data necessary to reveal the primary biochemical defect and the molecular genetic definition.

The diagnostic suspicion of a neurometabolic diseases in adults

- Subacute onset and slow progression
- Other affected cases in the family
- Inheritance and consanguineity
- Multisystem involvement

Inheritance

- Sporadic
- Autosomal recessive
- Autosomal dominant
- Pseudodominant
- X-linked
- Mitochondrial

SIGNS IN LATE ONSET GENETIC DYSMETABOLIC ENCEPHALO-NEURO-MYOPATHIES

CENTRAL NERVOUS SYSTEM	Dementia
	Epilepsy
	Ataxia
	Spasticity
	Extrapyramidal rigidity
	Choreo-atheosis
	Vascular changes
PERIPHERAL NERVOUS SYSTEM	Motor and sensory changes
	Decrease of motor and sensory nerve cunduction velocities
MUSCLE	Hypostenia-hytrophia
	Fasciculation
EYES	Rethynopathyes
	Optic atrophy
	Macular degeneration (cherry red spot)
	Juvenile cataract
	Abnormalities in eyes movements (ocular apraxia, vertical gaze paralysis, etc.)
EAR	Deafness
	BAERs changes
OTHERS	Visceral involvement (hearth, liver, etc.)
	Endocrine involvement (adrenal insufficiency, etc.)

SIGNS IN LATE ONSET GENETIC DYSMETABOLIC ENCEPHALO-NEURO-MYOPATHIES

CENTRAL NERVOUS SYSTEM

- Dementia
- Epilepsy
- Ataxia
- Spasticity
- Extrapyramidal rigidity
- Choreo-atheosis
- Vascular changes

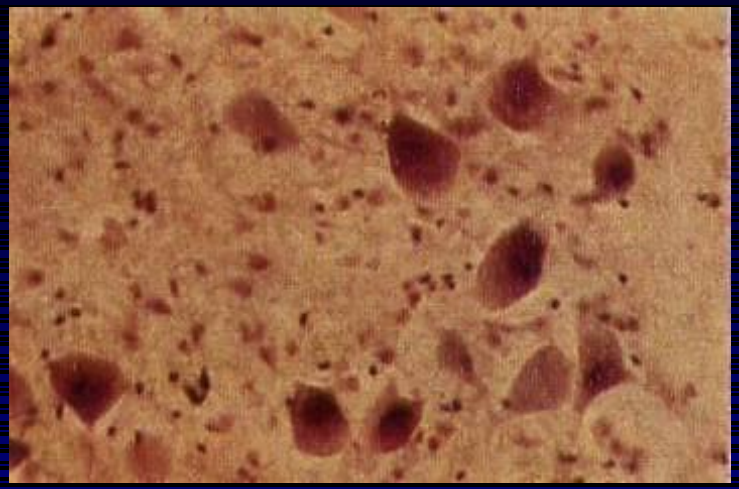
Multisystem involvement in late-onset neurometabolic disorders

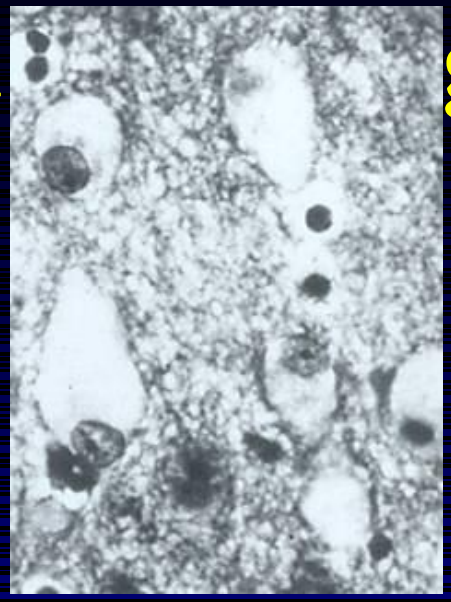
- **Diseases primarily affecting neurons** (meganeuritis, synaptic abnormalities, plasma membrane abnormalities, spheroidal axonal formations, dendrite abnormalities, storage of abnormal material in cerebral cortex, cerebellum and basal ganglia)
- **Diseases primarily involving myelin**

Diseases primarily affecting neurons

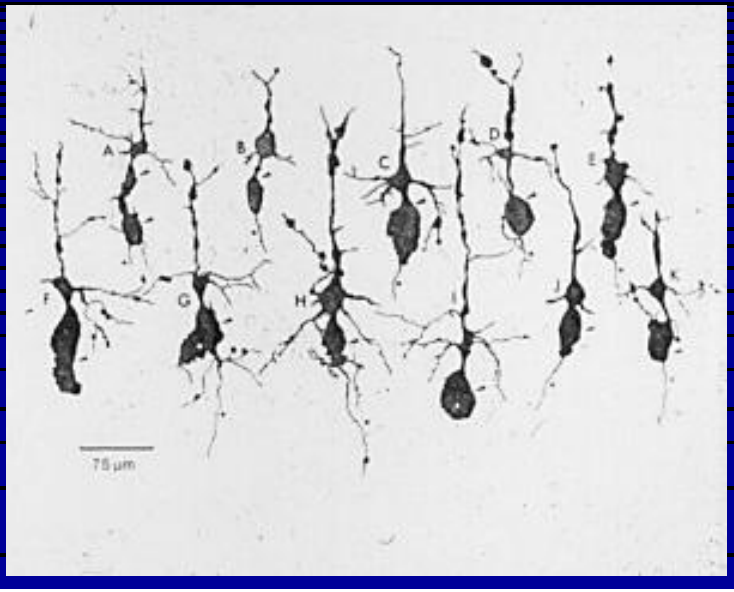
- GM1 gangliosidosis
- Gm2 gangliosidosis
- Gaucher disease
- Nieman Pick type C diseases

Mechanisms of nerv
dysfunciton in g





- Distention of nerve cells by fine granular material (Schaffer 1905)
- Storage of membrane cytoplasmatic bodies (MCBs) (Terry and Korey 1960)
- Distortion of synaptic structures (neuronal geometry) (Purpura and Suzuki 1976)

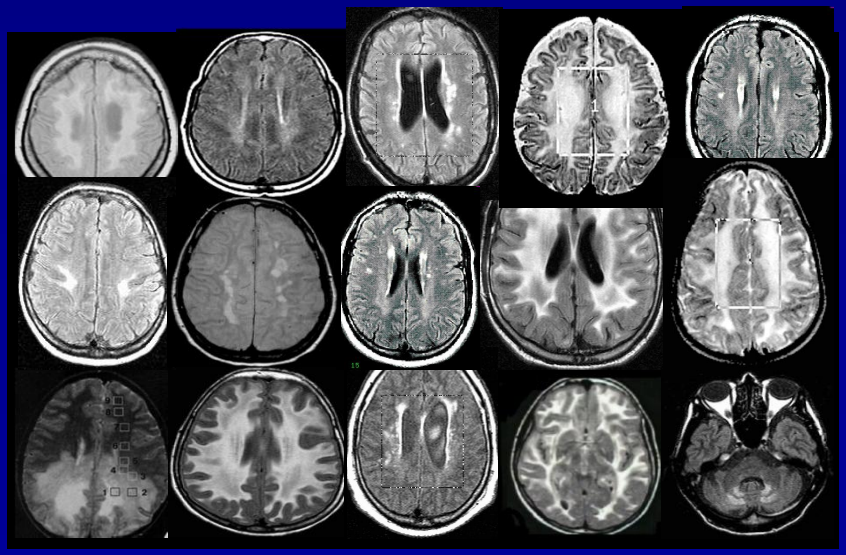


Chronic GM2 Gangliosidosis (deficiency of Hexosaminidase)

- **Severe psychiatric disturbances, with anxiety, psychosis, hallucinations, etc. and in final stage dementia**
- **Neurovegetative troubles**
- **Different neurologic phenotypes**
- **Caution in treatment psychiatric symptoms since imipramine inhibits Hexosaminidase A activity *(Palmeri and Federico, J Neurol Sci 1992, 110: 215-21)***

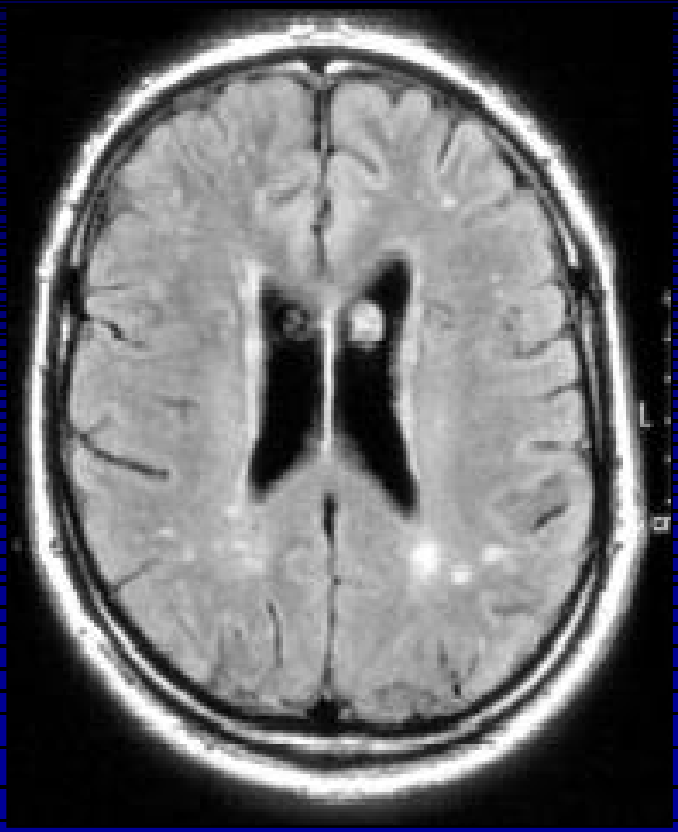
Diseases primarily involving myelin

- ***Central and peripheral myelin***
  - **Krabbe disease**
  - **Metachromatic leucodystrophy**
- ***Mainly peripheral myelin***
  - **Tangier disease**



Diseases primarily involving brain vascular system

- Fabry's disease
- CADASIL
- CARASIL
- ……..



PERIPHERAL NERVOUS SYSTEM

- Motor and sensory changes
- Decrease of motor and sensory nerve conduction velocities

MUSCLE

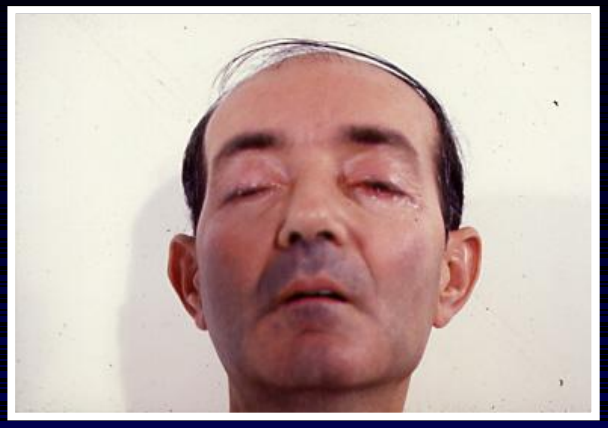
- Hypostenia-hytrophy- muscle weackness
- Fasciculations

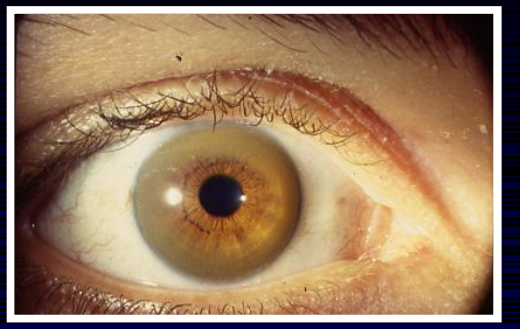
EAR

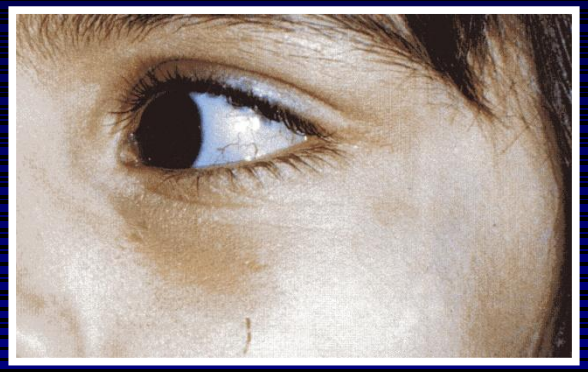
- Deafness
- BAERs changes

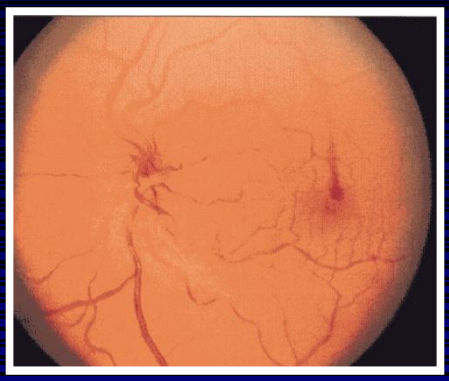
EYES

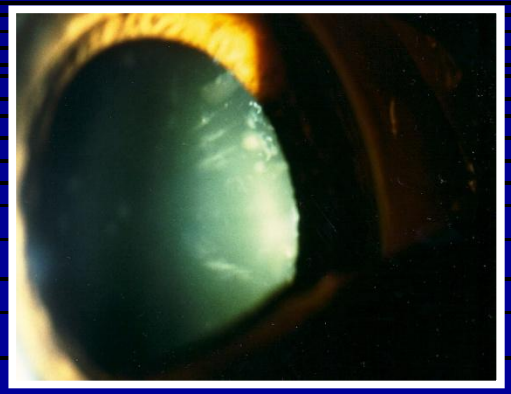
- Rethynopathies
- Optic atrophy
- Macular degeneration (cherry red spot)
- Juvenile cataract
- Abnormalities in eyes movements (ocular apraxia, vertical gaze paralysis, etc.)

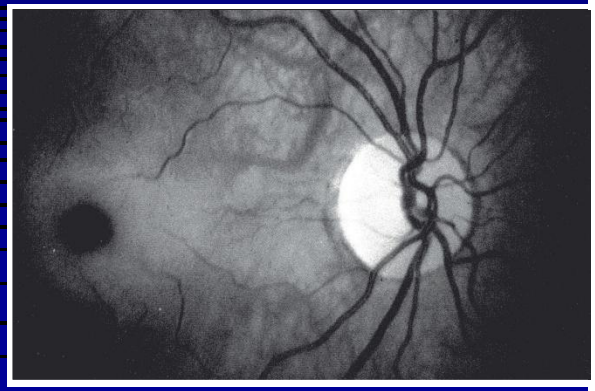




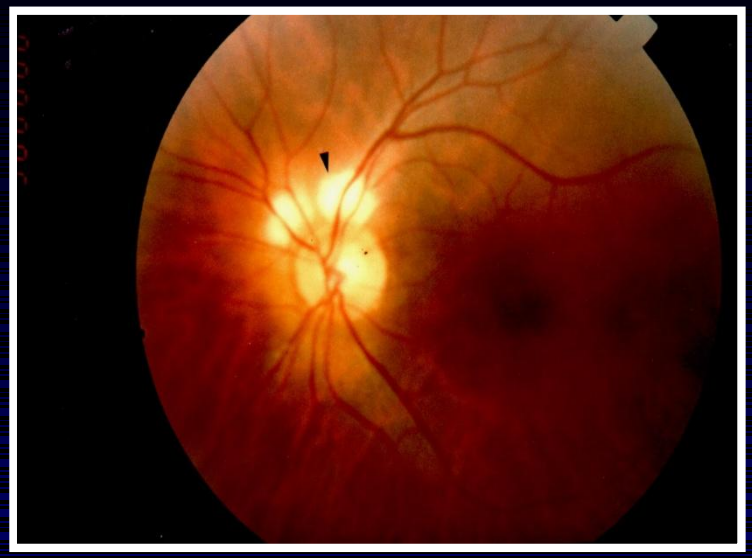


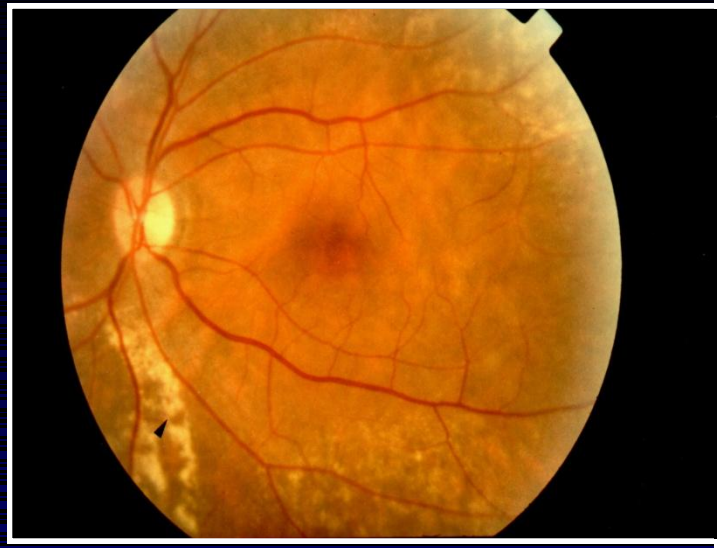


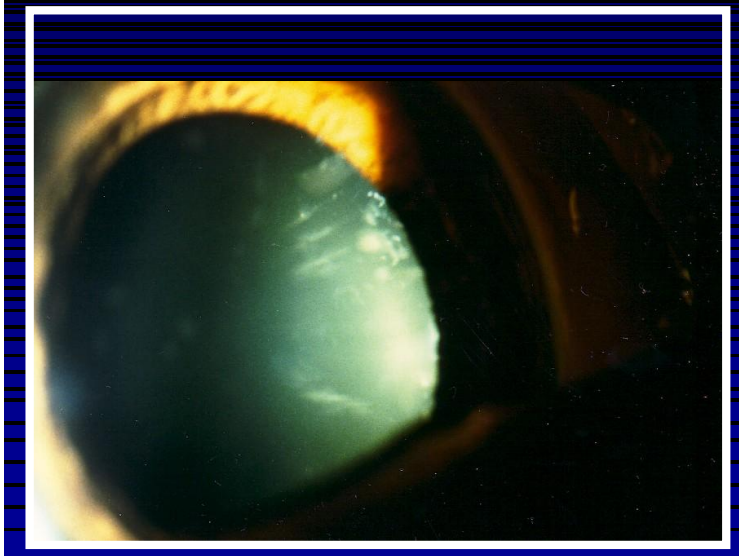




CTX
Ocular features







Myelinated nerve fibers
Cholesterol-like exudates along vascular arcades
Arteriolar narrowing and venous turgidity
Retinal pigmented epitelium atrophy with pigmentaary changes

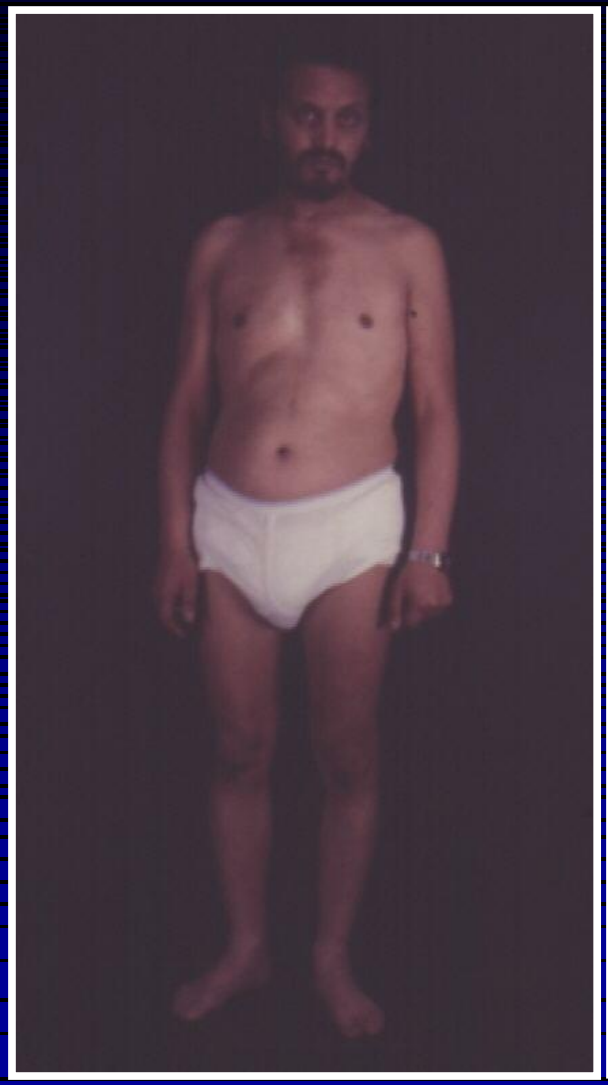
Dotti MT, Rufa A, Federico A. **Cerebrotendinous xanthomatosis: heterogeneity of clinical phenotype with evidence of previously undescribed ophthalmological findings.** ***J Inher Metab Dis 2001***

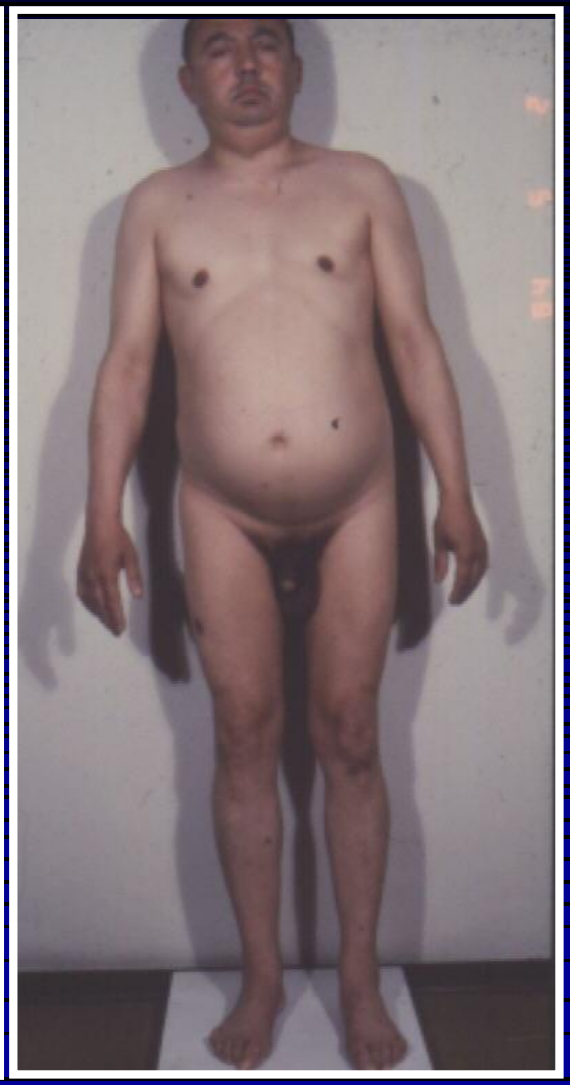
- **Inheritance: AR**
- **Symptoms: dystonia, chorea, myoclonus, parkinsonism, Vertical oculomotor apraxia, cerebellar ataxia, behavioral disorders, dementia, late-onset**

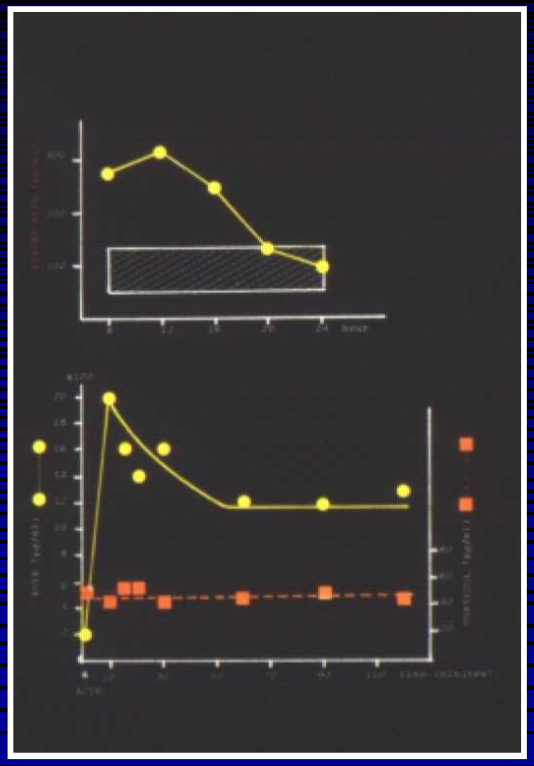
OTHERS

- Visceral involvement (hearth, liver, etc.)
- Endocrine involvement (adrenal insufficiency, diabetes, thyroid dysfunction etc.)

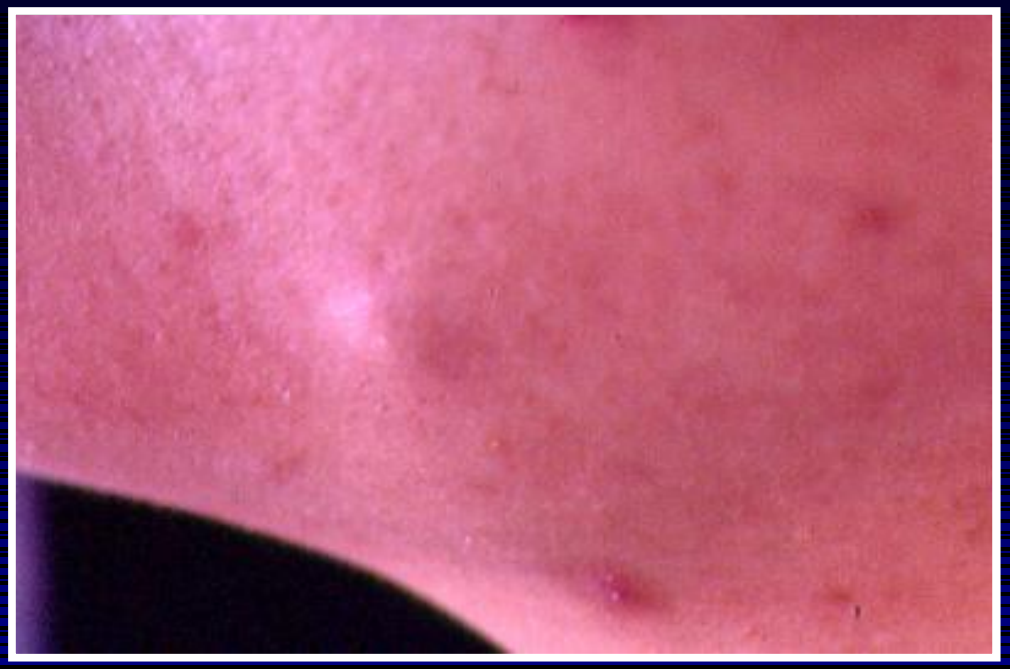
Adrenoleukodysrophy





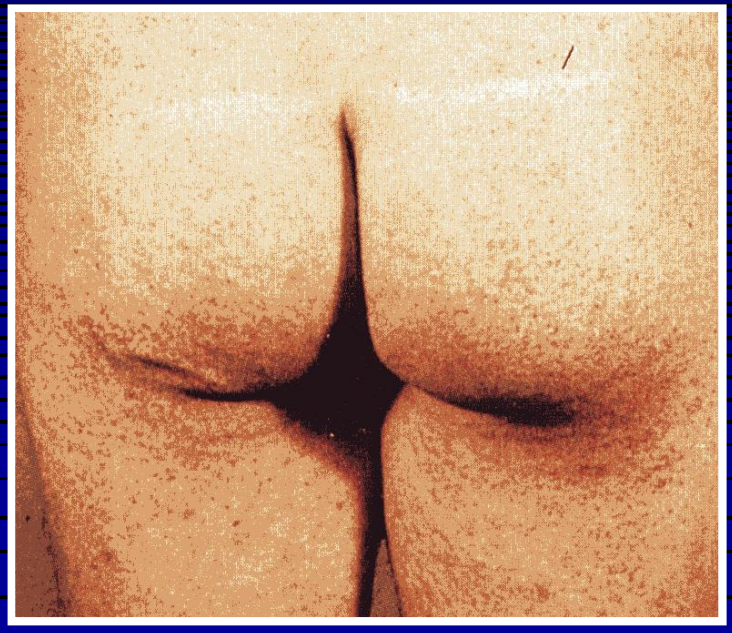


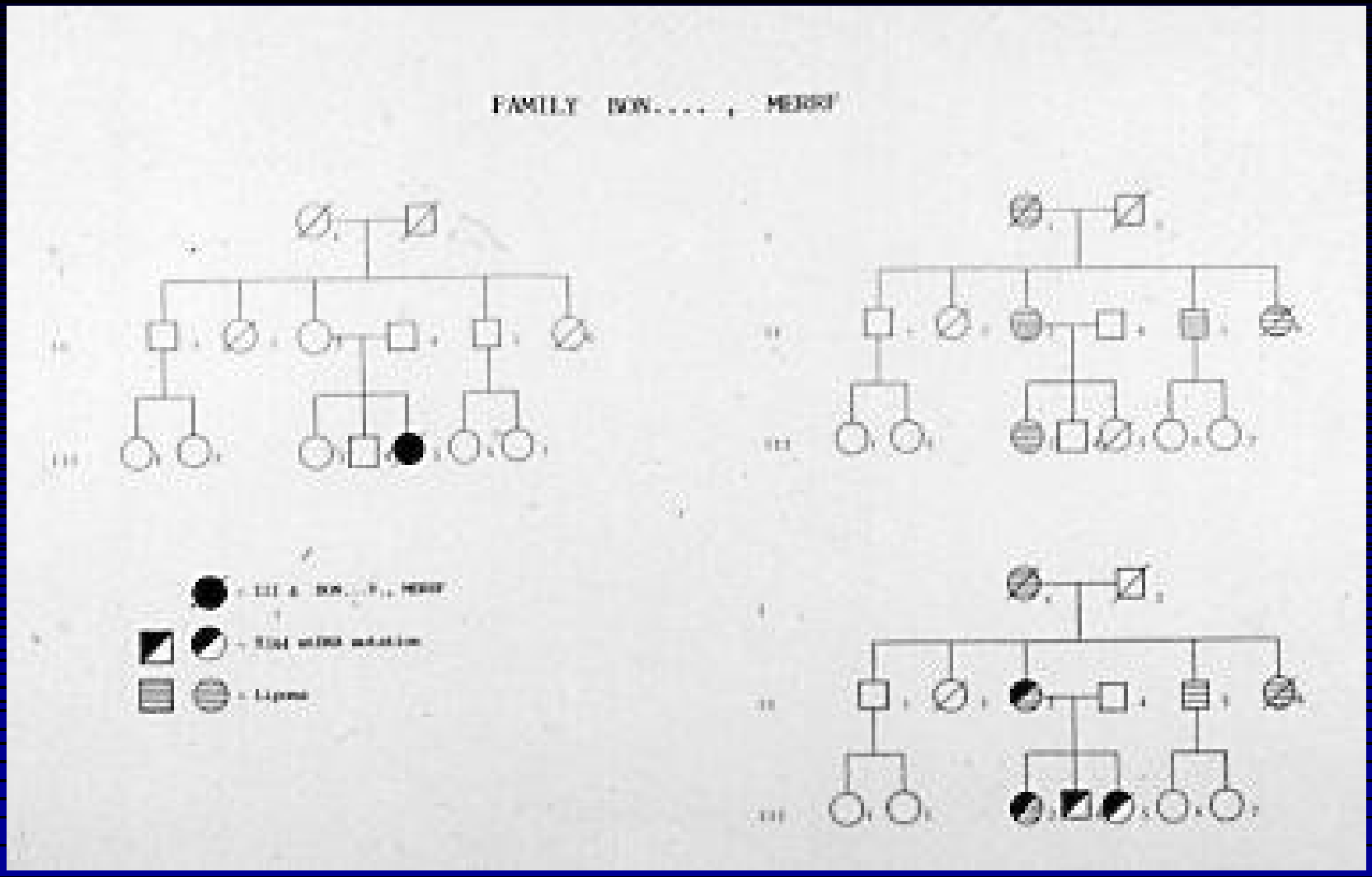
Lipoma and MERRF



Skin

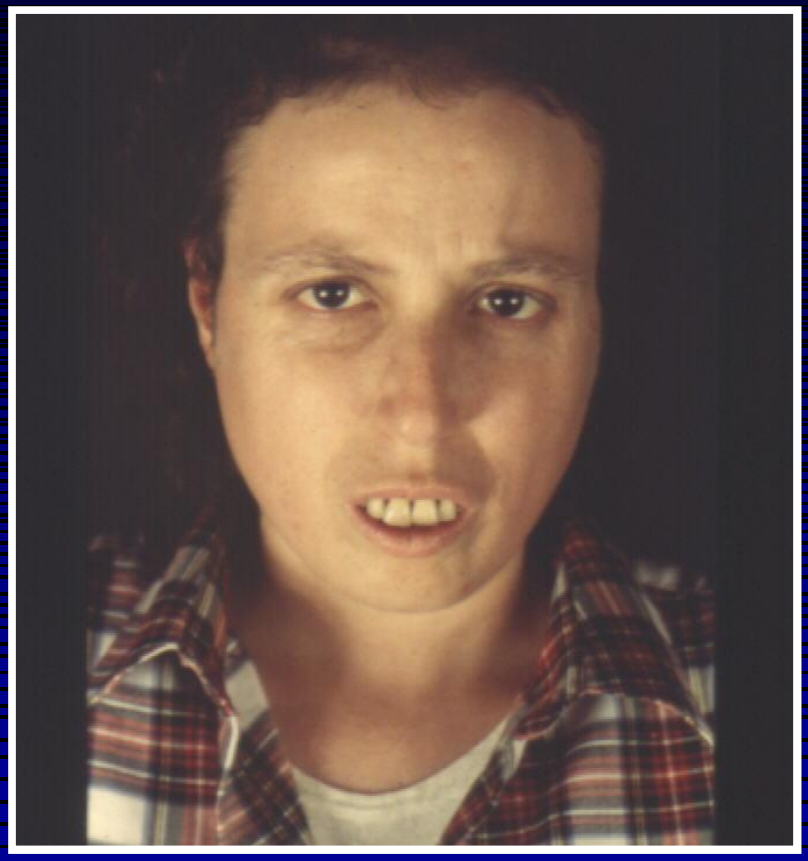
Angiokeratoma and Fabry



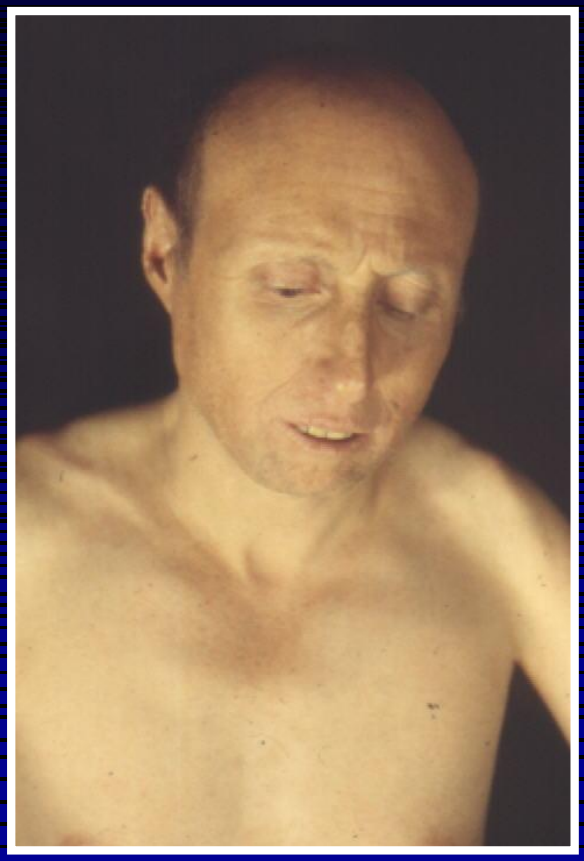

FAMILY BON... , MERRF

Two siblings with Werner's syndrome

Homozygosity for nt 2425 CGA(Arg)--TGA(Stp)



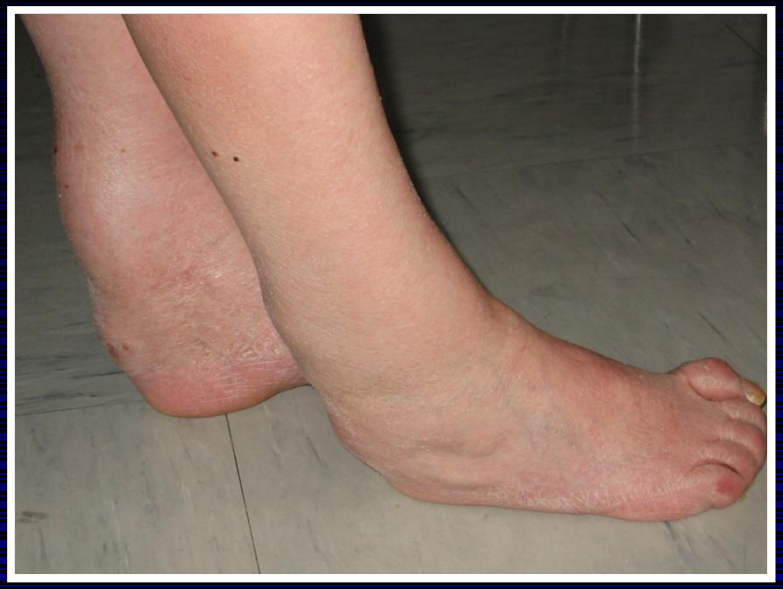
Vit...Giovanna, 33y

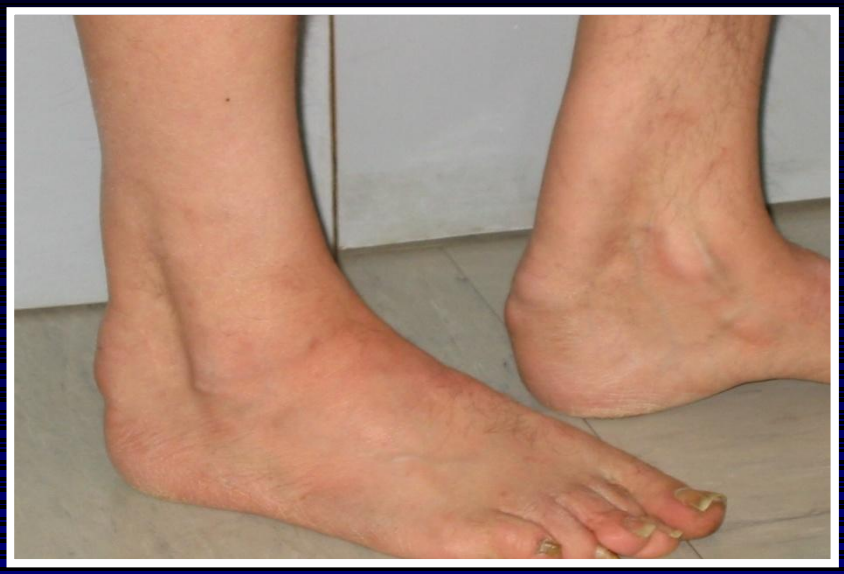


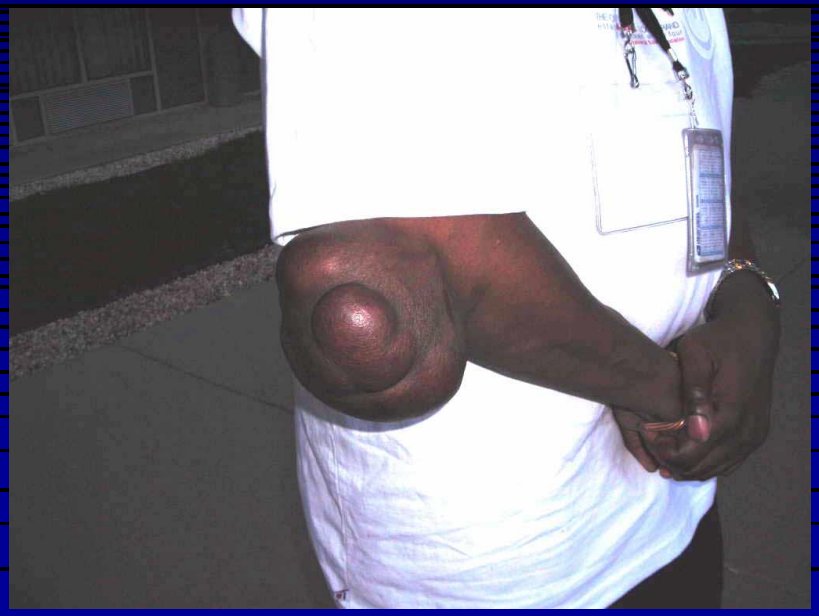
Vit....Angelo, 41y

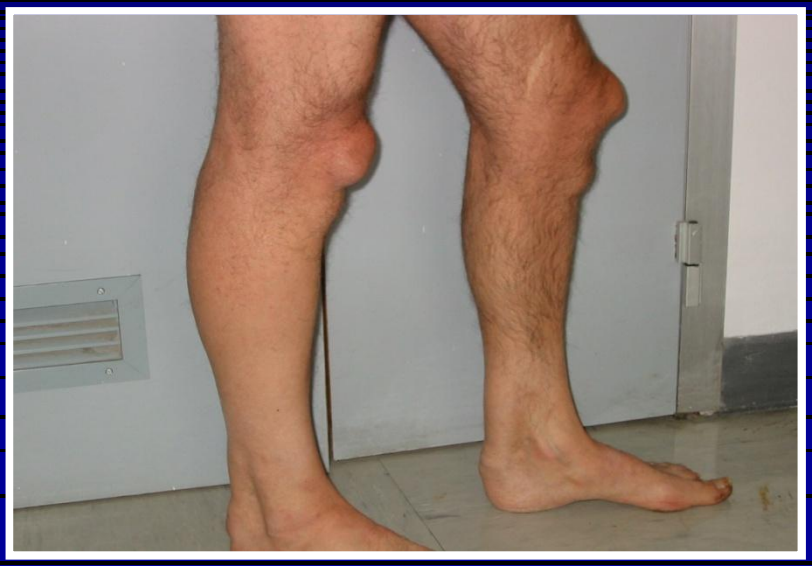
CTX

Tendon xanthomas









I- THE DIAGNOSTIC SUSPICION

Cerebrotendinous Xanthomatosis

Molecular genetic defects in the sterol 27-hydroxylase gene

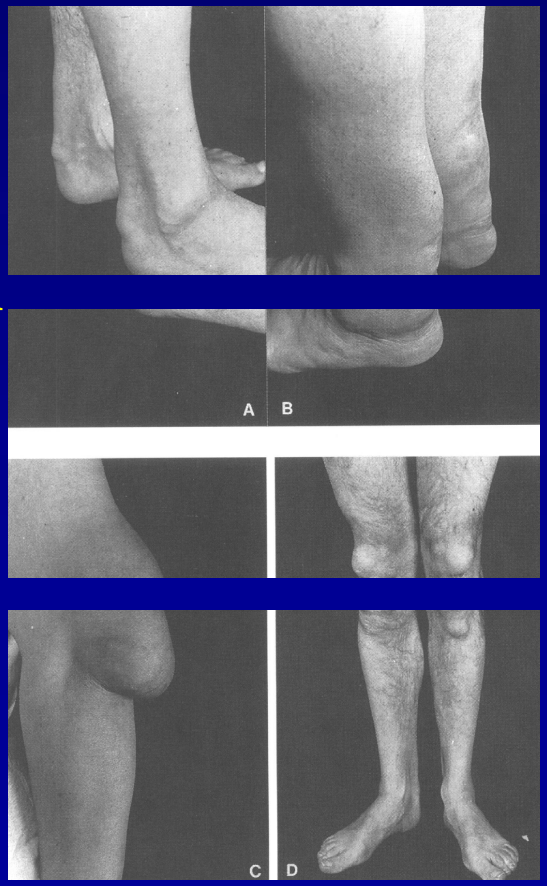
Deficiency of the mitochondrial enzyme sterol 27-hydroxylase

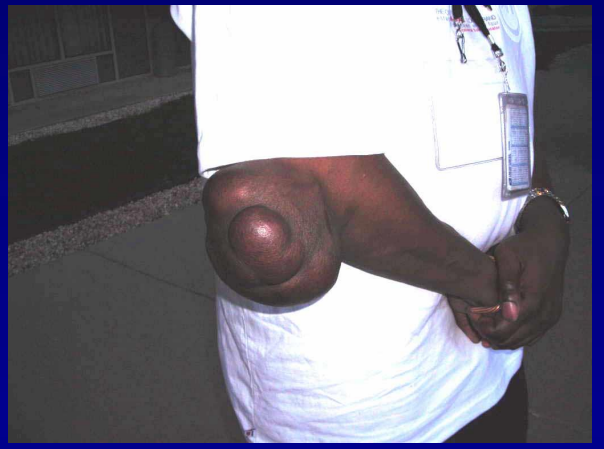
Increased serum level of cholestanol

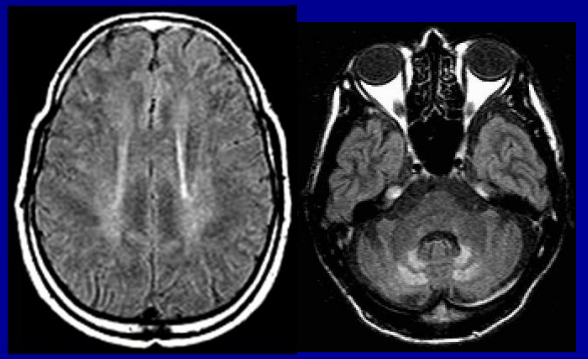
Clinical Features

- **Tendon xanthomas**
- **Juvenile cataracts**
- **Progressive neurological impairment including peripheral neuropathy, epilepsy, dementia, etc**
- **Osteoporosis**

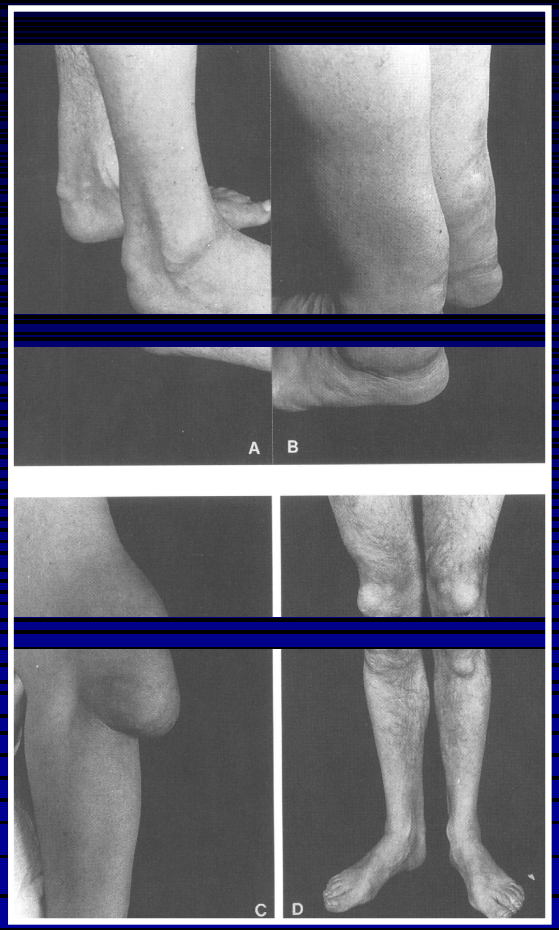
Variability of symptoms



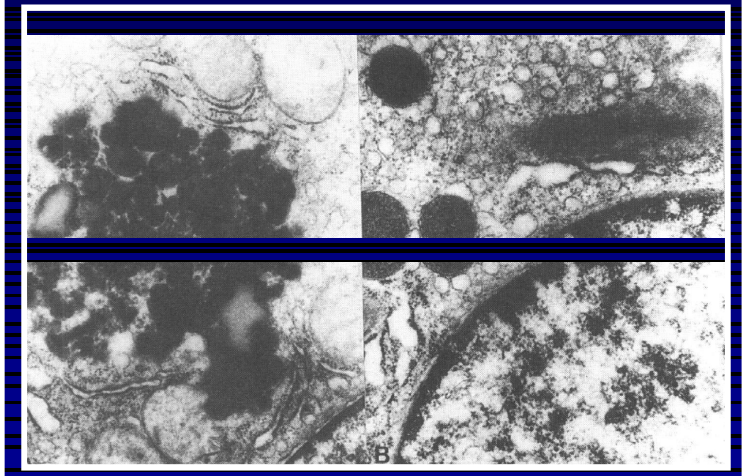




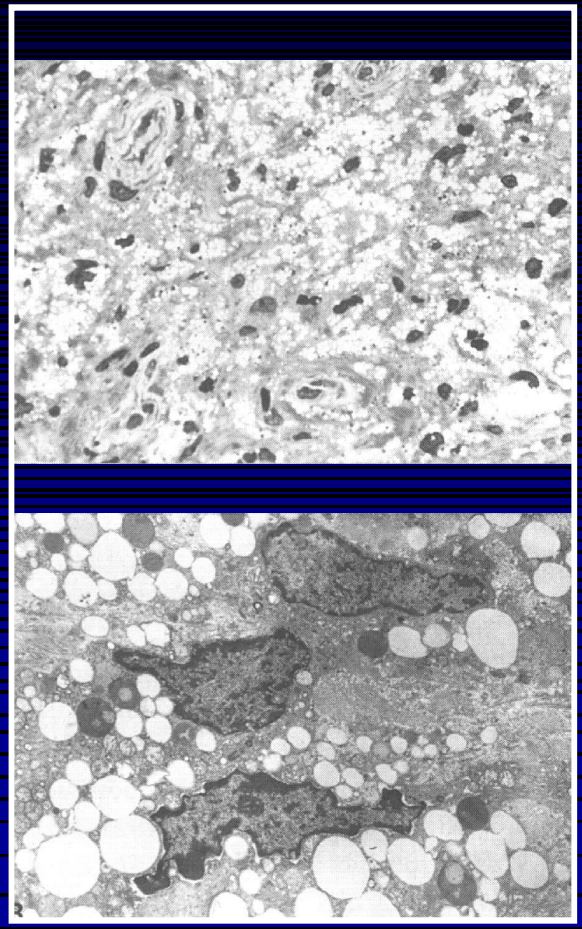
Cerebrotendinous Xanthomatosis



Tendon xanthomata



Liver abnormalities



Tendon xanthoma

Cerebrotendinous xanthomatosis as a multisystem disease mimicking premature ageing

Dotti MT, Salen G, Federico A.

Dev. Neurosciences, 13: 371-6, 1991

Cerebrotendinous Xanthomatosis

- Molecular genetic defects in the sterol 27-hydroxylase gene
- Deficiency of the mitochondrial enzyme sterol 27-hydroxylase
- Increased serum level of cholestanol

Clinical Features

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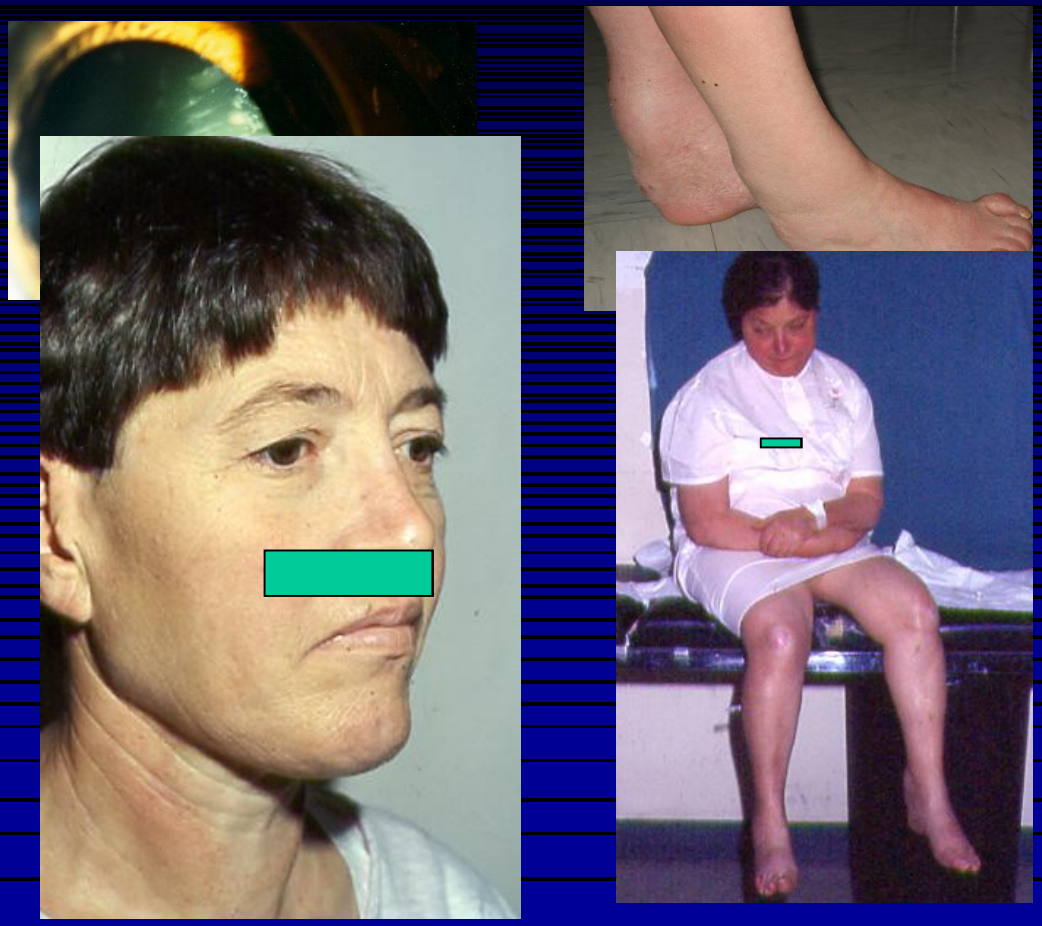
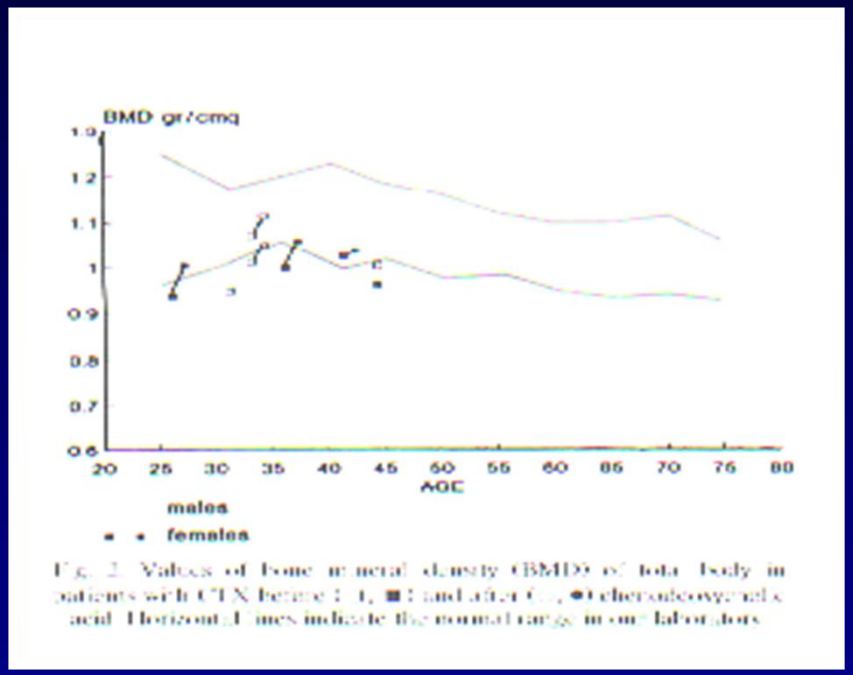


Cerebrotendinous xanthomatosis with predominant parkinsonian syndrome: further confirmation of the clinical heterogeneity

Dotti MT, Federico A, Garuti R, Calandra S.

Mov. Disord. 15: 1017-9, 2000



Cerebrotendinous xanthomatosis: pathophysiological study on bone metabolism

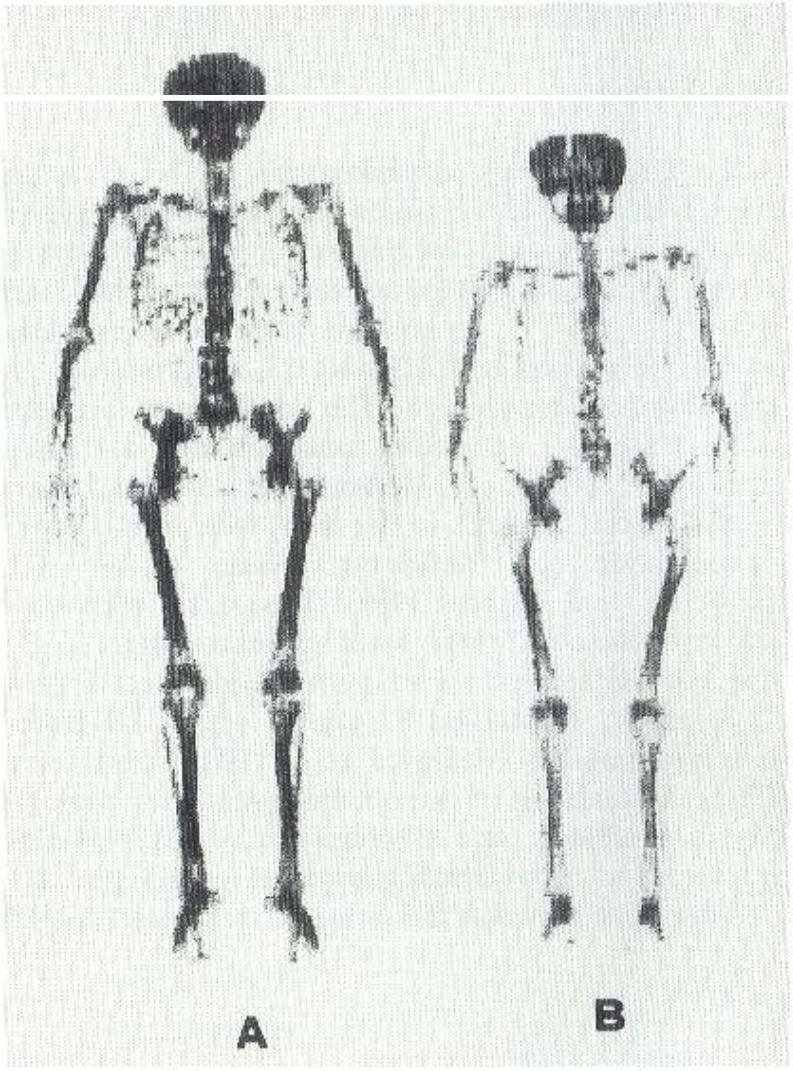
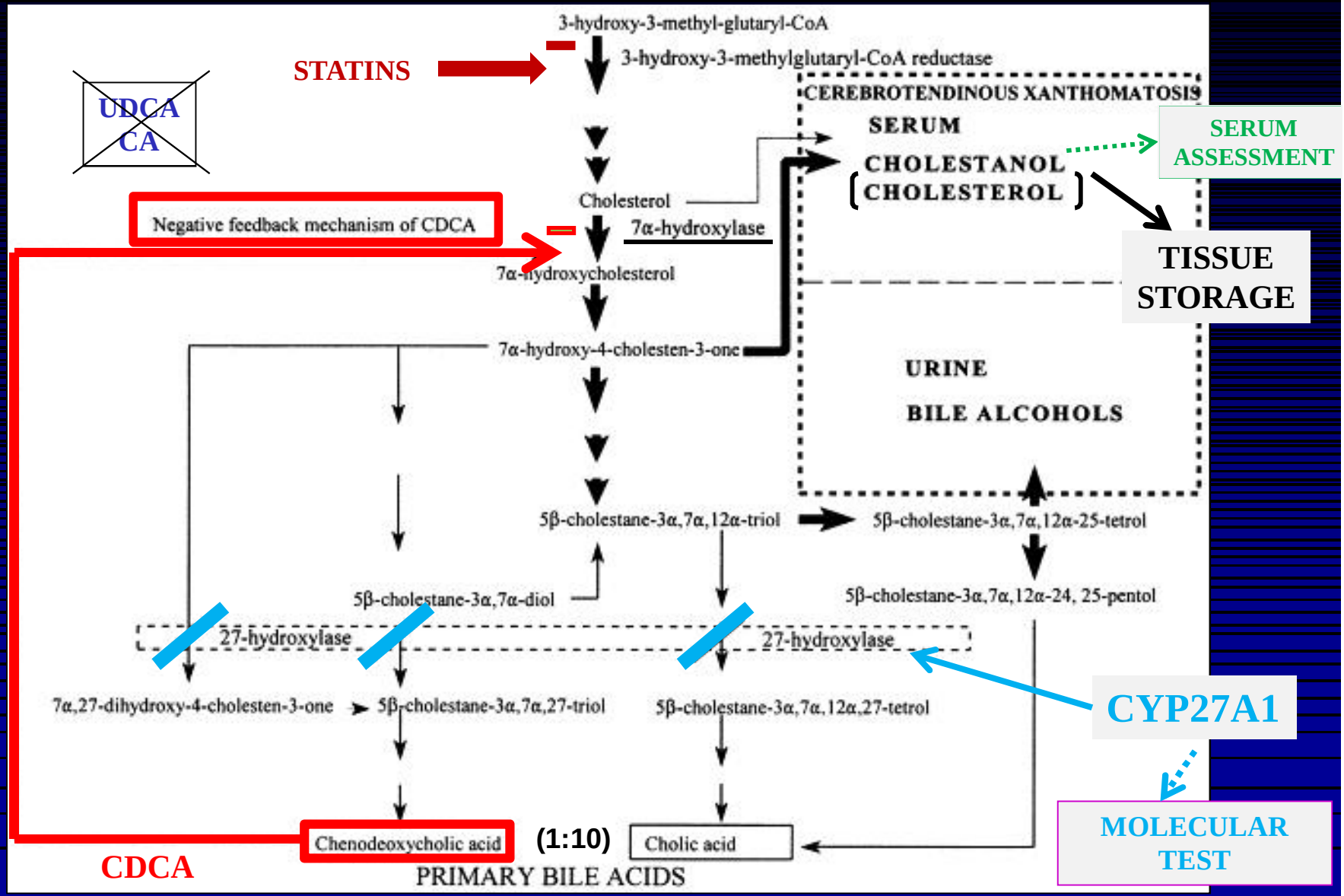


Fig. 1. Computer-generated images of total body scans of a normal subject (A, TBD: 1.095 g/cm^2) and a CTX patient (B, TBD: 0.948 g/cm^2).

Federico A, Dotti MT, Lore F, Nuti R.

J. Neurol. Sci. 115: 67-70, 1993

CTX: PATHOGENESIS AND TREATMENT



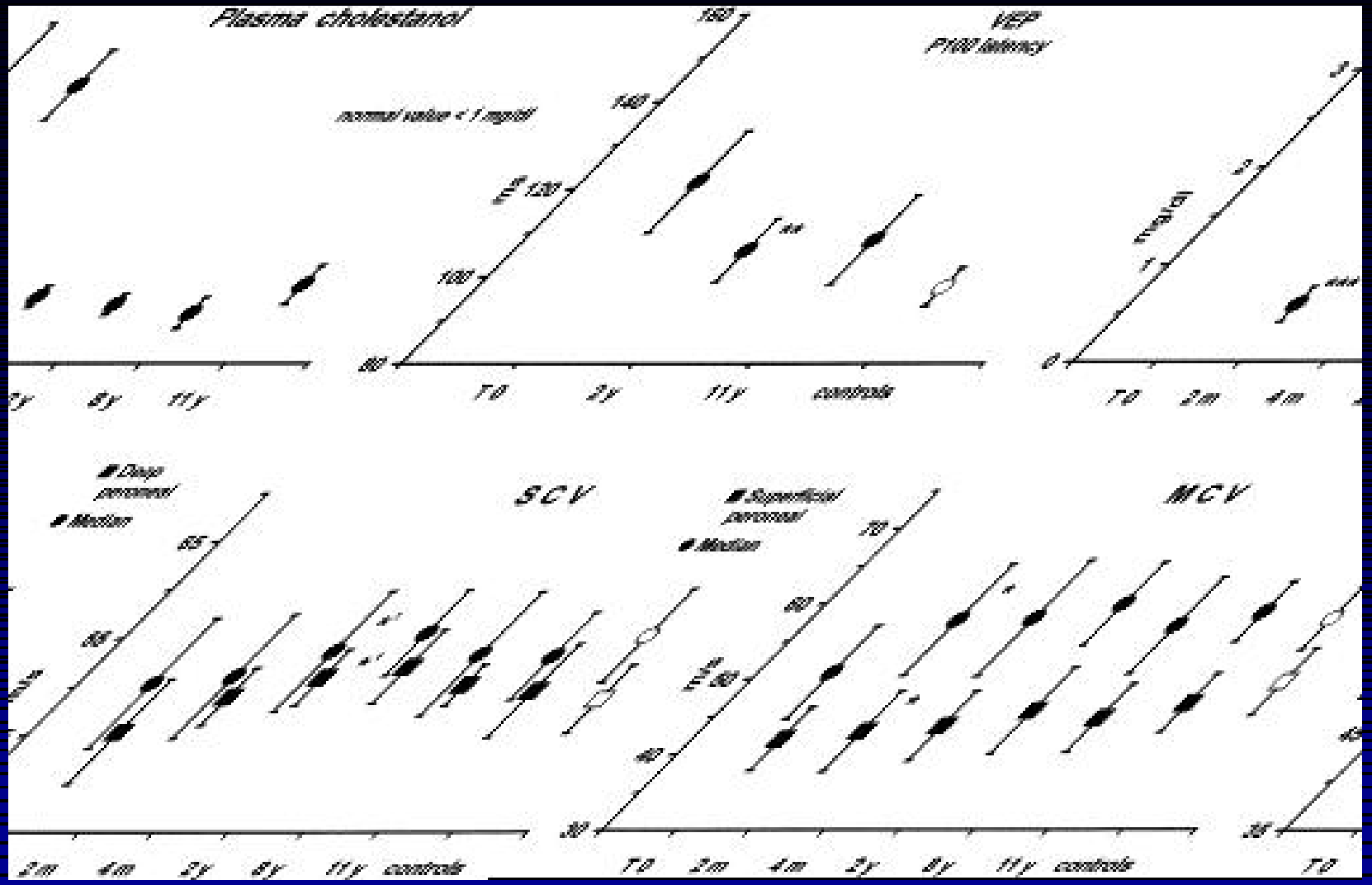
BILE ACIDS

- **NORMAL SUBJECTS**

  Cholic acid and chenodeoxycholic acid (80%) deoxycholic acid (20%) lithocholic acid (2-4%) The latter are derived from intestinal bacterial metabolism

- **CTX**

  Cholic acid is 80% of all the bile acids, **chenodeoxycholic acid is undetectable** and secondary bile acids (deoxycholic and lithocholic acids) are almost absent (Salen et al 1995)



Cerebrotendinous xanthomatosis:11 year treatment with Chenodeoxycholic acid in five patients. An electrophysiological study
Mondelli M et al. J. Neurol. Sci. 190:29-33, 2001

Chenodeoxycholic acid treatment in cerebrotendinous xanthomatosis in Italy

Federico A, Dotti MT

Neurology,2001

Therapy in CTX

- Chenodeoxycholic Acid:
  - decreased formation of bile alchools
  - decreased formation of cholestanol
  - reduction of cholestanol in plasma, tissues and brain
- HMG-CoA Reductase Inhibitors
  - decreased formation of cholestanol
  - decreased serum levels of cholestanol and cholesterol
- Combined therapy: additive effects or side effects

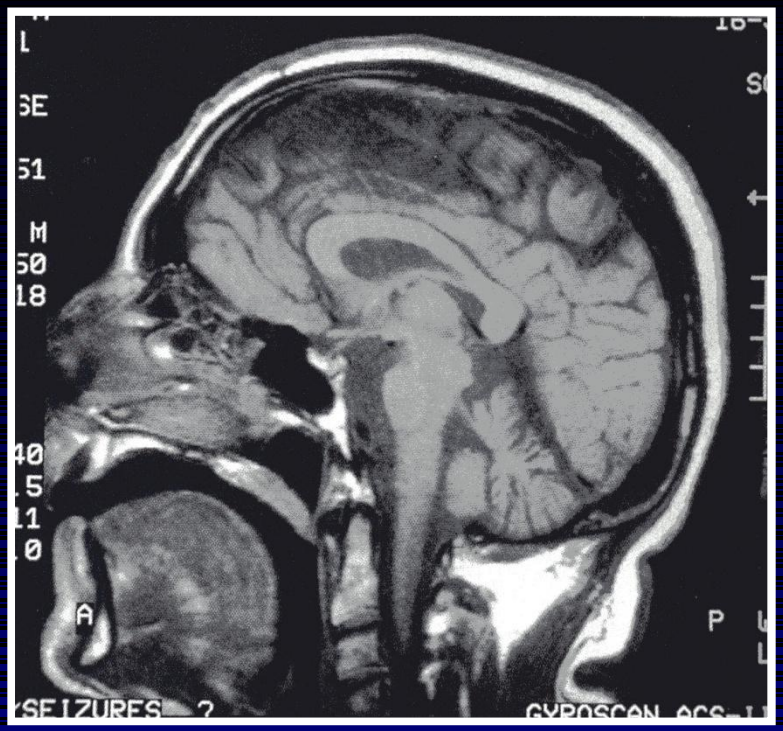
II- THE DIAGNOSTIC CONFIRMATION

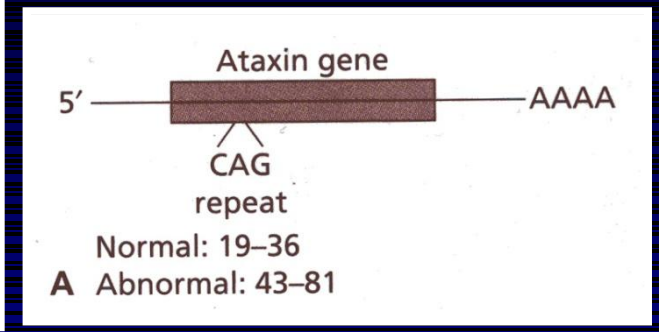
STRATEGY OF INVESTIGATION

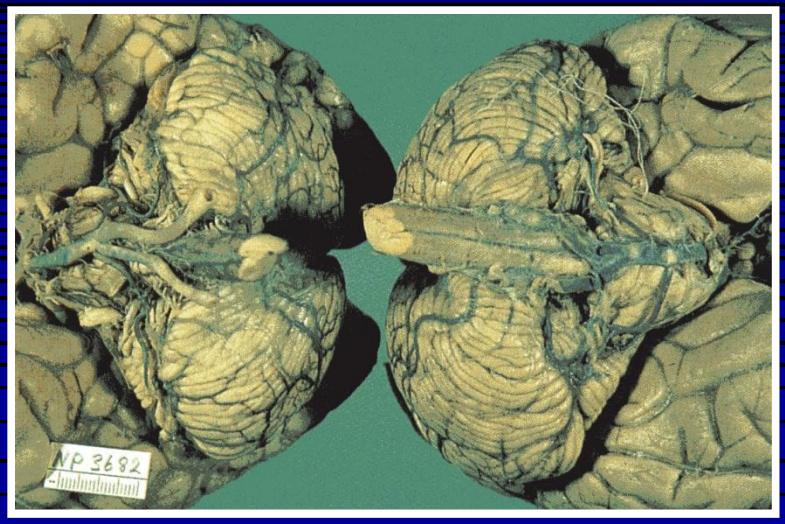
- **CLINICAL INVESTIGATIONS**
  - **CT and nMR**
  - **EEG**
  - **ERG**
  - **EMG and Nerve conduction velocities**
  - **PEV, BAERs, Somatosensory evoked potentials**
  - **Neuropsychologic tests**

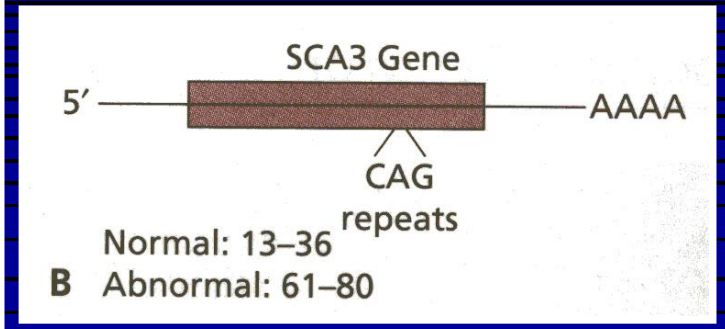
Neuroimaging

Dominant ataxia

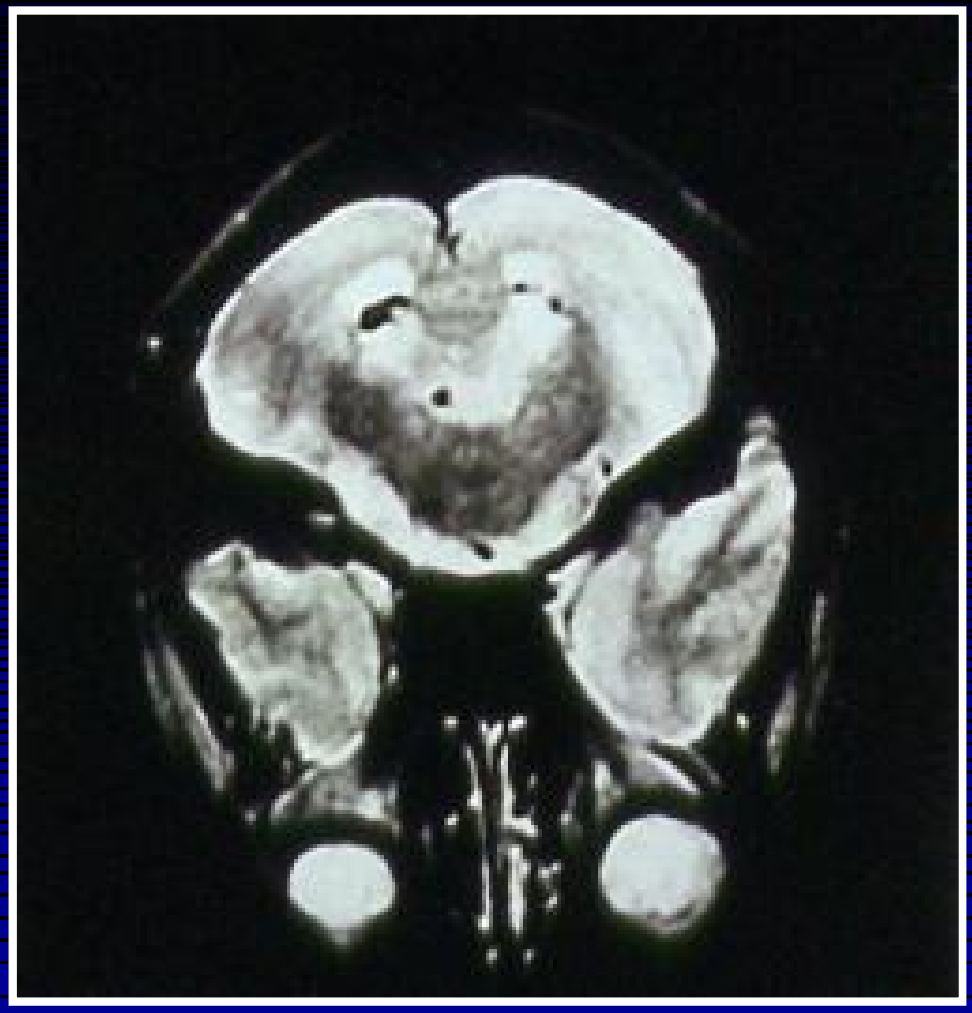




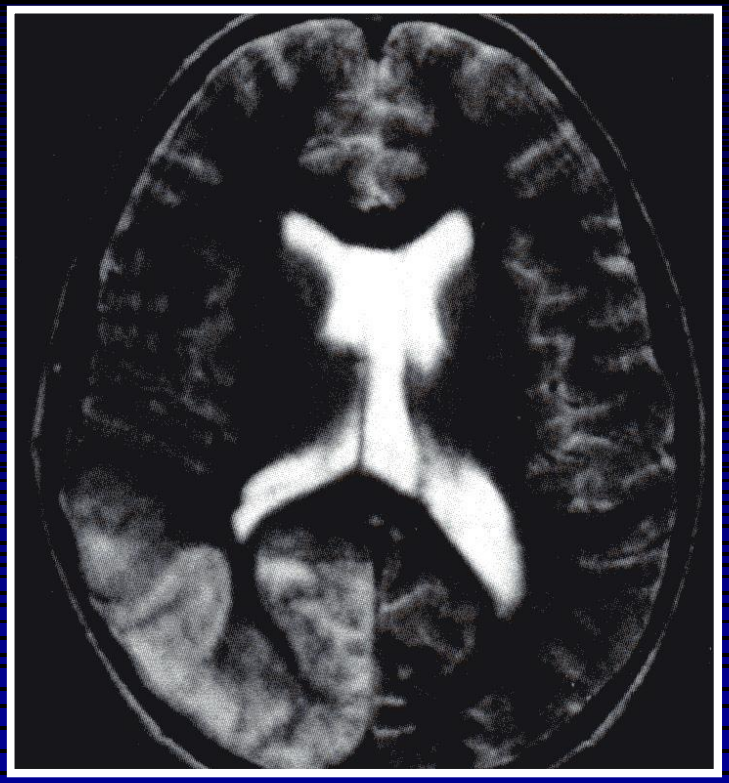




CTX

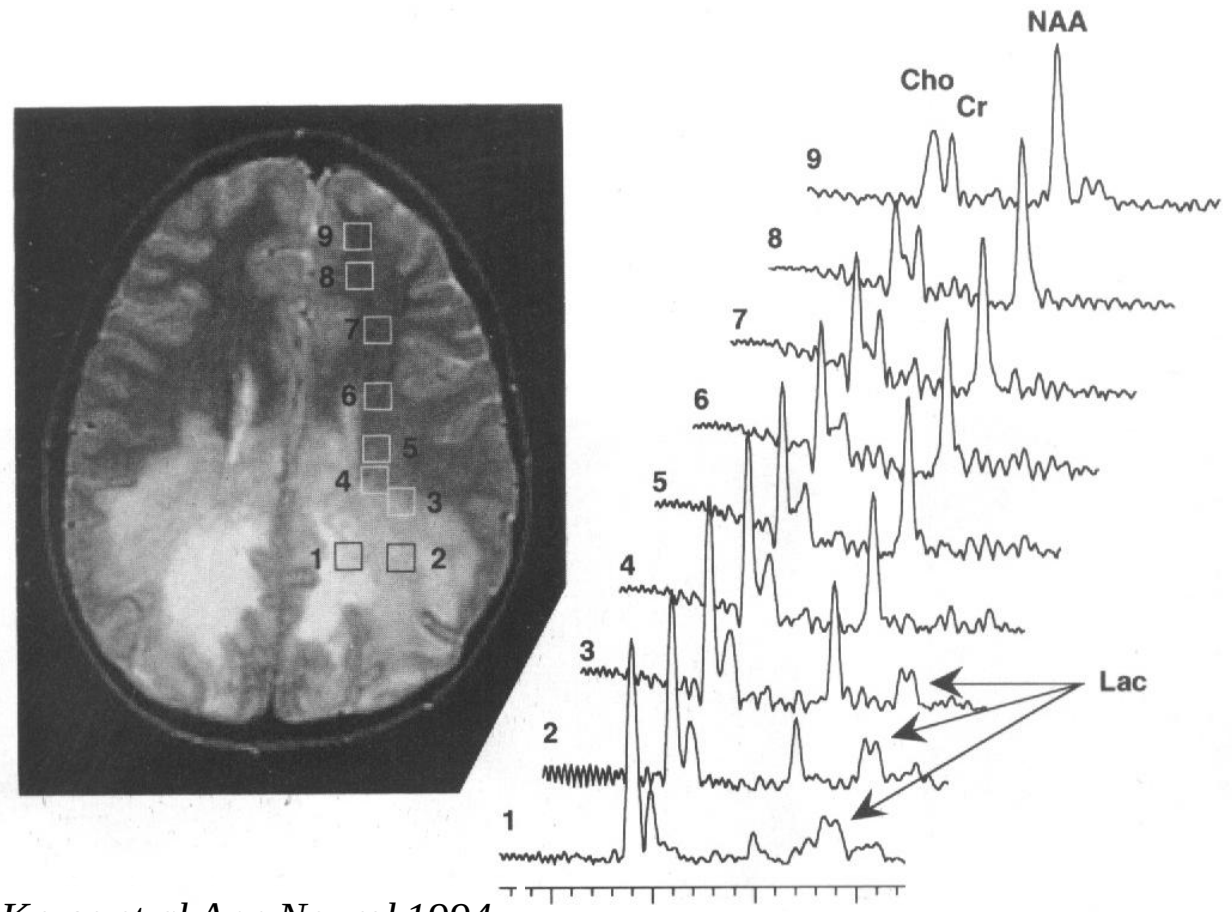


MELAS

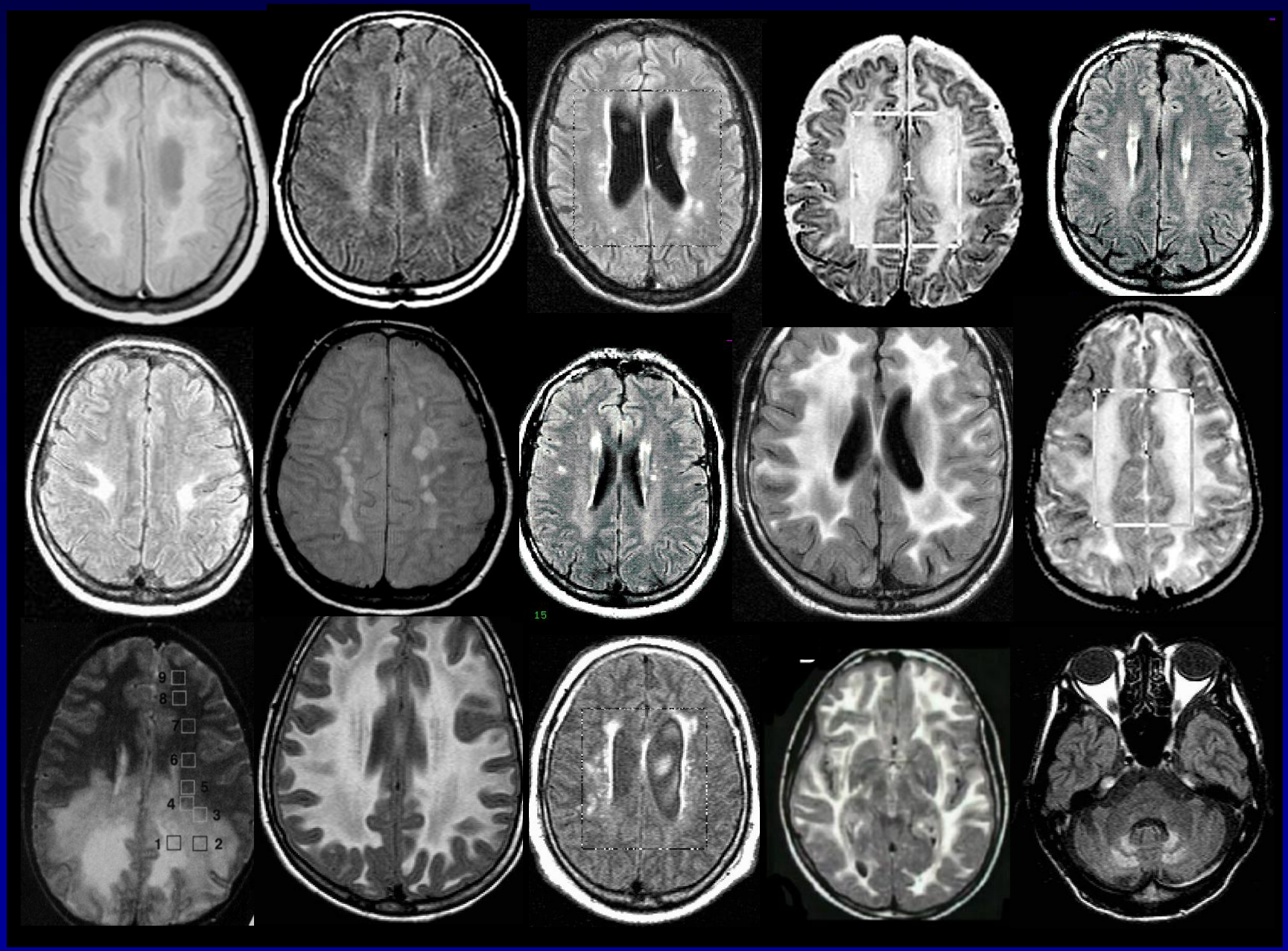


Adrenoleukodystrophy

Metabolic changes in Lesions & NAWM



Kruse et al Ann Neurol 1994


9
8
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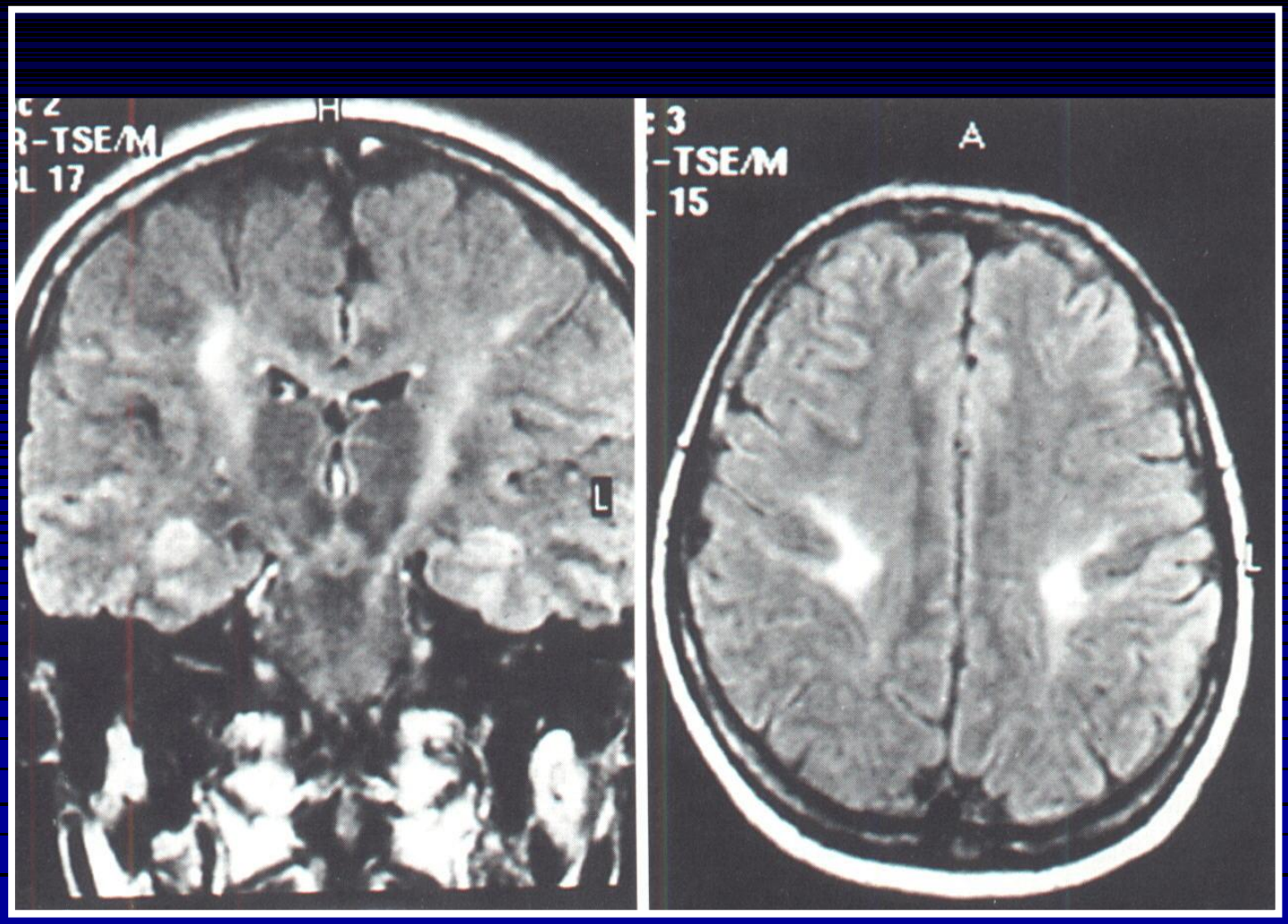
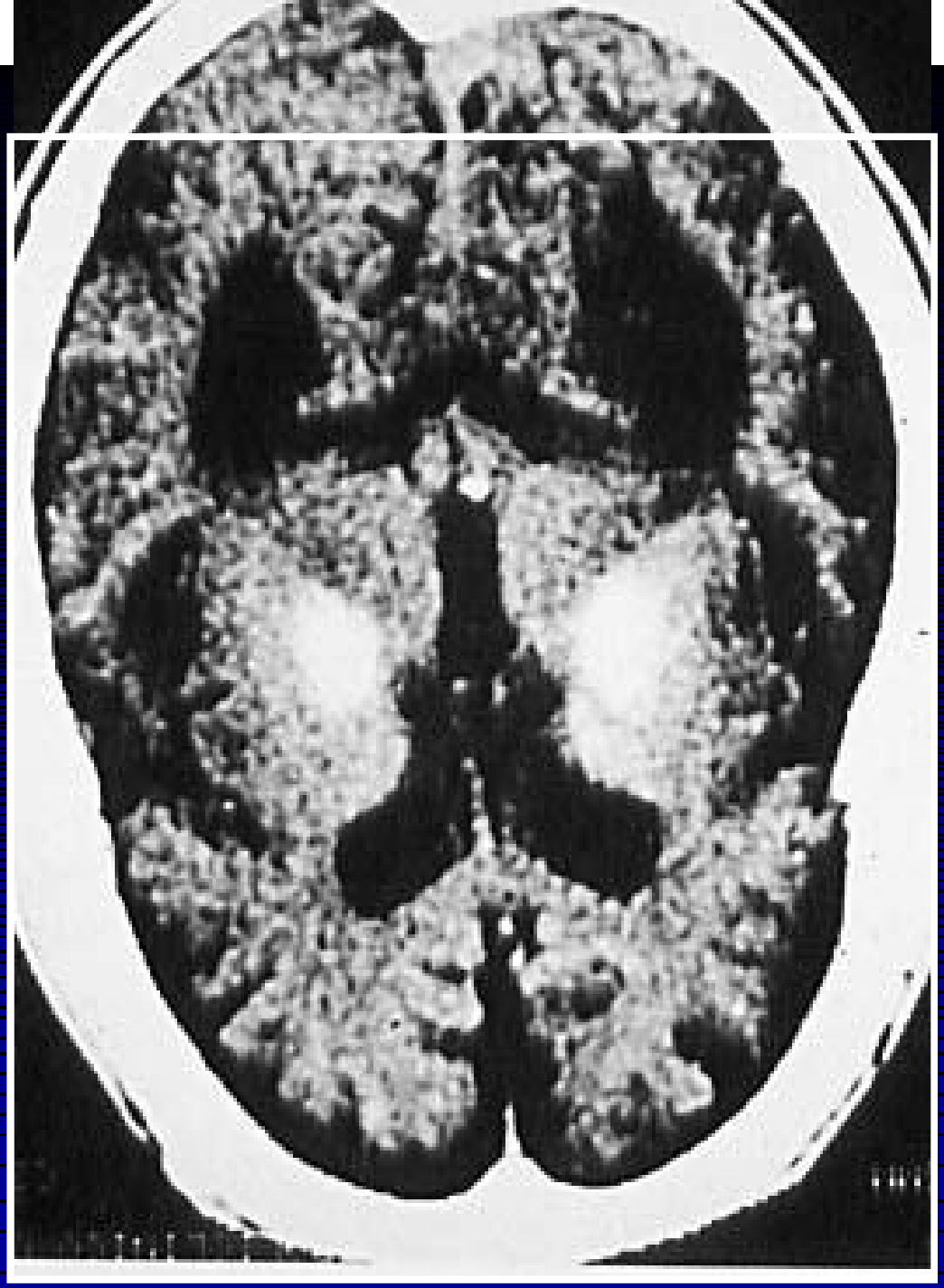
1
2
15

Adult Krabbe's disease

De Stefano et al. J.Neurol.247: 226-228, 2001

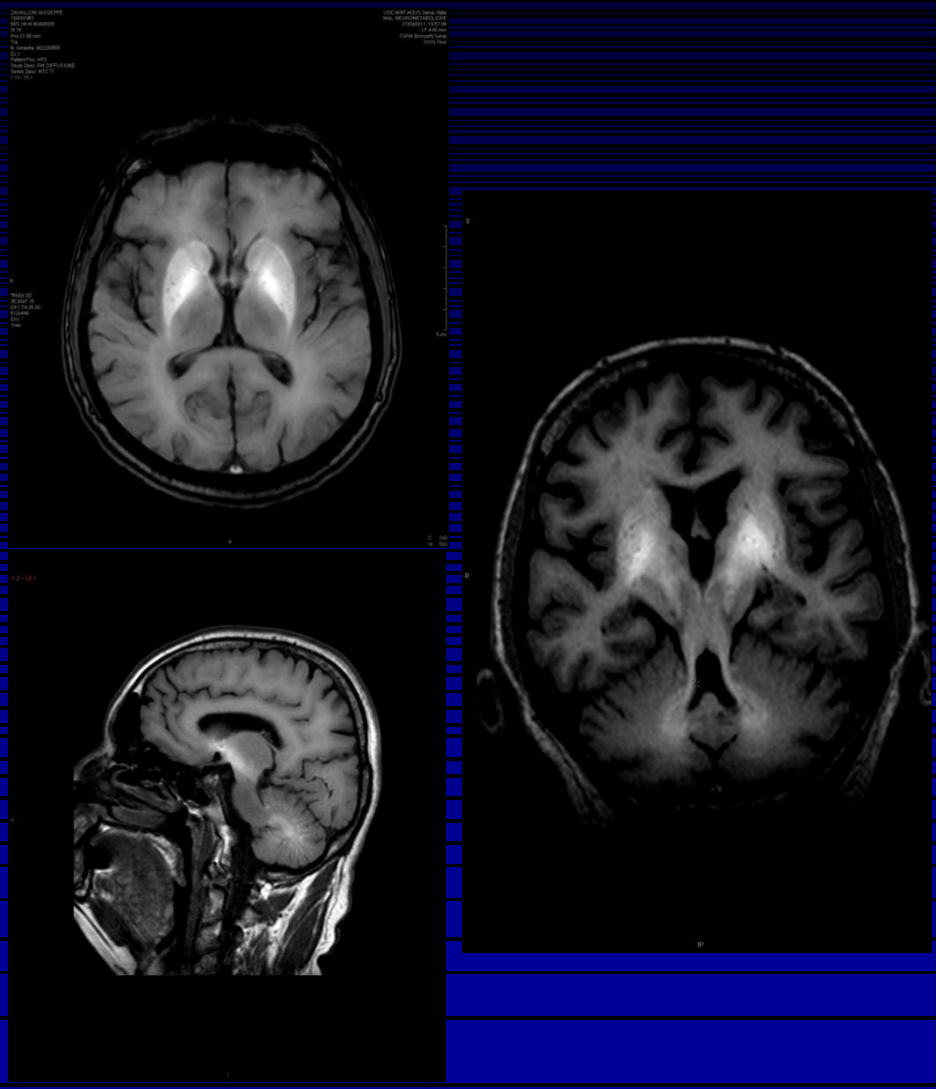




Autosomal recessive parkinsonism with hypermanganesaemia, polycythaemia, and chronic liver disease

Patient	1	2
gender	male	male
age	59	60
presentation	neurologic	neurologic
symptoms onset	47	57
polycythaemia	+	+
parkinsonism	+	+
hepatomegaly	+	+
liver ultrasound	steatosis	hyperplasia
liver parameters	normal	normal
MRI-T1 abn	+	+
DAT-SPECT	normal	normal
blood Mn	??	??

Hyperintense signal from the caudate, lentiform and dentate nuclei and cerebellar white matter in the T1 sequence but normal T2 sequence consistent with manganese deposition in these regions



Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease.

Quadri M, Federico A, et al.

Am J Hum Genet. 2012 Mar 9;90(3):467-77.

Autosomal recessive parkinsonism with hypermanganesaemia, polycythaemia,and chronic liver disease

DISODIUM CALCIUM EDEDATE	24-HOURS URINARY Mn (mcg/L)	BLOOD Mn LEVEL (mcg/L)	UPDRSIII	WALKING TEST
Baseline	1.06	106.0	27/108	18
Month 1	30.0	133.0	13/108	13
Month 2	76.0	101.0	10/108	10
Month 3	216.0	90	9/108	10
Month 4	219.0	4.2	8/108	8

Clinical and biochemical parameters in patient 1 at baseline and after monthly five-day courses of chelation therapy with disodium calcium edetate (20 mg/Kg twice/day)

Mov Disord. 2012 Jul;27(8):962.

HOT TOPICS

A New Treatable Genetic Disorder of Manganese Metabolism Causing Dystonia-Parkinsonism and Cirrhosis: The "New" Wilson's Disease?

Manganese (Mn) intoxication (manganism) causing dystonia-parkinsonism, often accompanied by psychiatric features, has been described in relation to several etiologies: Mn environmental overexposure, for example, in miners; in chronic liver disease from the failure of manganese hepatic clearance; in individuals receiving parenteral nutrition; and in drug addicts exposed to ephedrine-containing potassium permanganate. However, an autosomal-recessive dystonic syndrome from hypermanganesemia has been previously recognized, where the above-mentioned causes have been excluded, suggesting a genetic disorder of Mn metabolism.[1,2]

Recently, 2 independent reports published in the *American Journal of Human Genetics* described that homozygous mutations in the *SLC30A10* gene, on chromosome 1q41–q42, which encodes for a Mn transporter, are responsible for a syndrome of dystonia-parkinsonism, hypermanganesemia, cirrhosis, and polycythemia.[3,4] The authors carried out homozygosity mapping and functional studies in 10 families, and the 20 affected members were found to have mutations in the *SLC30A10* gene. In 8 families, the 17 affected members presented with young-onset (2–14 years) generalized dystonia, whereas in 1 family, the affected member had paraparesis and no dystonia. Interestingly, in 1 family from Italy the 2 affected members presented with late-onset (ages 47 and 57 years) asymmetric parkinsonism and early postural instability.

This exciting discovery is clinically important for a number of reasons. First, this disorder is potentially treatable, and therefore the diagnosis should not be missed. Treatment with chelation therapy (calcium sodium edetate and oral iron) can prevent the fatal consequences of cirrhosis but also alleviates disability, as several patients had become wheelchair bound when untreated and improved considerably after treatment. Thus, this disorder, along with Wilson's disease, is the only potentially treatable inherited metal storage disorder described to date. Second, it would be interesting to investigate patients with manganism attributed to other causes, for mutations or polymorphisms in this gene that may explain why some individuals may be more prone to developing manganism than others when overexposed to Mn. Additional individuals and families need to be investigated.

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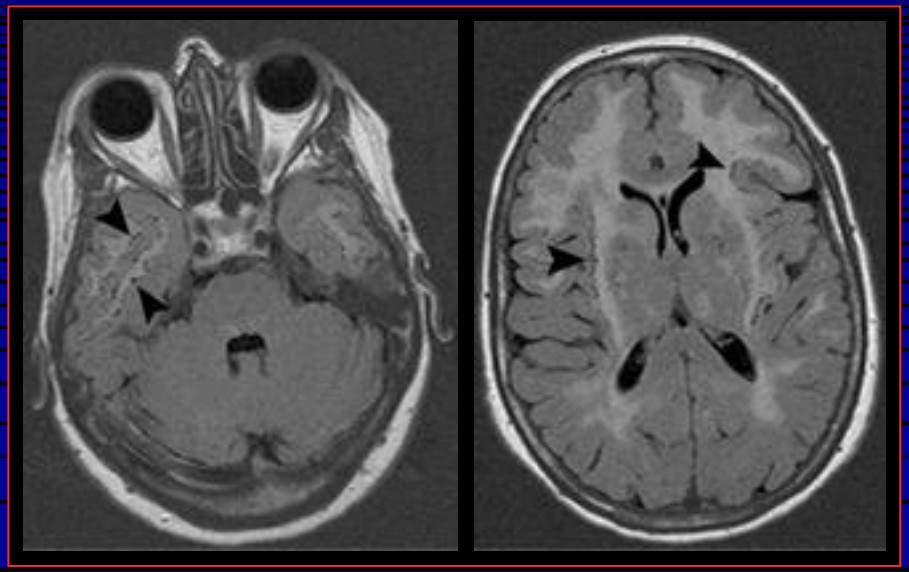
Kailash P. Bhatia, FRCP
Sobell Department of Motor Neuroscience and Movement Disorders
UCL Institute of Neurology, London, United Kingdom

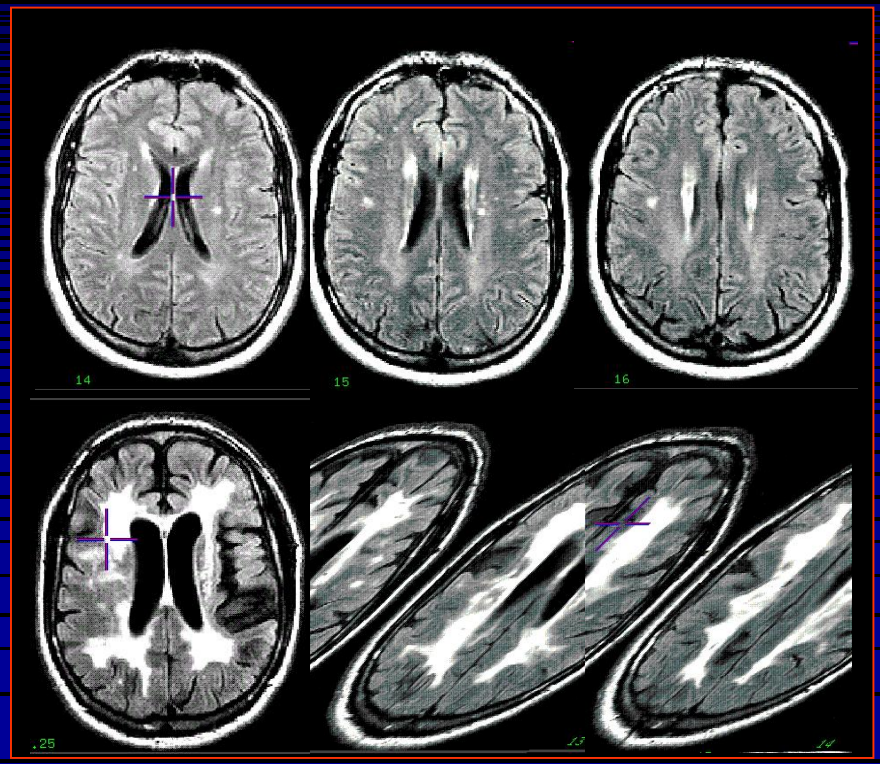
References

1. Tuschl K, Mills PB, Parsons H, et al. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia—a new metabolic disorder. J Inherit Metab Dis 2008;31:151–163.
2. Brna P, Gordon K, Dooley JM, Price V. Manganese toxicity in a child with iron deficiency and polycythemia. J Child Neurol 2011; 26:891–894.
3. Tuschl K, Clayton PT, Gospe SM Jr, et al. Syndrome of hepatic cirrhosis, dystonia, polycythemia and hypermanganesemia—caused by mutation in *SLC30A10*, a manganese transporter in man. Am J Hum Genet. 2012;90(3):457–466.
4. Quadri M, Federico A, Zhao T, et al. Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. Am J Hum Genet 2012;90: 467–477.

CADASIL/MRI

The white matter abnormalities are strongly suggestive, but often undistiguishable from other neurologic disorders (MS, SCVD, LD)



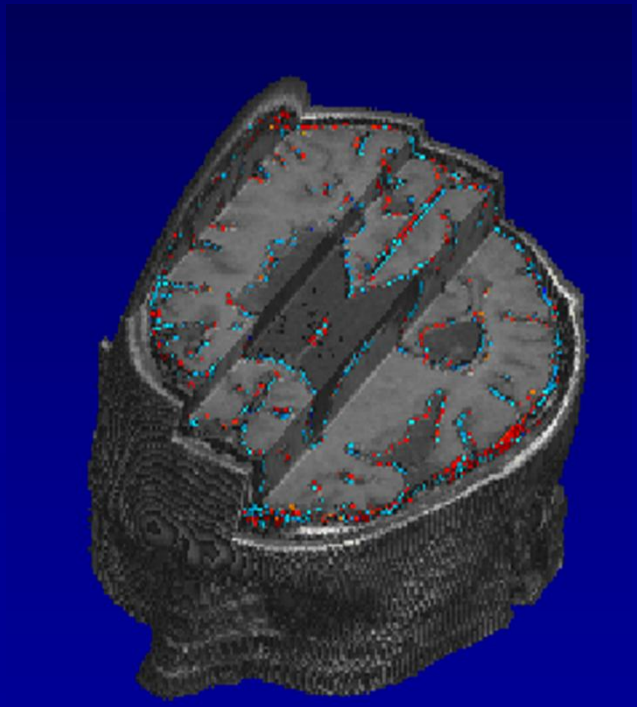


Brain Atrophy

Structural Image Evaluation of Normalised Atrophy

The SIENA software provides accurate, fully automatic measurement of atrophy using edge motion

- Ø Longitudinal, Cross Sectional & Regional
- Ø Accurate and fully automatic
- Ø Measures atrophy & brain change
- Ø Proven for a range of slice thicknesses
- Ø Proven for a range of MRI sequences
- Ø Correction for scanner geometry drifts
- Ø Accuracy 0.2% of brain volume



FMRIB Oxford

MORPHOLOGICAL EVIDENCE OF METABOLIC DYSFUNCTION

Lysosomal storage cells

peripheral leukocytes

bone narrow

tissues

Peroxysomal abnormalities

Mitochondrial abnormalities

muscle

platelets

tissues

ENZYME DEFICIENCY

Serum

Leukocytes

Cultured fibroblasts

Platelets

Urine

Tissues

MOLECULAR GENETICS STUDIES

STRATEGY OF INVESTIGATION

Lysosomal storage cells in peripheral leukocytes

in bone marrow

in tissues

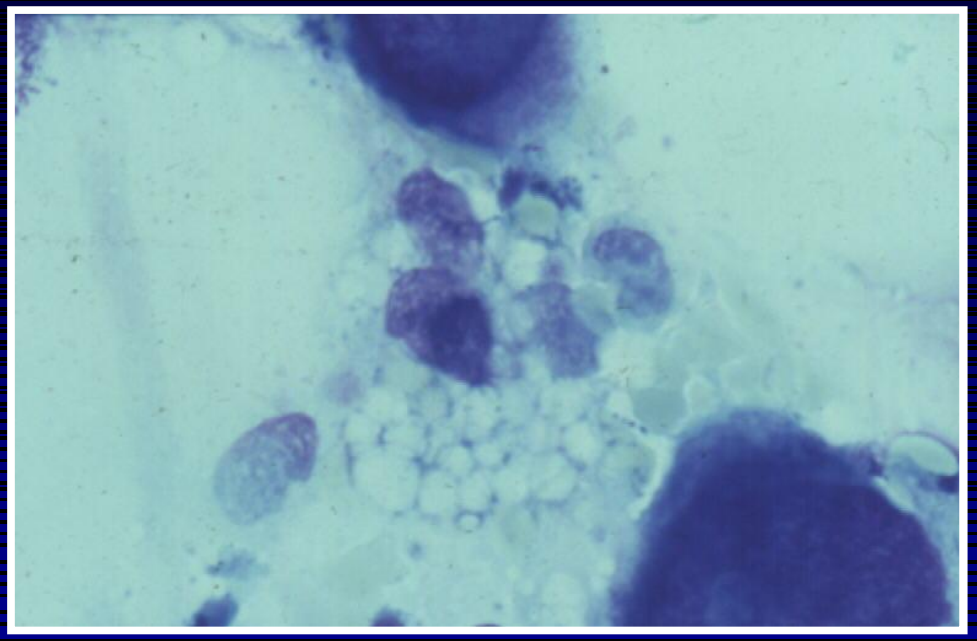
Perixosomal abnormalities

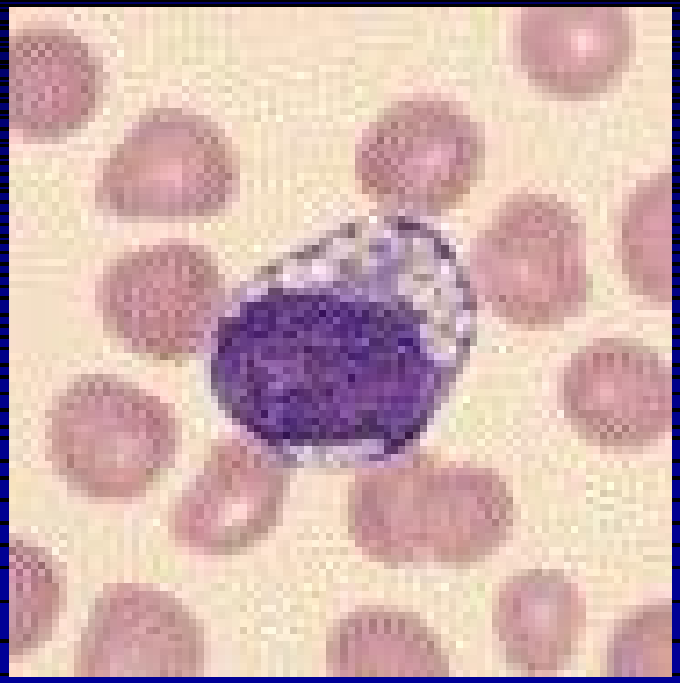
Mitochondrial abnormalities in muscle

in platelets

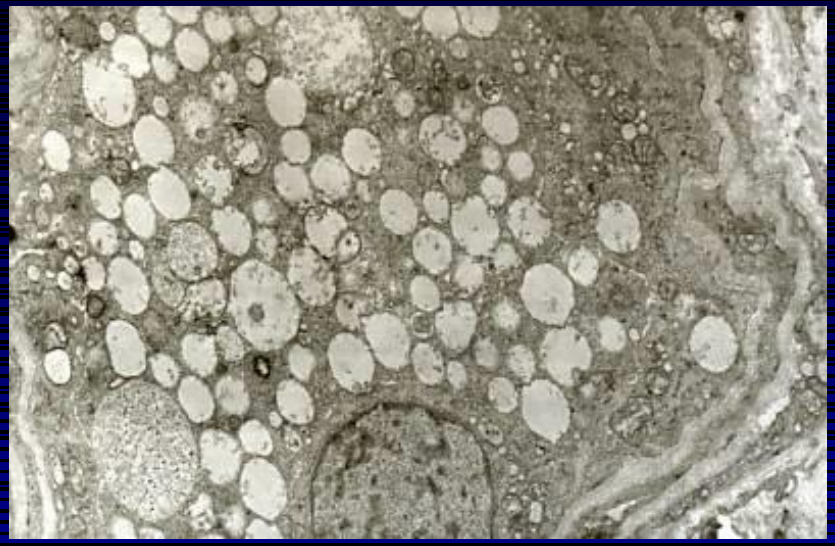
in other tissues

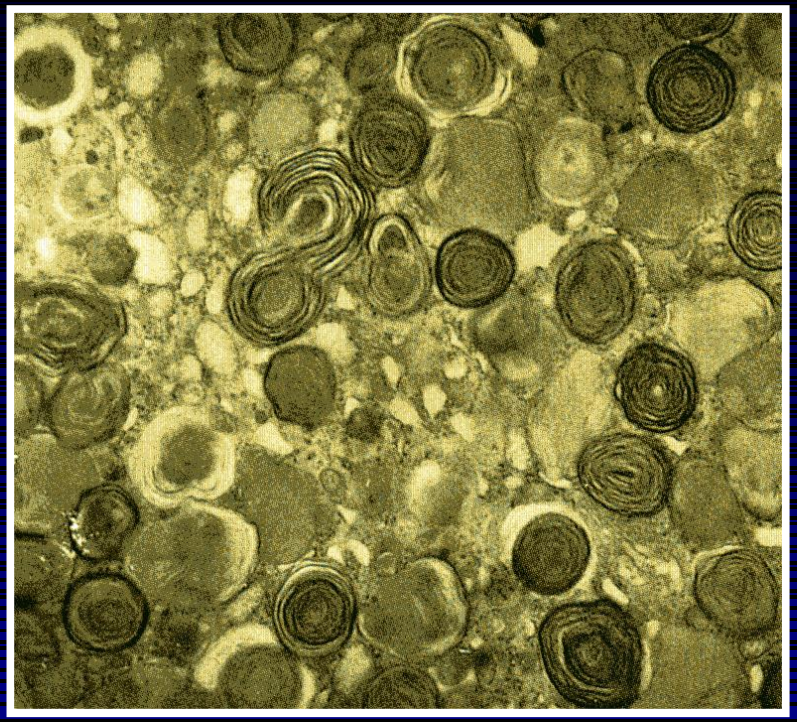
Vacuolated macrophage in MLD



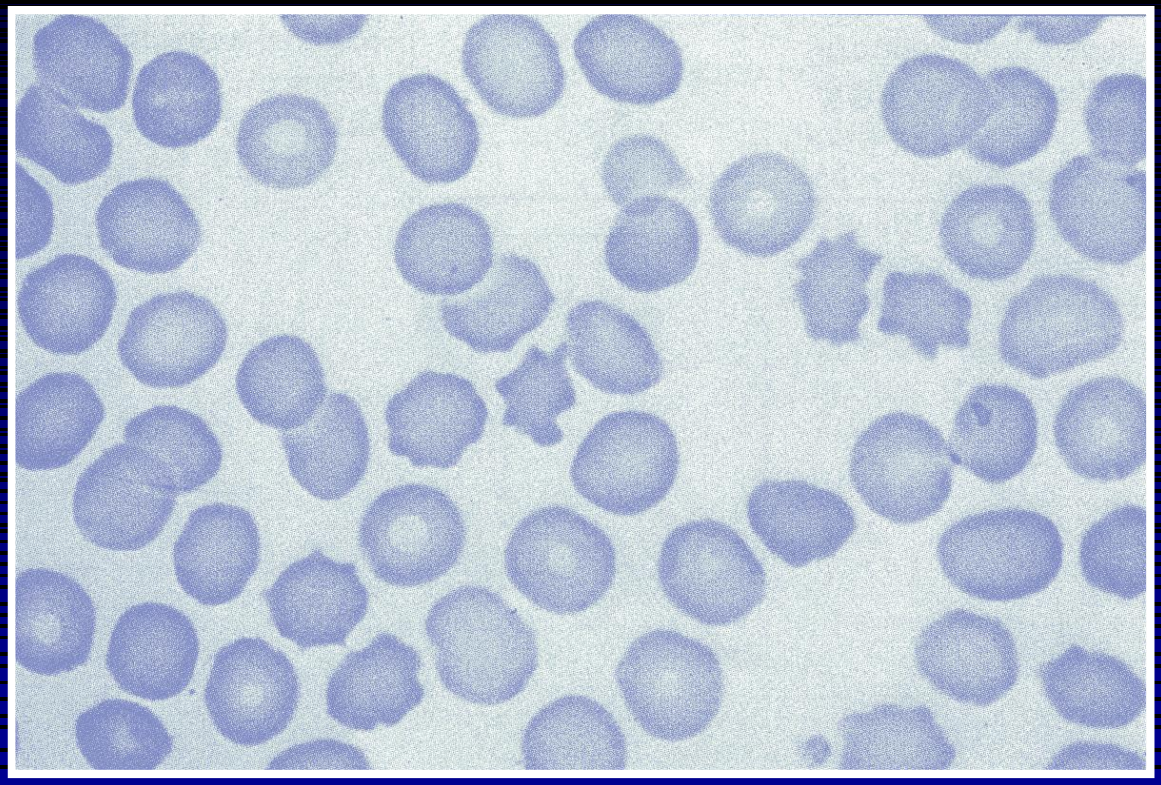


Lysosomal diseases

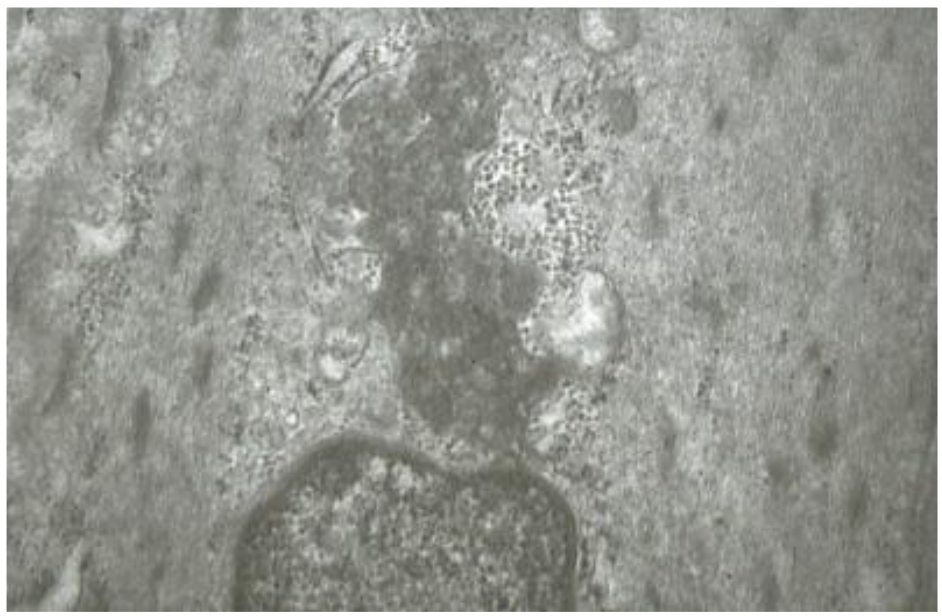


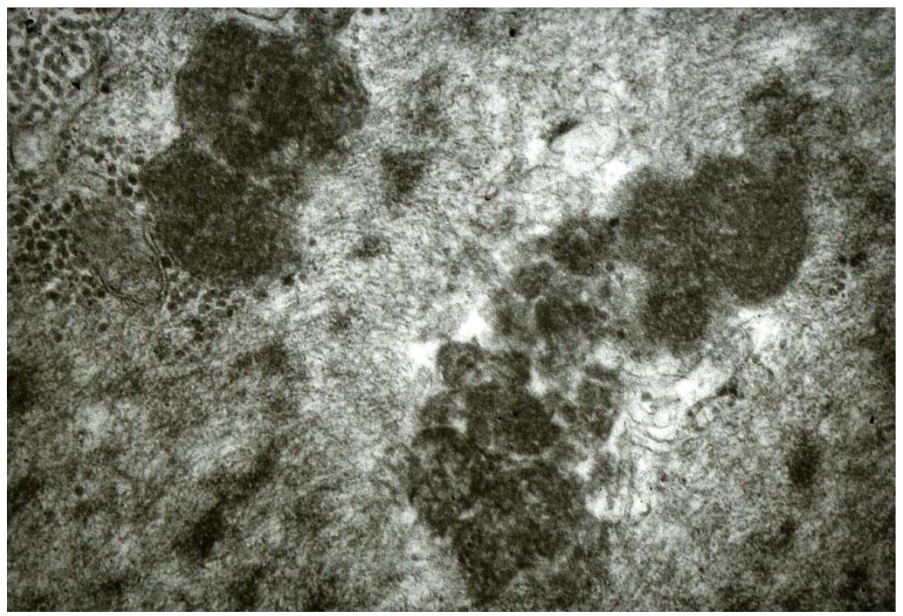


Acantocytes



Ceroid-lipofuscinosis





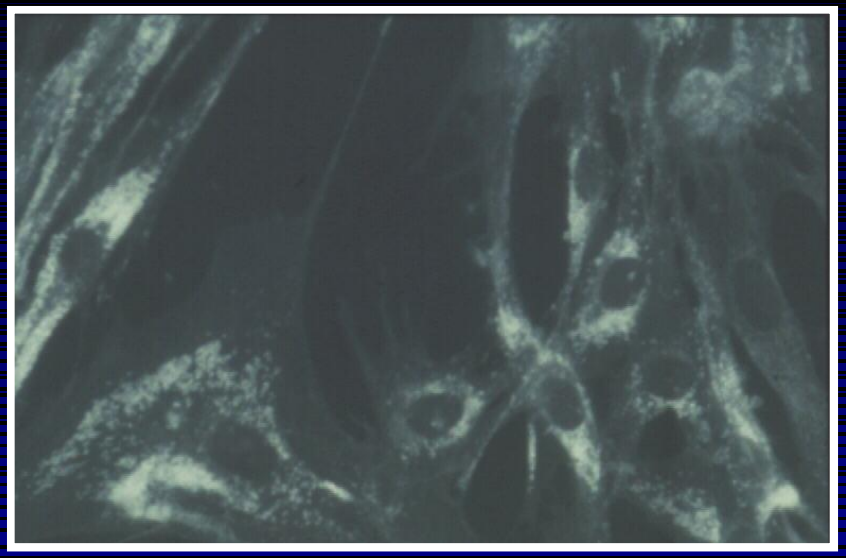
Disappearence of skin lipofuscin storage and marked clinical improvement in adult onset celiac disease and severe vit E deficiency after chronic vit E supplementation

Battisti C, Dotti MT, Formichi P, Bonuccelli U, Malandrini A, Carrai M, Tripodi SA, Federico A

J. Submicrosc. Cytol. Pathol 28: 339-334, 1996

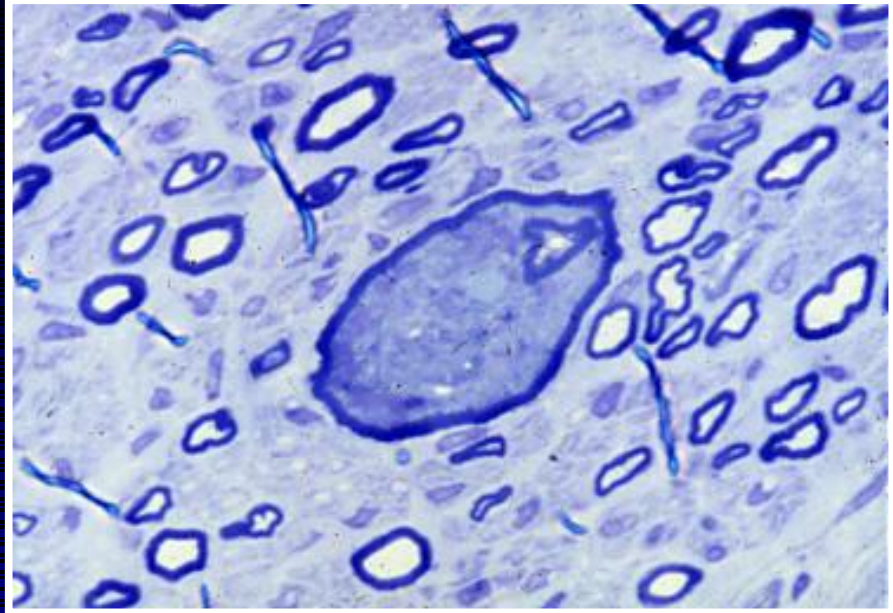
Filippin stain in fibroblasts

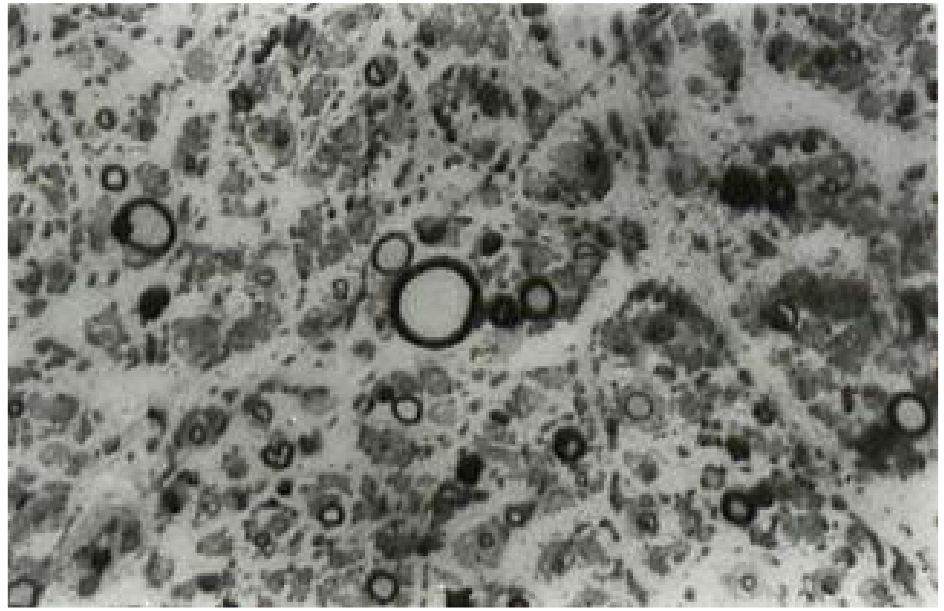
Control

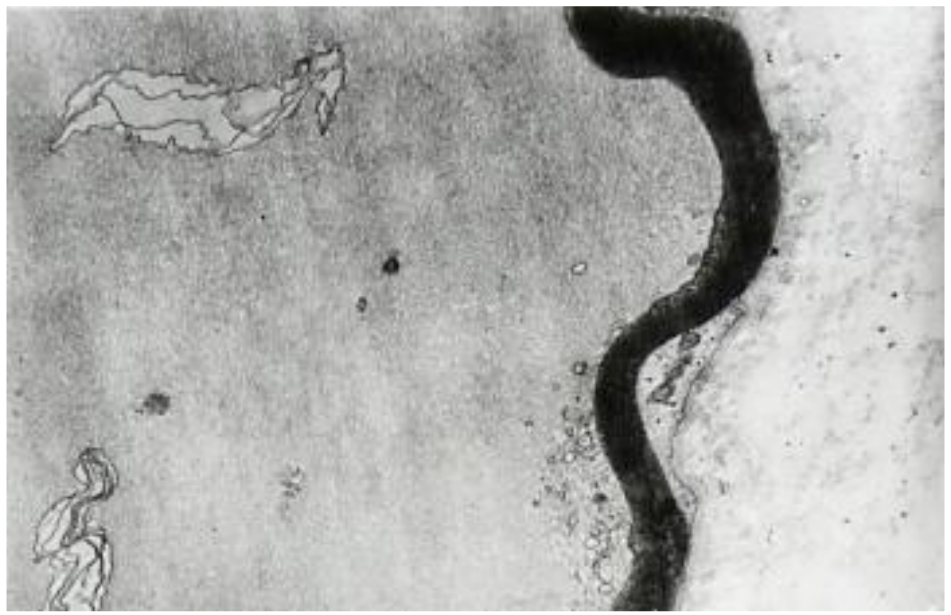


Niemann Pick C

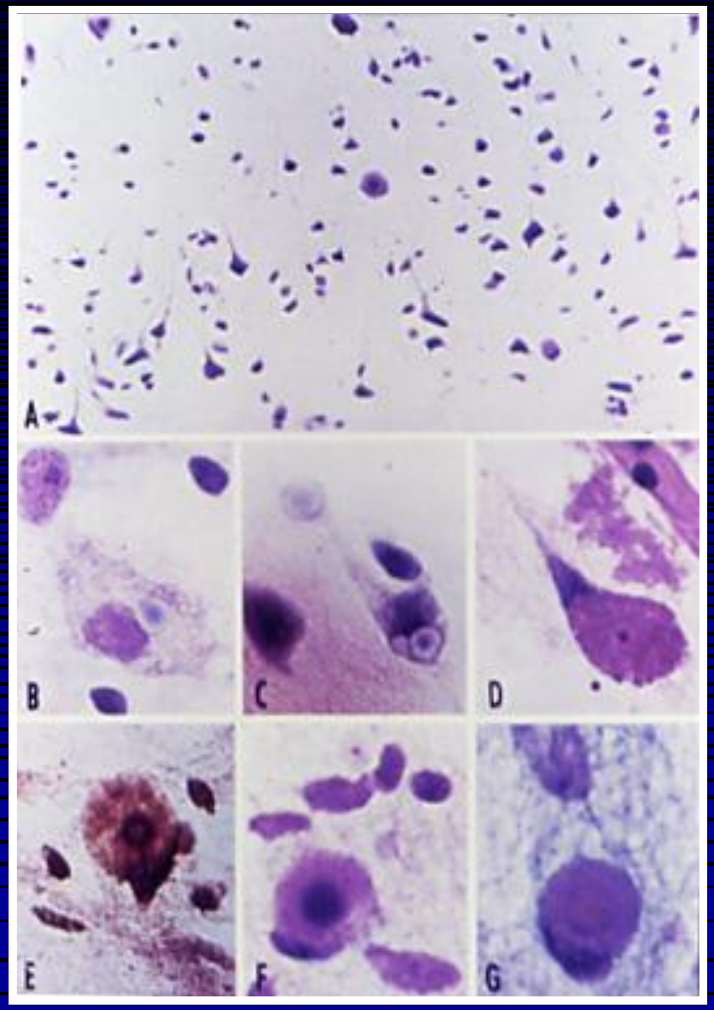
Gian axonal neuropathy



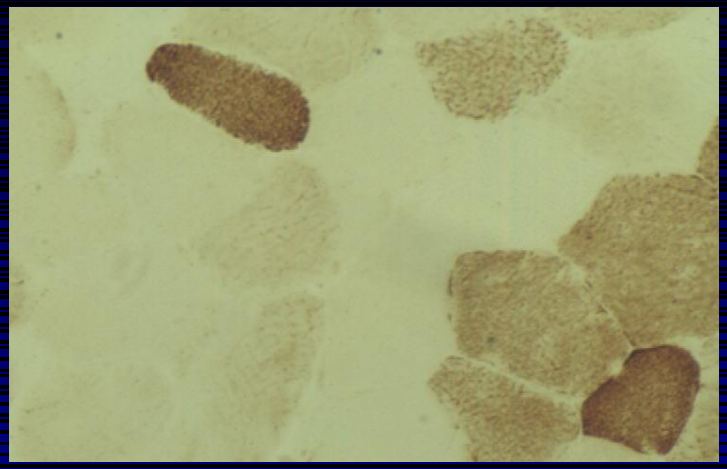


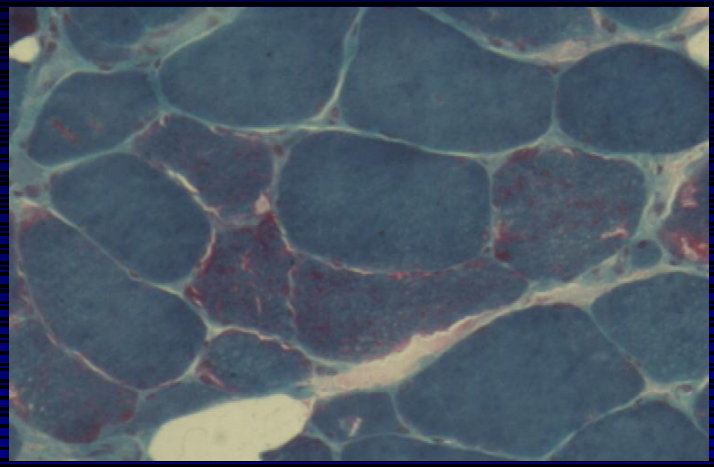


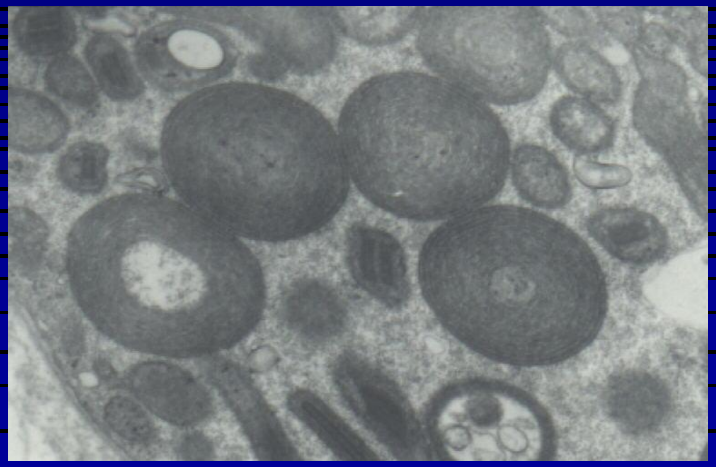
M. Lafora

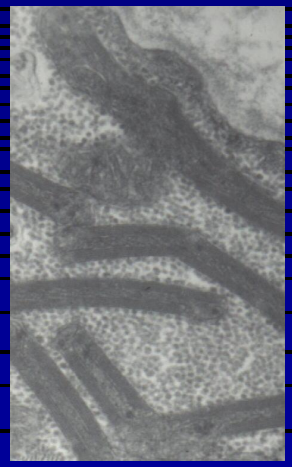


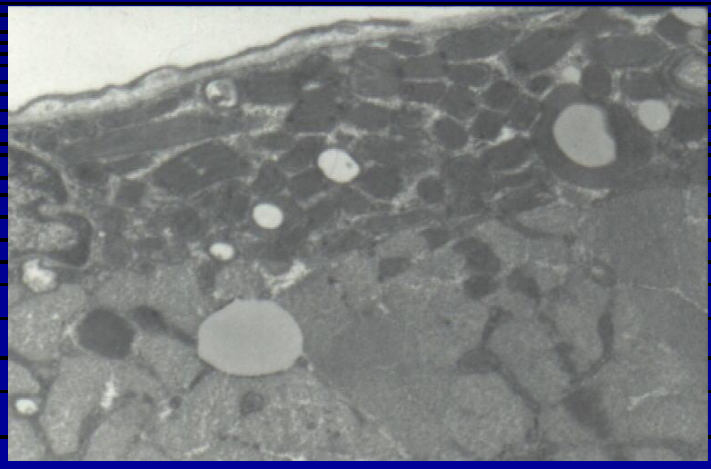
Mitochondrial cytopathy



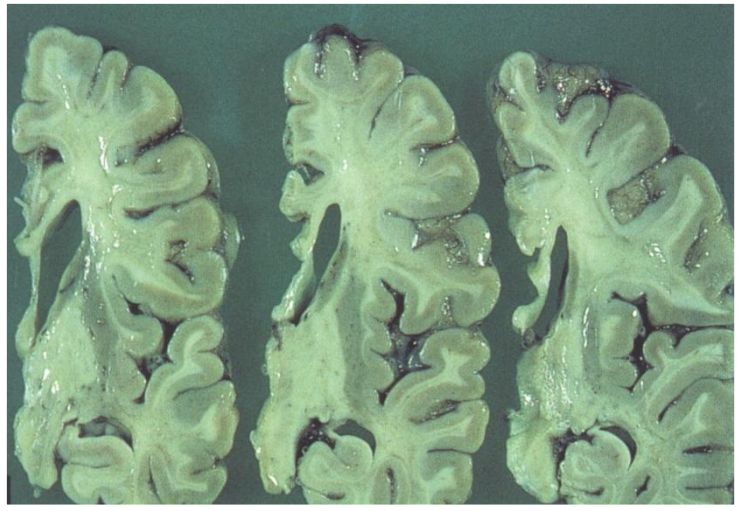


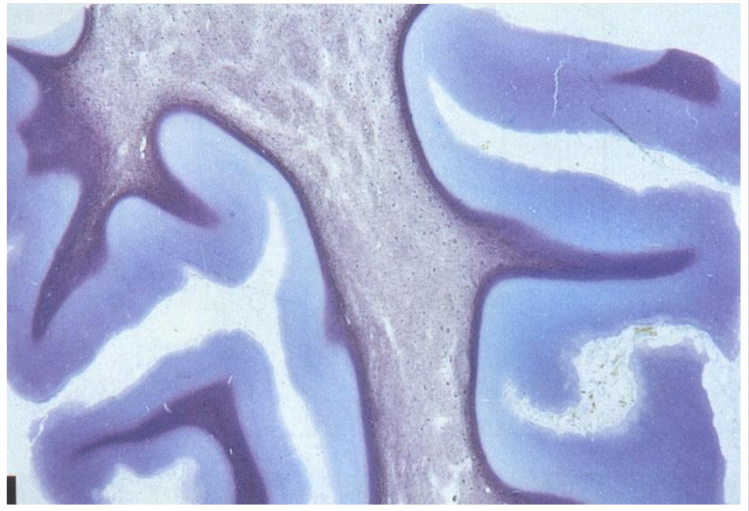


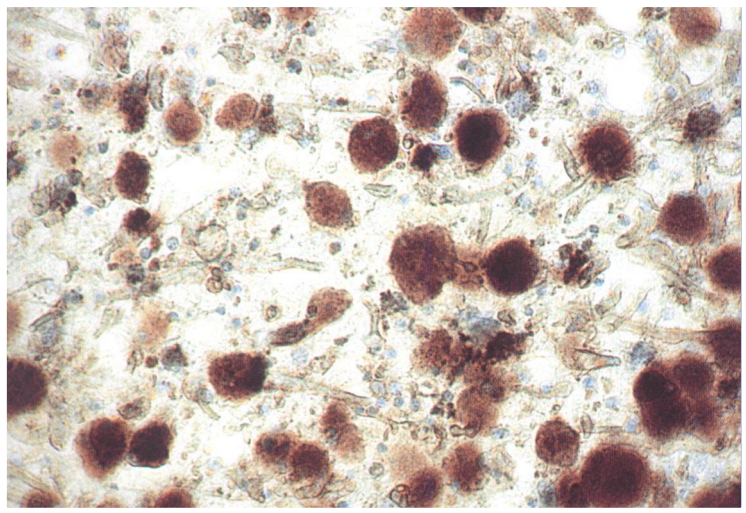


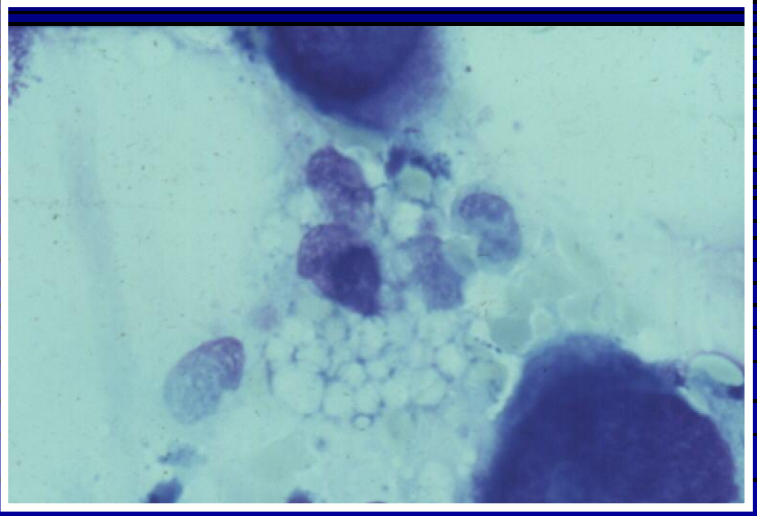


Metachromatic Leukodystrophy









STRATEGY OF INVESTIGATION

URINE
- oligosaccharides
- glycolipids
- aminoacids

SERUM
- pyruvate-lactate
- organic acids
- carnitine
- aminoacids
- long- chain fatty acids
- fatty acid (cholestanol, fitanic acid, ecc)
- glycolipids
- vitamin E
- hormones (cortisol, ACTH, ecc)

STRATEGY OF INVESTIGATION

ENZYME DEFICIENCY Serum

Leukocytes

Cultured fibroblasts

Platelets

Urine

Tissues

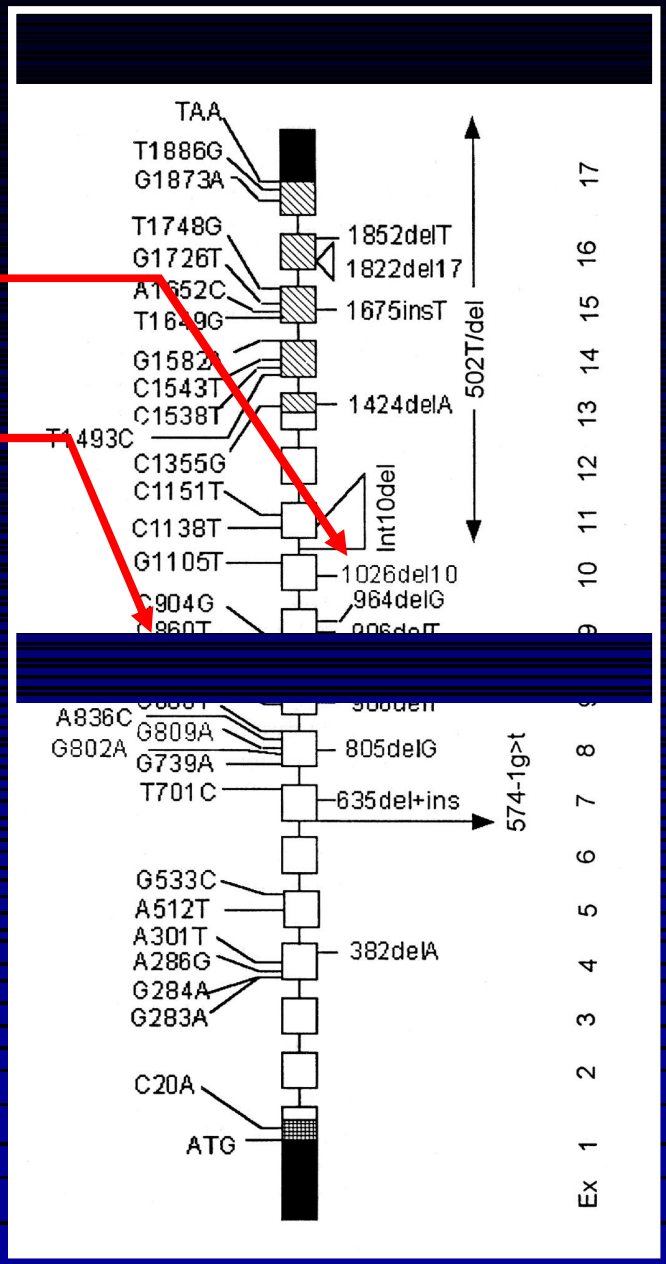
MOLECULAR GENETIC ANALYSIS

Adult-Onset KD
GALC Gene Analysis

Mutations

1026del10

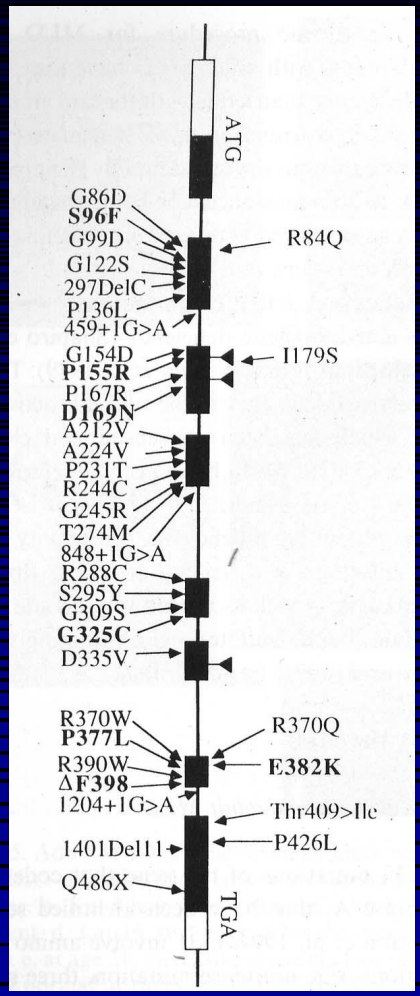
G809A



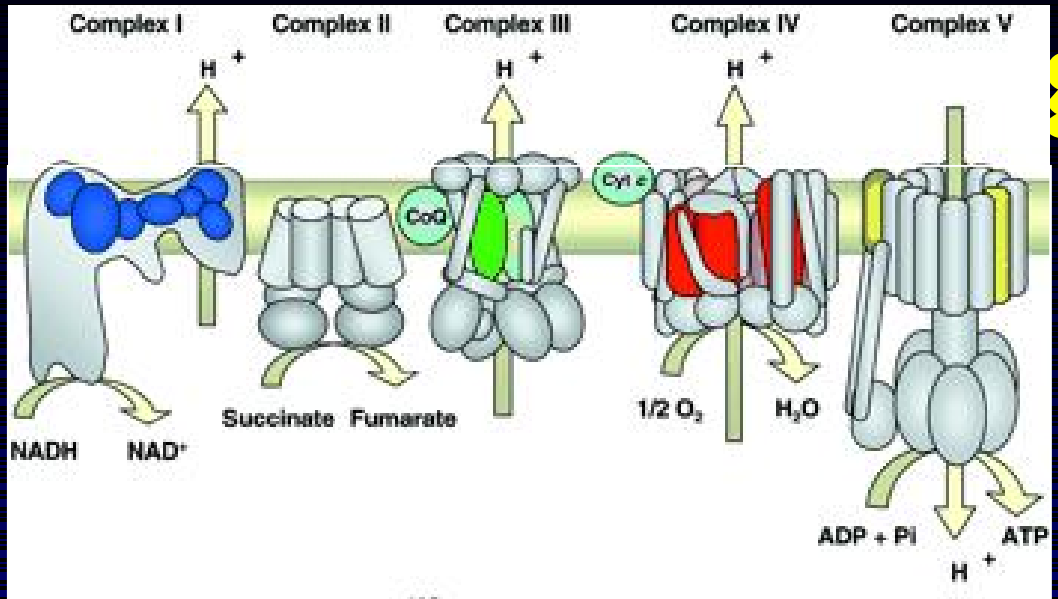
- Two mutations previoulsy reported in patients with infantile and adult forms of KD
- Complexity in the interpretation of disease-causing mutation

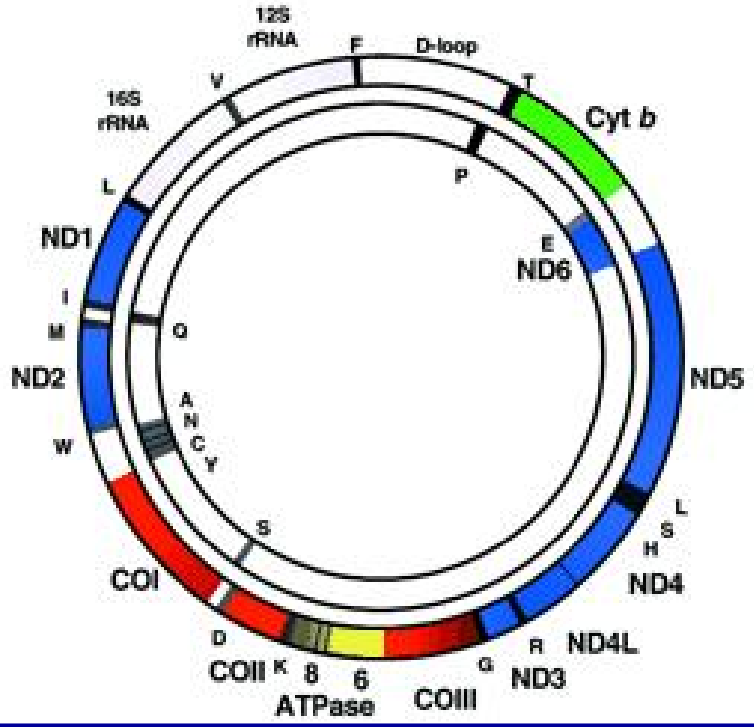
Metachromatic leucodystrophy

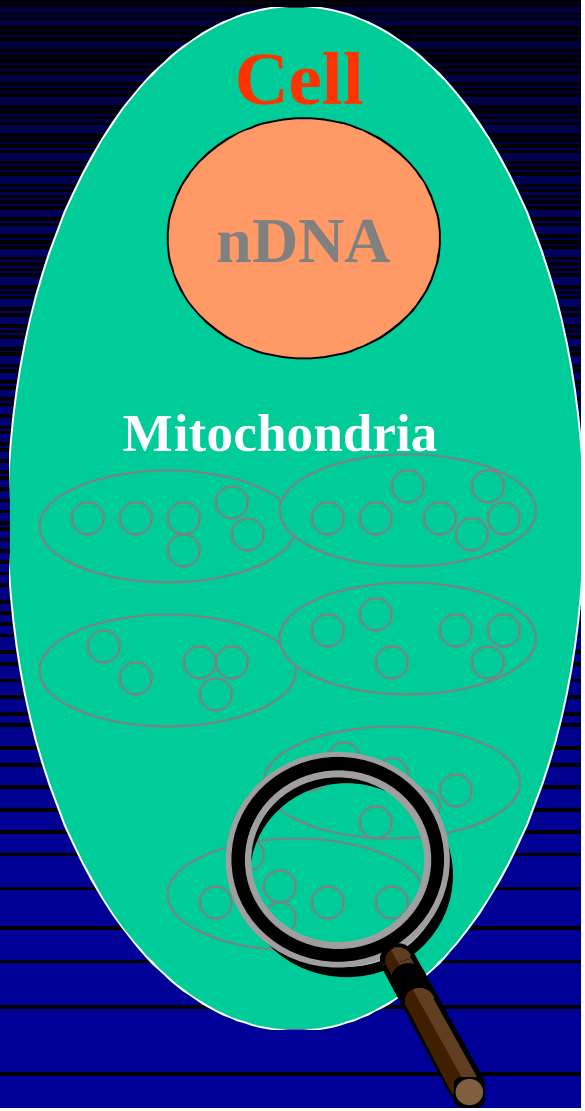
- The three clinical forms are characterized by different levels of ASA activity (severely deficient in early form and with a significant residual activity in adult)
- Variation in residual ASA activity differently regulates substrate storage in lysosomes and consequently influences the clinical evolution



genome


Complex I
Complex II
Complex III
Complex IV
Complex V
H +
H +
H +
CoQ
Cyt c
NADH
NAD+
Succinate
Fumarate
1/2 O2
H2O
ADP + Pi
ATP
H +


12S rRNA
F
D-loop
T
Cyt b
P
E
ND6
16S rRNA
V
L
ND1
I
M
Q
ND2
W
A
N
C
Y
S
ND5
L
S
H
ND4
COI
D
COII
K
8
6
ATPase
COIII
G
R
ND3
ND4L


Cell
nDNA
Mitochondria

Pathogenesis of Late onset neurometabolic diseases

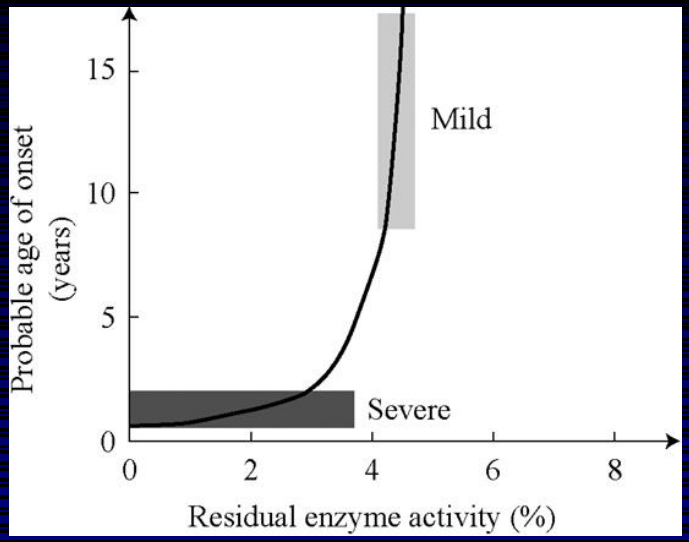
- If a subject is born with an abnormal DNA which give rise to an abnormal genetic product manifestating as a disease, how can the phenomenon of late onset of symptoms be explained?

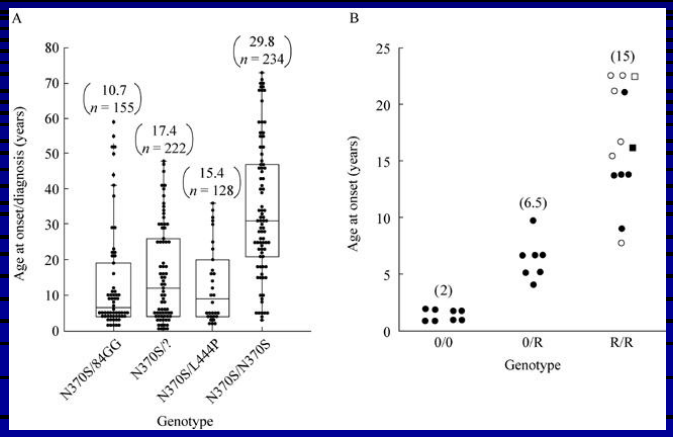
Pathogenesis of Late onset neurometabolic diseases

- **The slow evolution of the adult forms of the neurometabolic diseases may be correlated with a degree of *residual enzyme activity* sufficient to allow embryonic and post-natal development and nervous system function by manifesting in clinical symptoms only in adulthood.**

Pathogenesis of Late onset neurometabolic diseases

- The clinical characteristics of the disease would depend on the *speed with which the substrate accumulates*.
- A very severe enzyme deficiency completely arrests metabolism, originating a rapidly progressive disease, with early onset
- If there is still some residual enzyme activity (10-30%), it may be sufficient to degrade most of substrates, originating a less severe form, with late onset and slow progression





What can cell biology tell us about heterogeneity in lysosomal storage diseases?
V. Gieselmann
Acta Paediatrica, 2005; Vol. 94, (Suppl. 447): pp 80-86

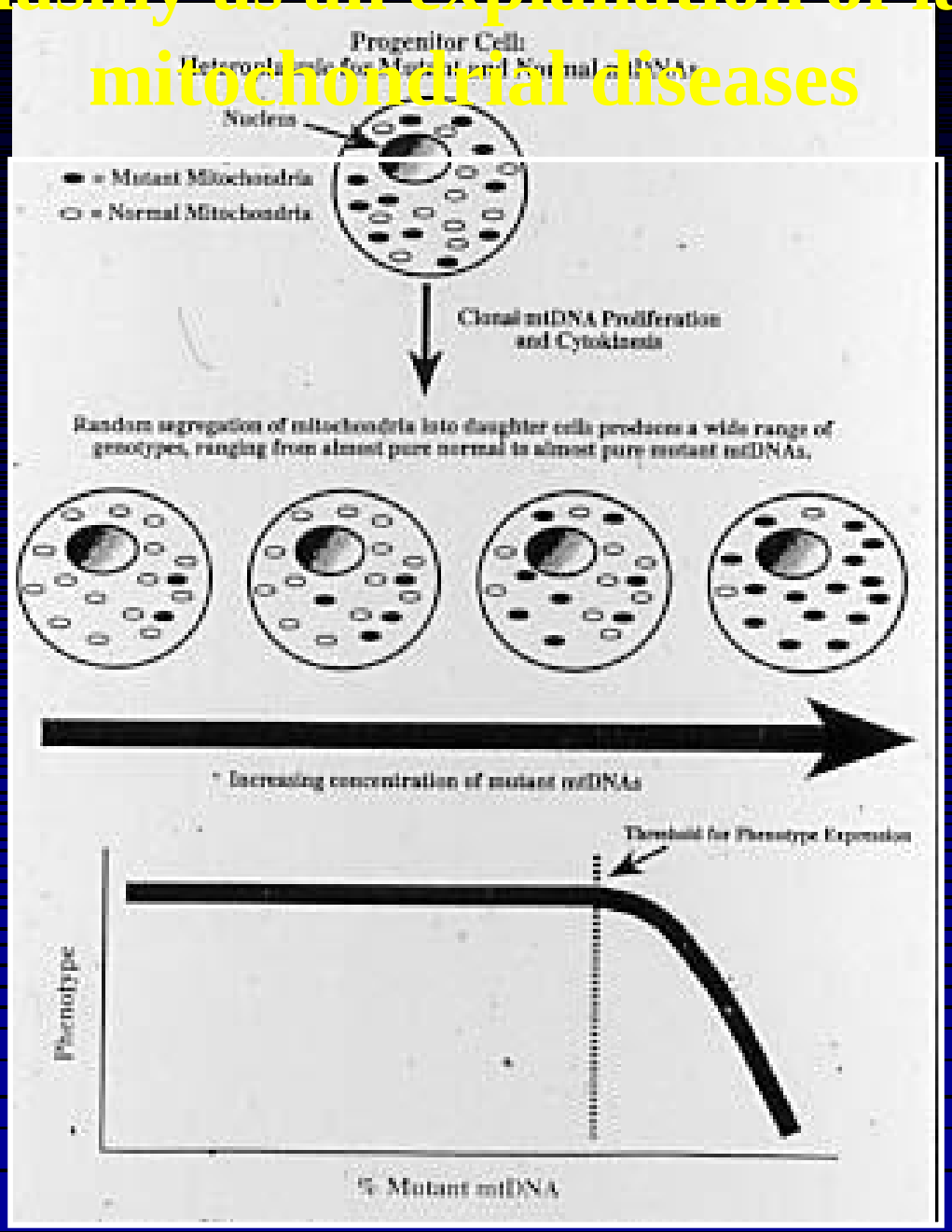
Pathogenesis of Late onset neurometabolic diseases

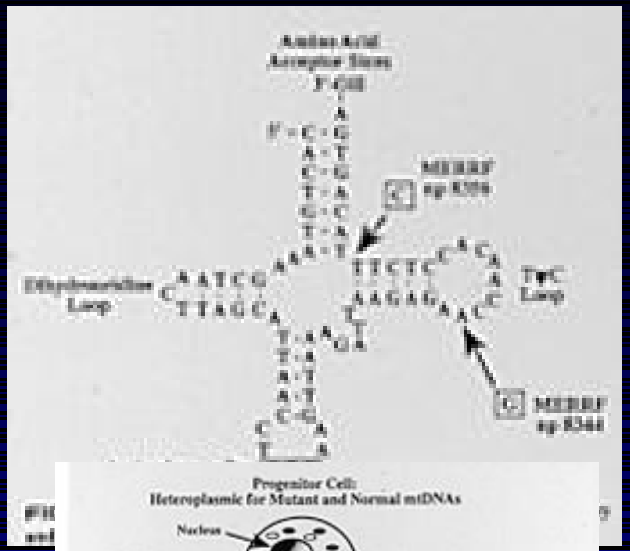
- This data suggests the existence of a complex system of biochemical and molecular regulation of enzyme activity that may be inpaired in different ways in early and late-onset diseases.

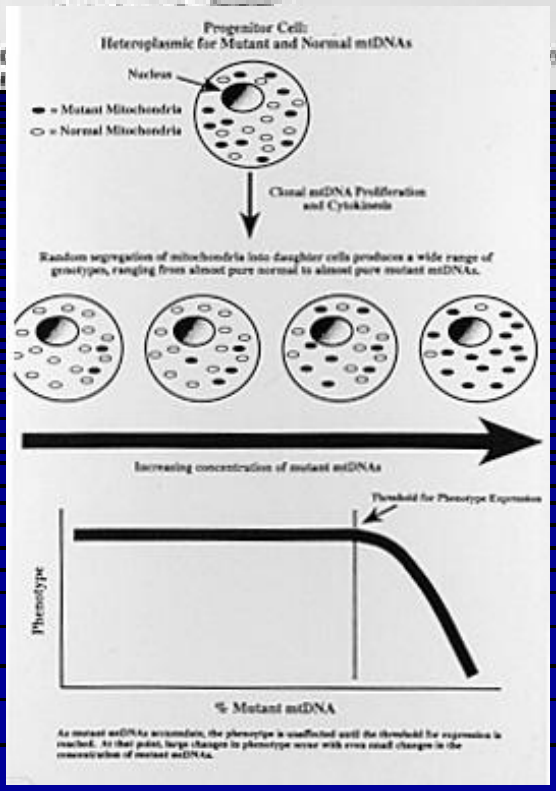
Pathogenesis of Late onset neurometabolic diseases (enzyme function impairement)

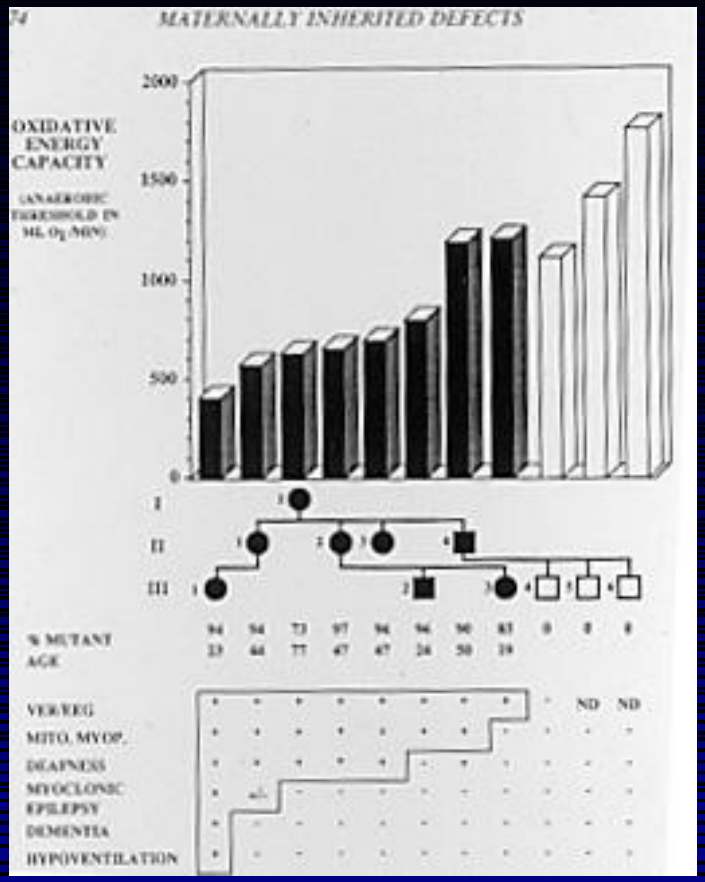
- Point mutation of the structural gene, with production of a protein that is not able to easily bind the substrate
- Insertion of a pair of bases or DNA deletion giving rise to protein devoid of catalytic activity
- Changes of proteins associated with maturation of the enzyme leading to the synthesis of a less stable immature form of the enzyme
- Faster degradation of the enzyme
- Enzyme carrier defect
- Abnormality of an enzyme activating factor

Heteroplasmy as an explanation of late onset mitochondrial diseases




Amino Acid
Acceptor Stem
T ψ C
Dihydrouridine
Loop
T ψ C
Loop
MERRF
MERRF


Progenitor Cell:
Heteroplasmic for Mutant and Normal mtDNAs
Nucleus
= Mutant Mitochondria
= Normal Mitochondria
Clonal mtDNA Proliferation
and Cytokinesis
Random segregation of mitochondria into daughter cells produces a wide range of genotypes, ranging from almost pure normal to almost pure mutant mtDNAs.
Increasing concentration of mutant mtDNAs
Threshold for Phenotype Expression
Phenotype
% Mutant mtDNA


MATERNALLY INHERITED DEFECTS
OXIDATIVE
ENERGY
CAPACITY
2000
1500
1000
500
0
I
II
III
% MUTANT
AGE
94 94 73 97 94 96 90 83 0 0 0
23 44 77 47 47 24 50 19
VER/EEG
MITO. MYOP.
DEAFNESS
MYOCLONIC
EPILEPSY
DEMENTIA
HYPOVENTILATION
ND ND

Late onset mitochondrial diseases

- The number of mitochondria with mutant mitDNA varies with the severity of the clinical symptoms and with age.
- With ageing, many hearth, diaphragm and skeletal muscle cells in man and rats loss COX activity, even in absence of pathology.
- It seems likely that changes in mitochondrial genome, toghether with other mutations, can play an important role in the phenomena of physiologic aging.

Late onset mitochondrial diseases

- MitDNA is more vulnerable than nuclear DNA
- It is more exposed to free radicals and does not seem to have adequate repair mechanisms.
- Mitochondrial with mutant mitDNA have a greater replication capacity than normal DNA (abnormal mitochondria can replace normal ones)
- In mitochondrial diseases and normal ageing, a mosaic distribution of fibrocells with mutant mitDNA in muscle may be caused by the different involvement of specific cell factors which can influence the speed of mutation, replication and repair of mitDNA, leading to the progressive replacement of healthy mitDNA with the mutant variety.

Selective vulnerability to a metabolic factor of different CNS cells

- **The regulation of enzyme synthesis and cell turnover can vary in different types of cells: *neurons with long axons and large synaptic terminals can differ in metabolic capacity from short interneurons.***

- **The saturation of residual enzyme activity is reached more quickly in some cells than in others.**

- **In agreement with the hypothesis of critical metabolic flow, a certain turnover of intermediate metabolites in a given metabolic pathway is necessary to maintain normal function; turnover can vary from one functional system to another.**

- **Residual capacity to degrade certain substrates may be selectively affected in more vulnerable systems**

Phenotypic heterogeneity in neurometabolic diseases

Globoid cell leucodystrophy: a family with both late infantile and adult type.

Vedru P. et al. Neurology 41:1382,1991

X-linked adrono-myeloneuropathy associated with 14 novel ALD-gene mutations: no correlation between type of mutation and age of onset.

Wichers M. et al. Hum. Genet. 105:116,1999

Clinical variability of phenotype

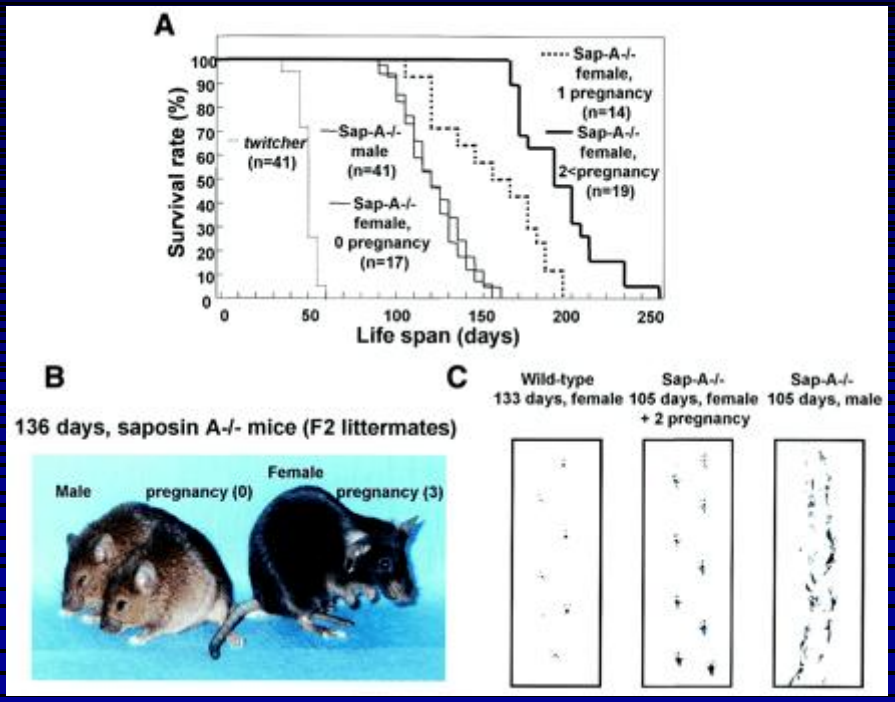
- Gene-gene interaction
- Gene-environment interaction

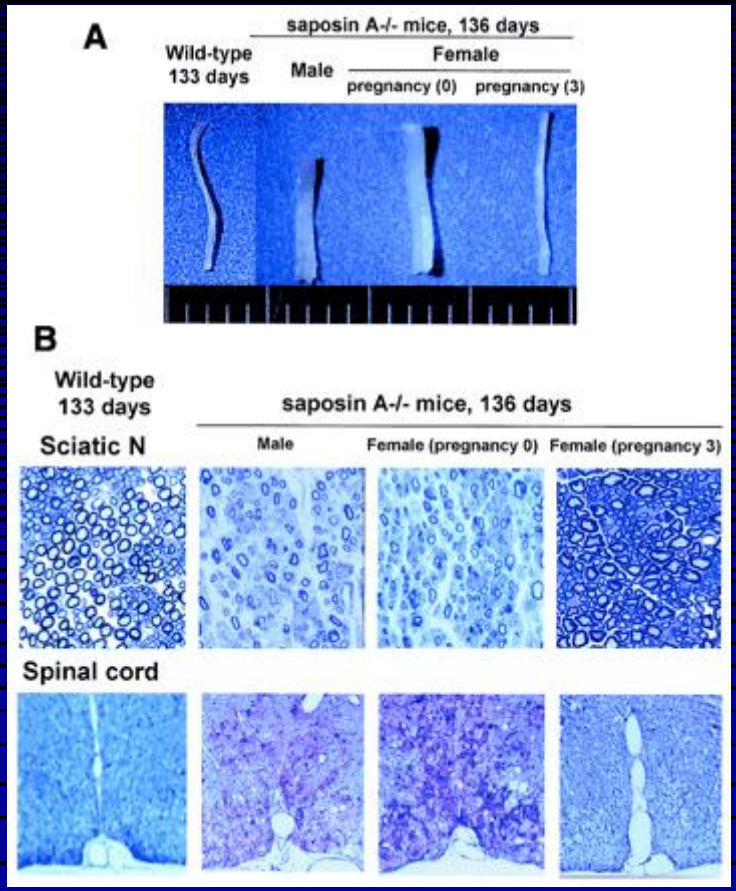
Gene-gene interaction

The example of ApoE genotype

Other endogenous factors

Matsuda J, Vanier MT, Saito Y, Suzuki K, Suzuki K. Dramatic phenotypic improvement during pregnancy in a genetic leukodystrophy: estrogen appears to be a critical factor. Hum Mol Genet. 2001 Nov 1;10(23):2709-15



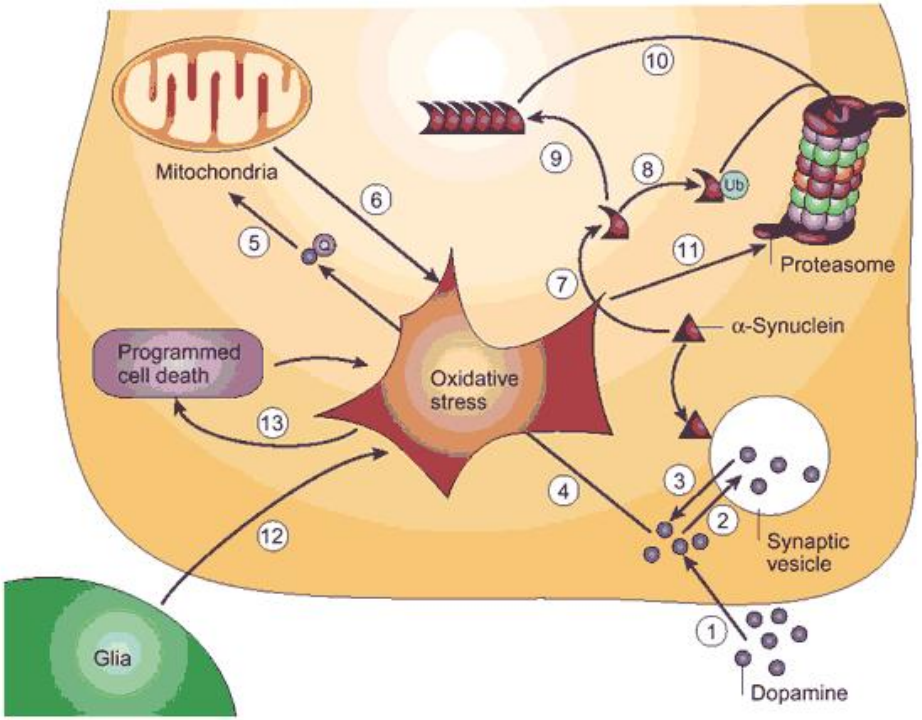


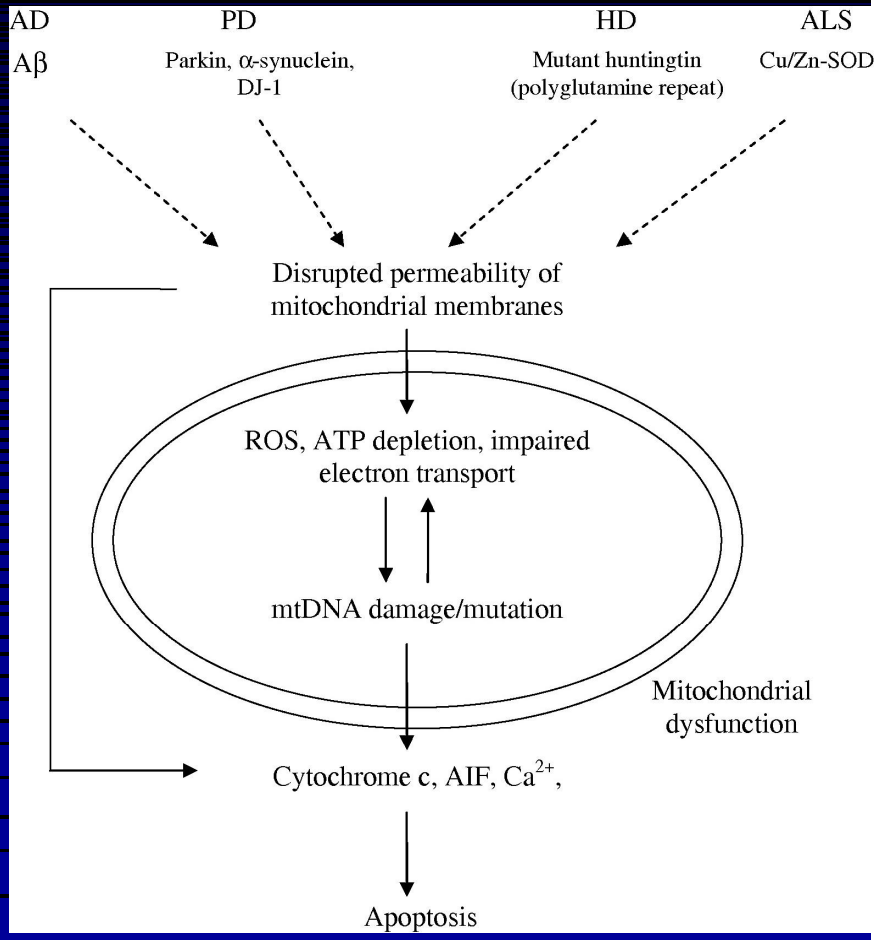
Interference of the primary enzyme defect with other metabolic pathways

Formichi P, Radi E, Battisti C, Pasqui A, Pompella G, Lazzerini PE, Laghi-Pasini F, Leonini A, Di Stefano A, Federico A.

Psychosine-induced apoptosis and cytokine activation in immune peripheral cells of Krabbe patients.

J Cell Physiol. 2007 Sep;212(3):737-43.


Mitochondria
Ub
Proteasome
α-Synuclein
Programmed cell death
Oxidative stress
Synaptic vesicle
Glia
Dopamine
1
2
3
4
5
6
7
8
9
10
11
12
13


AD
Aβ
PD
Parkin, α-synuclein, DJ-1
HD
Mutant huntingtin (polyglutamine repeat)
ALS
Cu/Zn-SOD
Disrupted permeability of mitochondrial membranes
ROS, ATP depletion, impaired electron transport
mtDNA damage/mutation
Mitochondrial dysfunction
Cytochrome c, AIF, Ca^{2+},
Apoptosis

Niemann-Pick type C disease: accelerated neurofibrillary tangle formation and amyloid deposition associated with apolipoprotein E epsilon4 homozygosity

M. Simons et al.

Ann. Neurol. 52: 351-354, 2002

Exogenous factors modulating fenotypes

- Toxic factors
- Traumatic factors

Interaction of drugs on genotype

- 15 years old,female,health.Obesity since childhood.
- Severe dietary restriction,and use of anorexiziting drugs as phentermine,fenfluoramine,diethylpropion for 1 year.
- Ataxia with cerebellar atrophy at MR
- Normal biochemistry,muscle biopsy
- mitDNA analysis showed intergenomic 6bp delection,usually not considetred pathogenetic
- Interaction of drugs with mitDNA(??)

Hereditary optic atrophy (Leber's disease)

Dotti et al., A case of ethambuthol-induced optic neuropathy harbouring the primary mitocondrial LHON mutation at 11778.

J. Neurol. 245:302,1998

- Onset at 54 y old age after etambutol use as treatment for tubercolosis

Amiodarone and neurologic disorders

- MT Dotti and A. Federico: Amiodarone induced parkinsonism: a case report and pathogenetic discussion. *Mov Disord*. 10: 233-3, 1995

- Palmeri S, Battisti C, Malandrini A, Federico A. Amiodarone induced lipidosis similar to Niemann Pick C disease. Biochemical and morphological study. *Life Sci*. 57: 1963-71, 1995

- Federico A et al. Amiodarone affects membrane water permeability properties of human erytrocytes and rat mitochondria. *Eur J Pharmacol* 304: 237-41, 1996

Traumatic factors

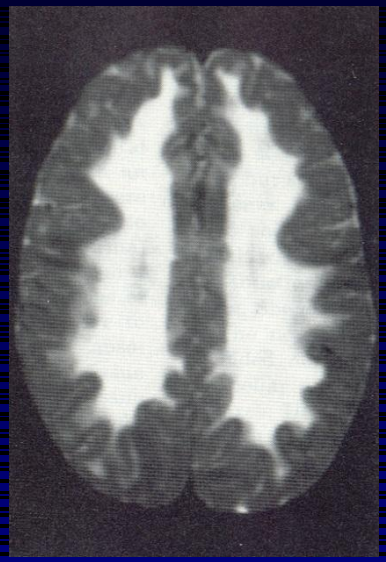
Very late onset adrenoleukodystrophy: possible precipitation of demyelination by a contusion.

Weller et al. Neurology 42: 367,1992

Can head injury influence the site of demyelination in ADL?

Wilkinson I.A. et al., Dev. Med. Child Neurol. 29: 784, 1987

Fright and VWMD



- Vermeulen G, Seidl R, Mercimek-Mahmutoglu S, Rotteveel JJ, Scheper GC, van der Knaap MS.

  Fright is a provoking factor in vanishing white matter disease. Ann Neurol. 2005 Apr;57(4):560-3.

- Kaczorowska M, Kuczynski D, Jurkiewicz E, Scheper GC, van der Knaap MS, Jozwiak S. Acute fright induces onset of symptoms in vanishing white matter disease-case report. Eur J Paediatr Neurol. 2006 Jul;10(4):192-3

Mutations in eIF2B

eIF2B activity decrease

Decrease in protein synthesis in conditions of cellular stress

An increase of mutated protein in endoplasmic reticulum activated the

Unfolded Protein Response (UPR),

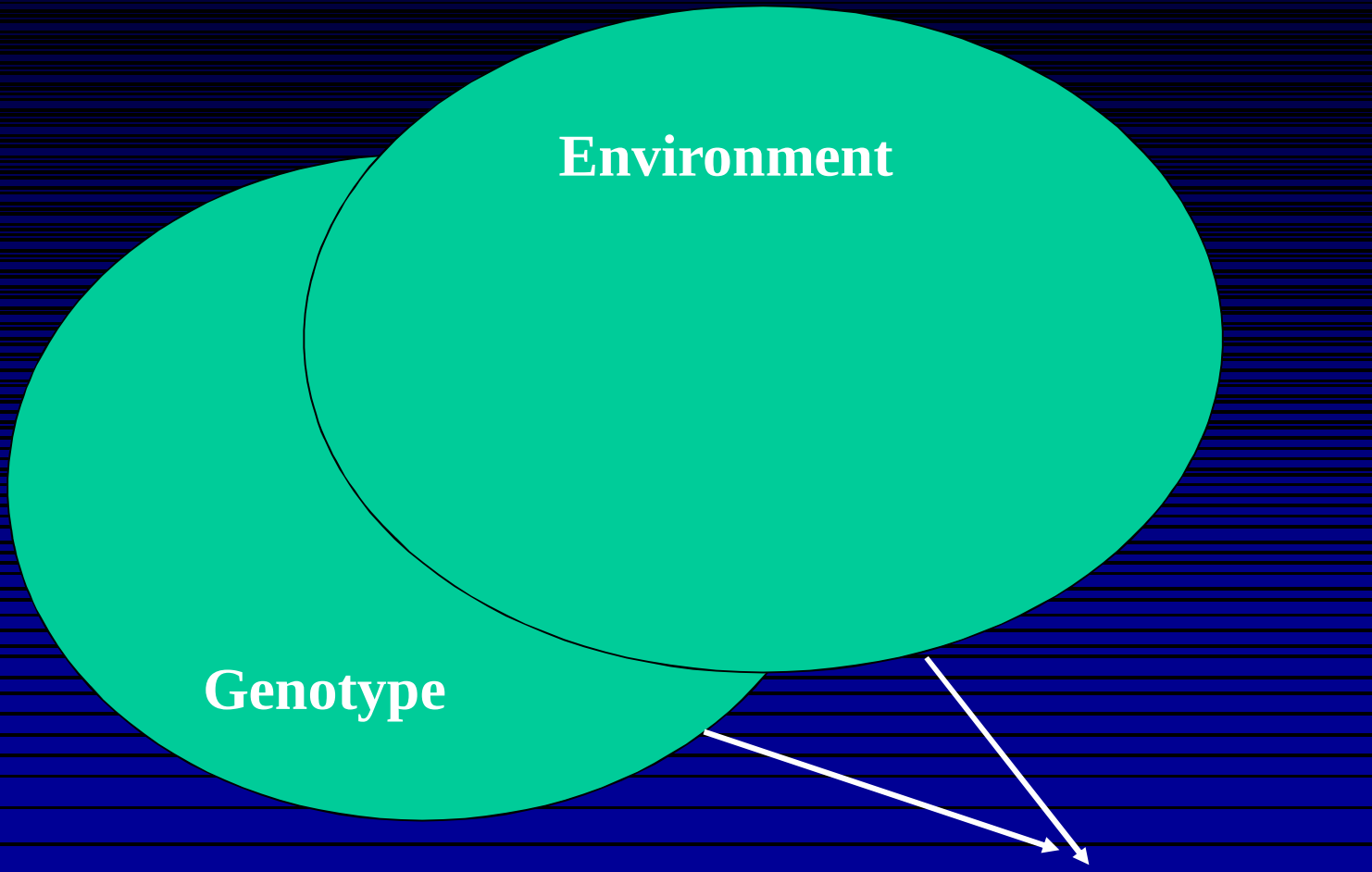
a compensatory mechanism with inhibition of new protein synthesis and stimulation of signals involved in life and in proapoptotic mechanisms

Mutation in each of five subunits of translation Initiation Factor eIF2B can cause Leucoencephalopathy with Vanishing White Matter

M. S. van der Knaap et al

Ann. Neurol 51: 264-270, 2002

GENE-ENVIRONMENT INTERACTION

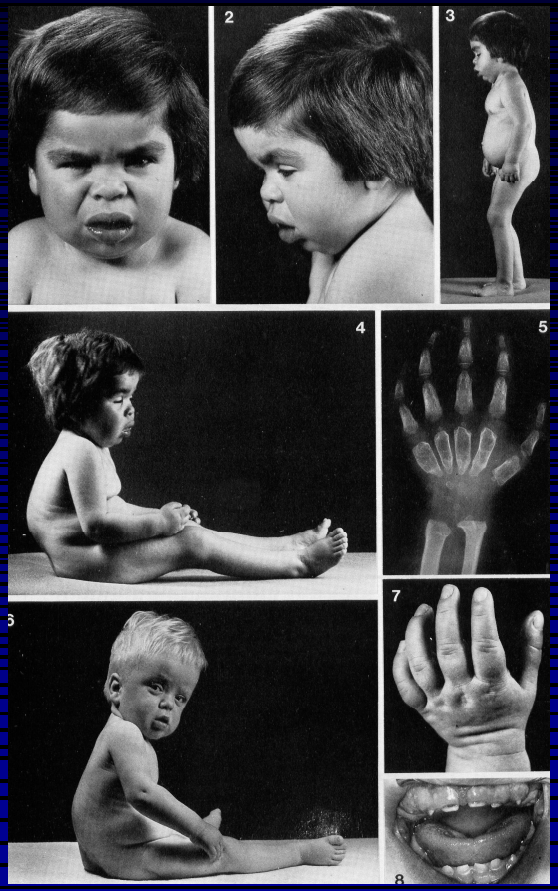


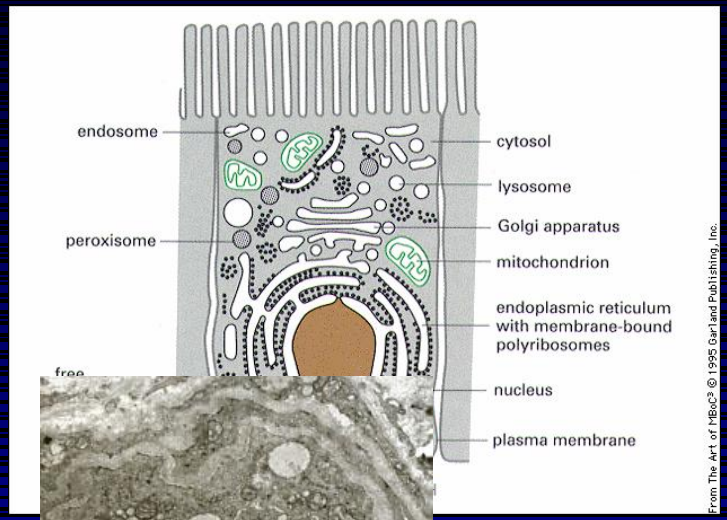
Neurometabolic genetic diseases

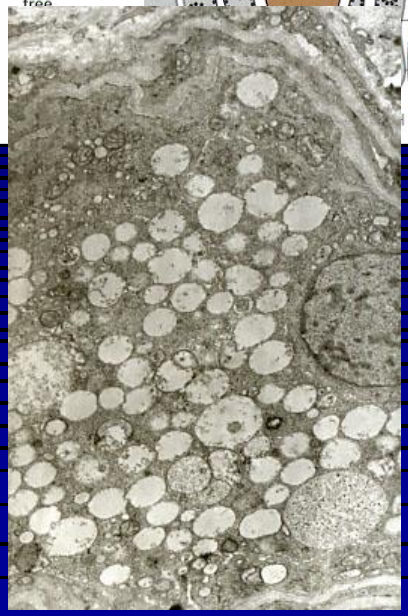
- Storage material for a primary lysosomal dysfunction of lipid metabolism
- Plasma membrane lipid changes due to peroxisomal impairement
- Cell cholesterol trafficking disturbancies
- Energy metabolism impairment
- Aminoacid and organic acid disorders
- Chromosomal instability and Dna repair changes
- Cell nutrients and metal impairments
- Small brain vessels dysfunction

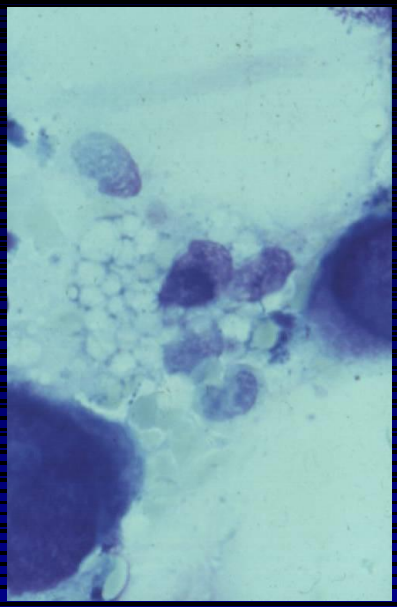
From patients to new knowledges on physiopathology

Lysosomal diseases and lysosomes



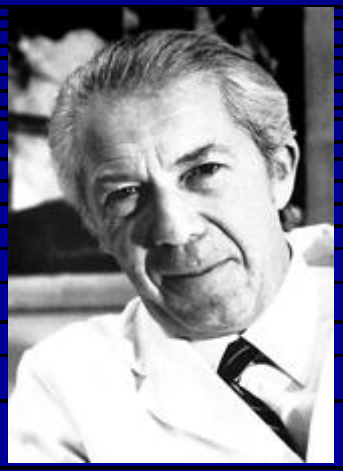




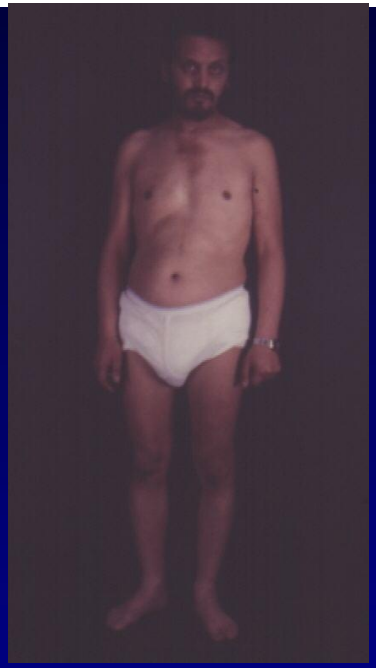


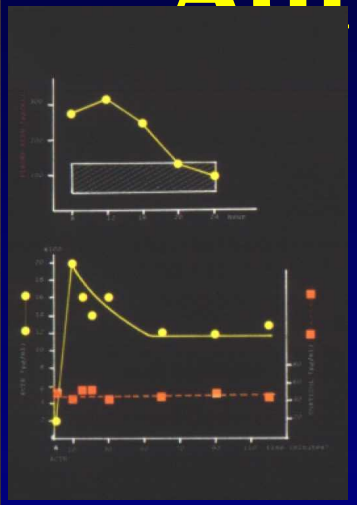
1965: De Duve

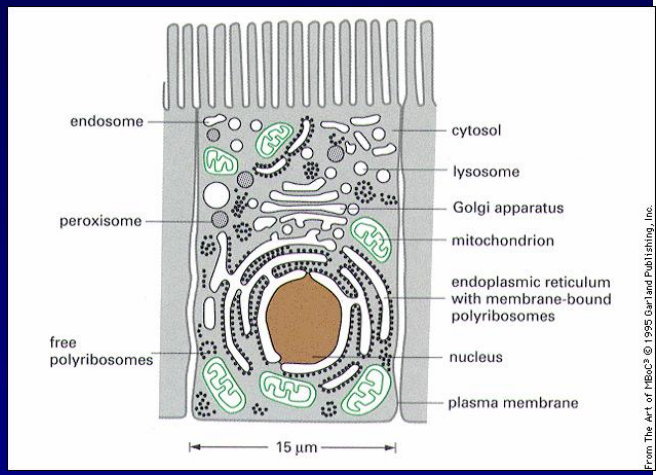
1974: Nobel Prize

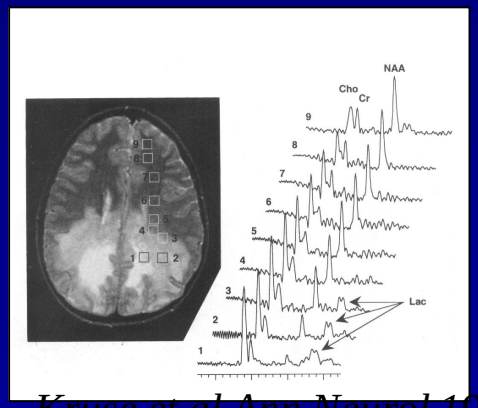


Adrenoleucodystrophy



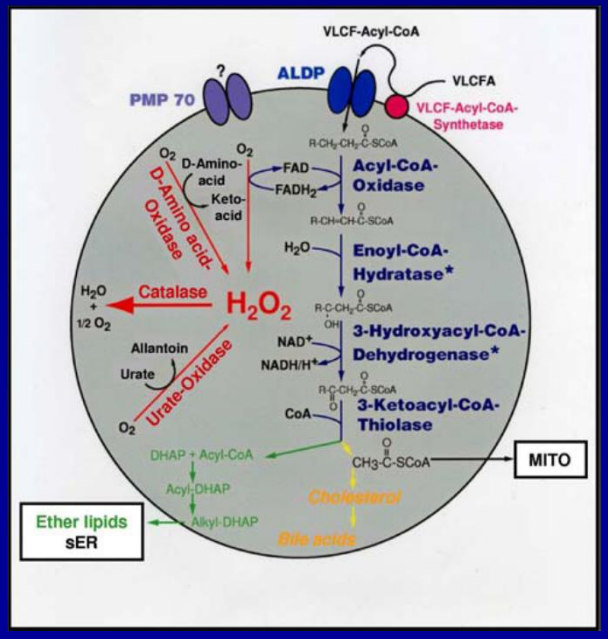






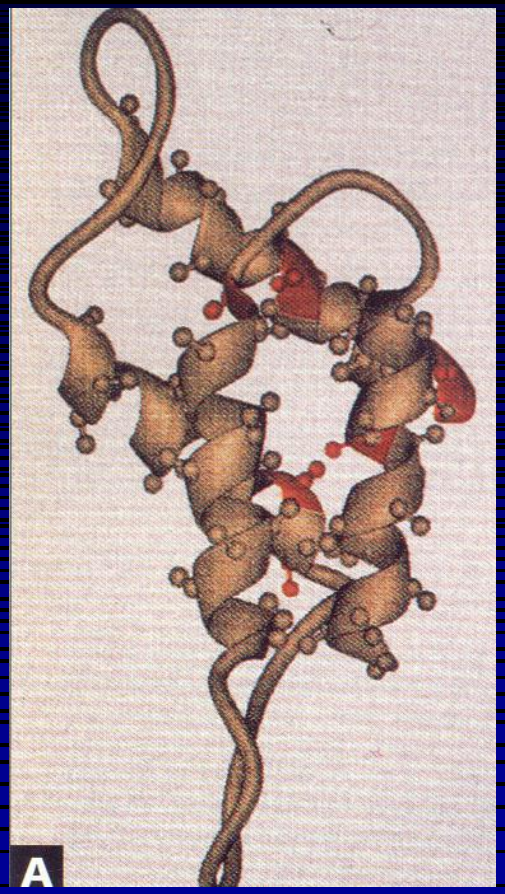
Kruse et al Ann Neurol 1994

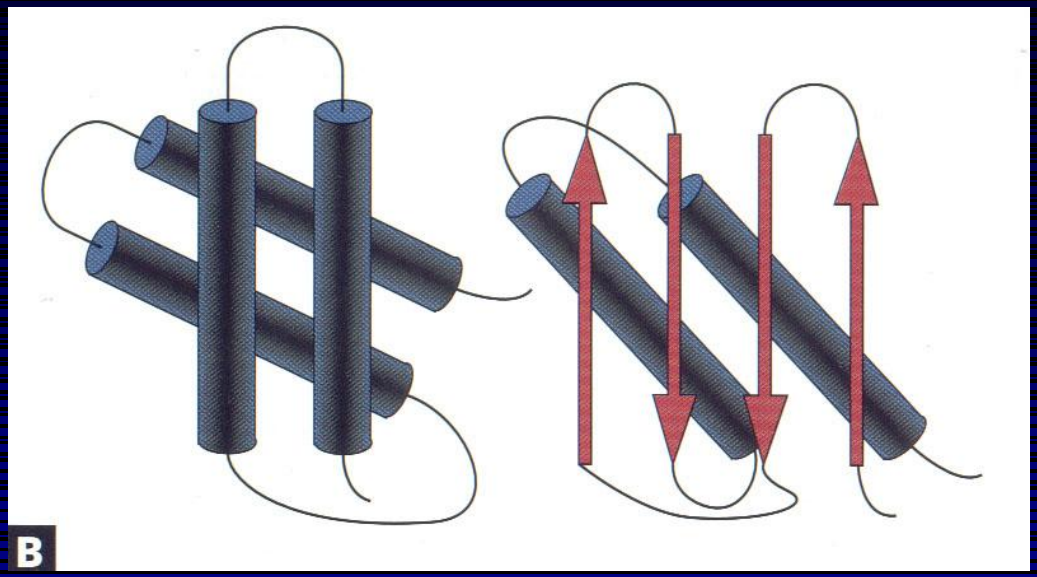
- **ADL gene codifies for a protein, one of the 4th carriers linked to the structure of ATP, localized on the peroxysomal membrane**
- **More than 300 mutations have been detected (www.x-adl-nh.com)**



15 tipi di enzimi
- Ossidasi e catalasi
- Beta-ossidazione ac grassi a lunga catena (C24-C26)
- Sintesi di plasmalogeni (fosfolipidi presenti nella mielina e nel PDGF)

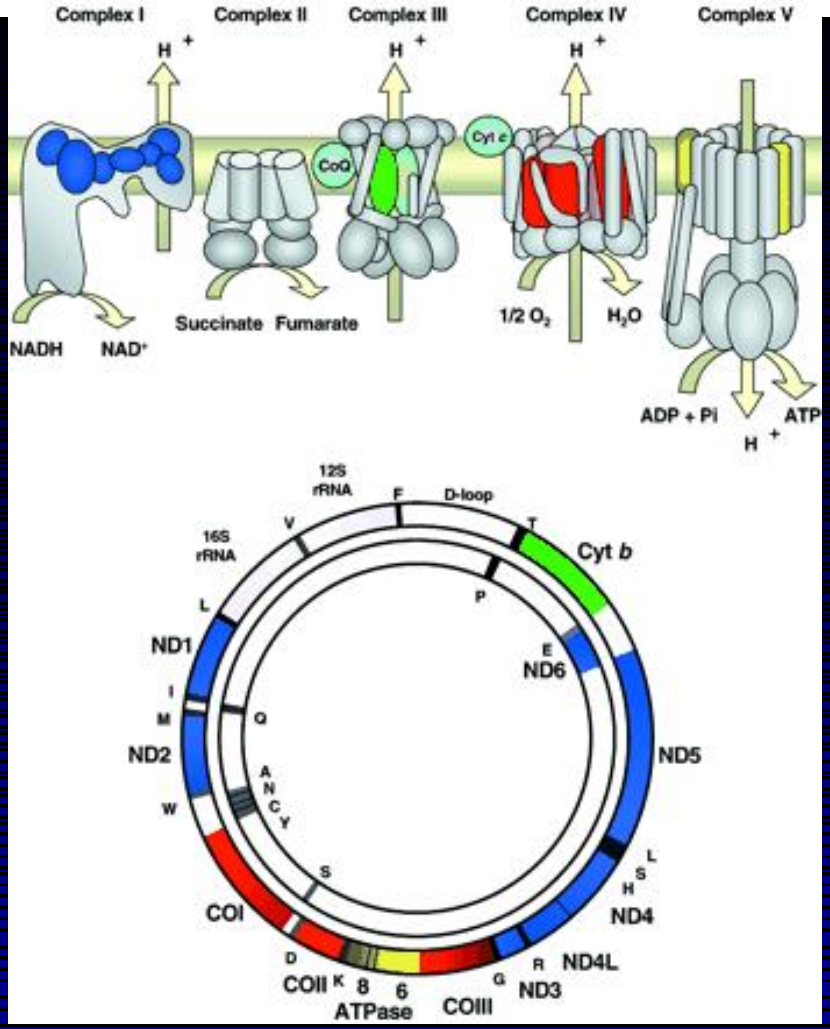
Prionic encephalopathies and prions

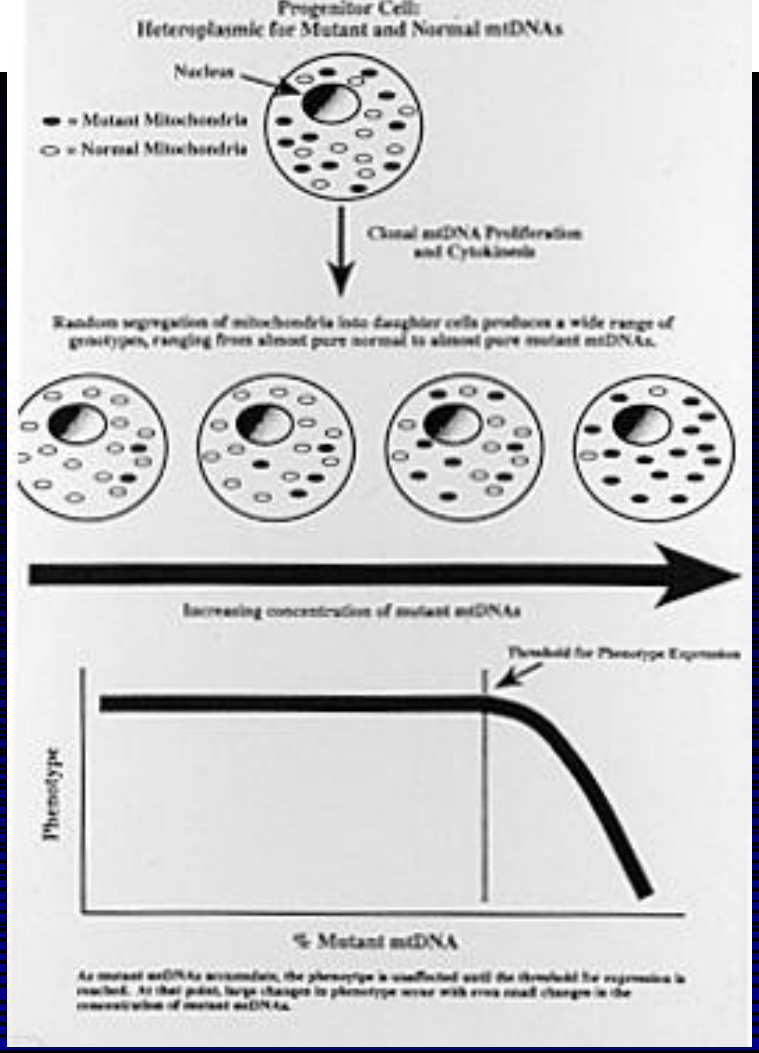




S. Prusiner,

Nobel Prize 1997

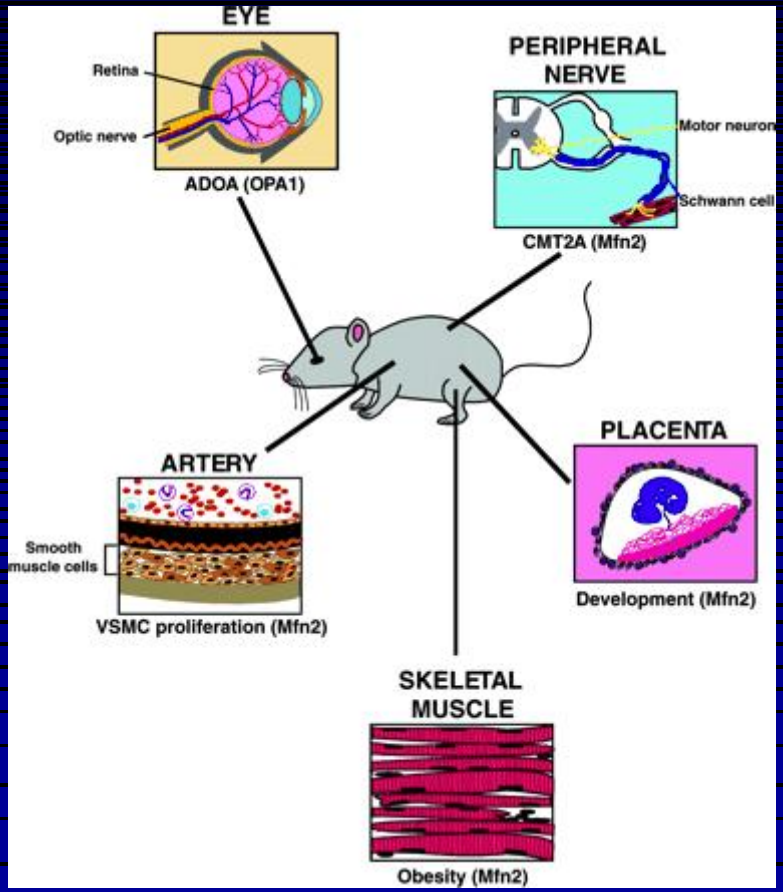


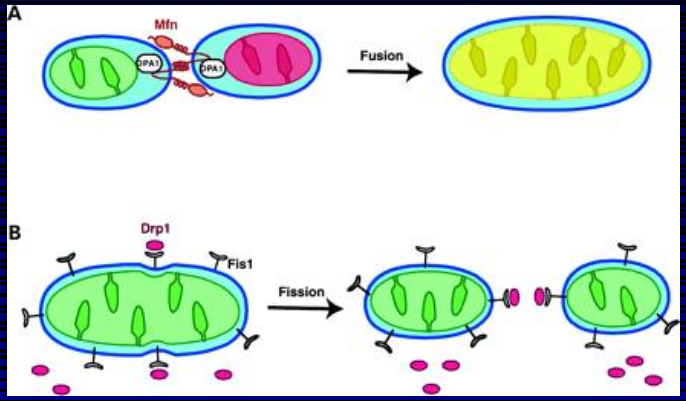


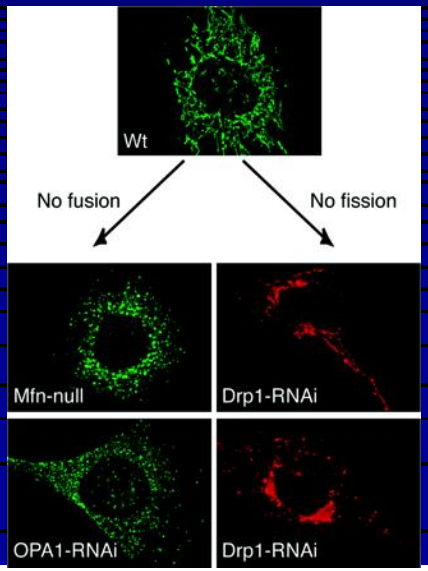
Reddy PH, Beal MF.
Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease.
Trends Mol Med. 2008 Feb;14(2):45-53.

Chung KW, et al. Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain. 2006 Aug;129(Pt 8):2103-18

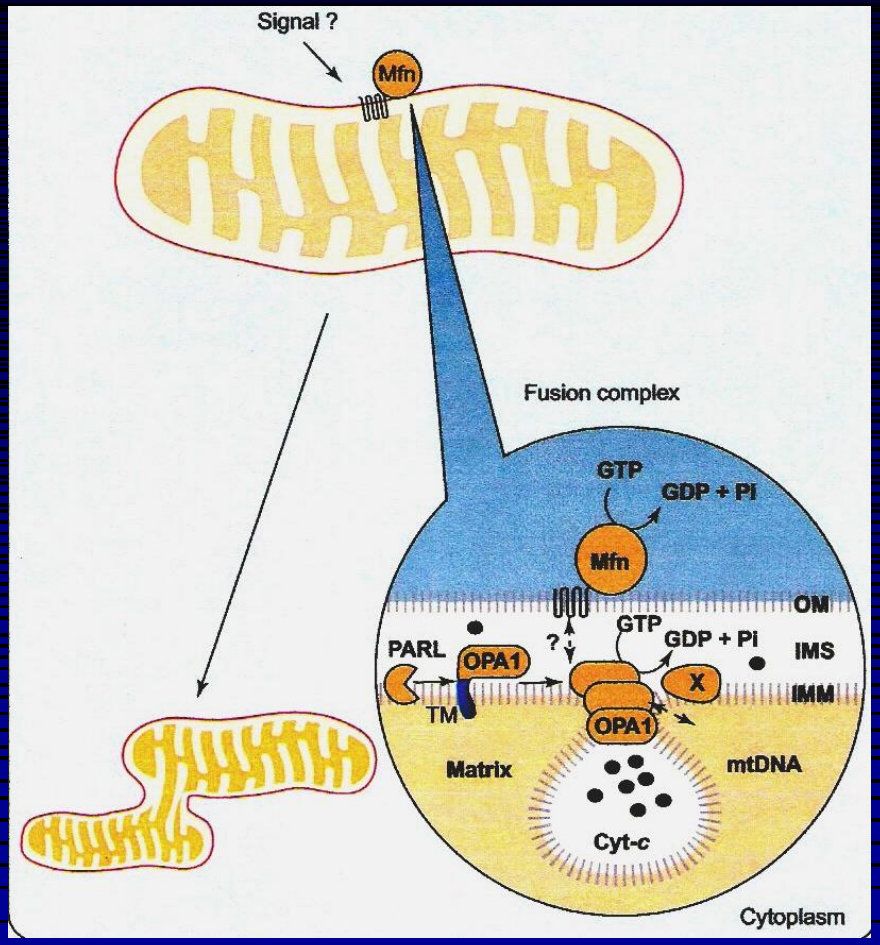
Jahani-Asl A, et al. Mitofusin 2 protects cerebellar granule neurons against injury-induced cell death J Biol Chem. 2007 Aug 17;282(33):23788-98



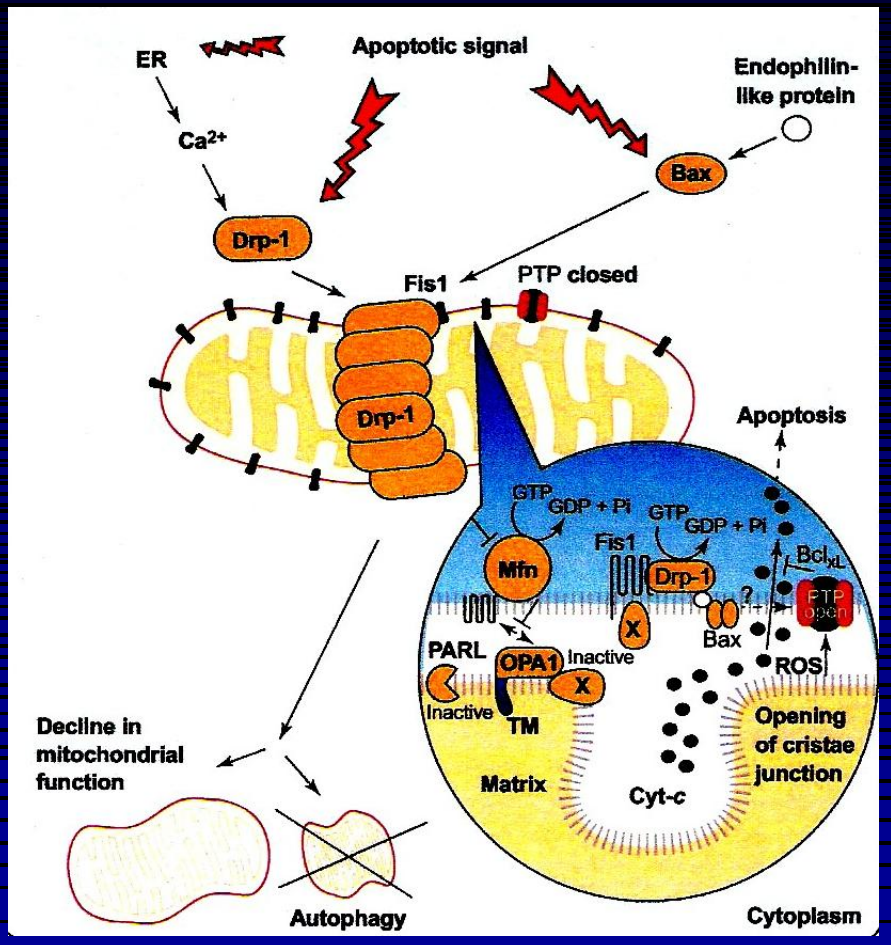




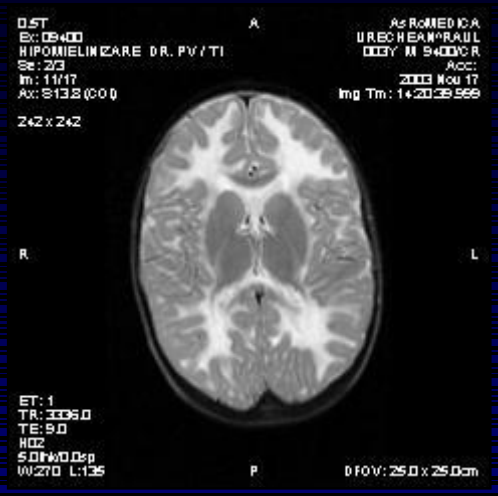
Mitochondrial fusion

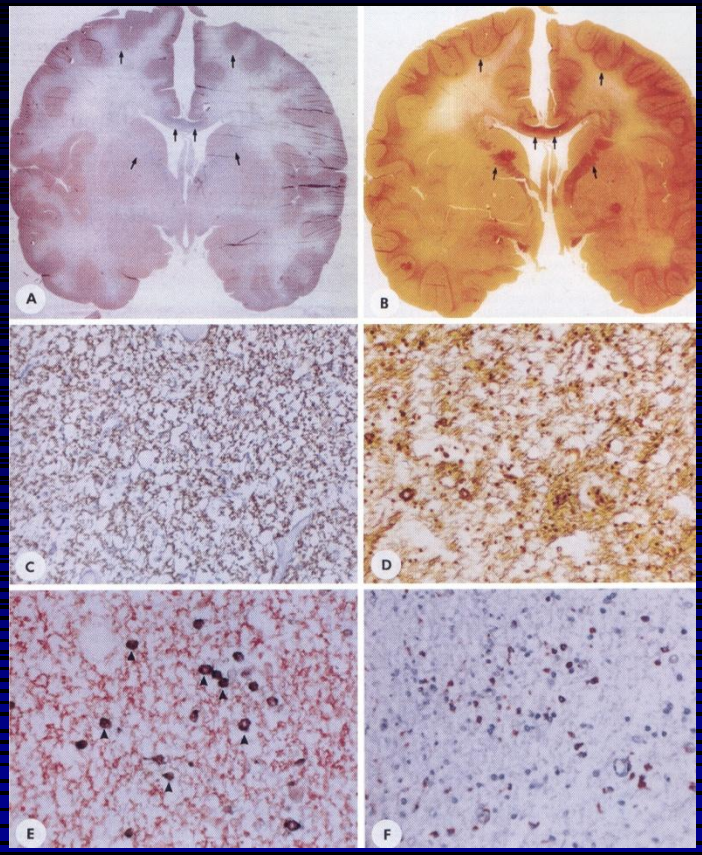


Mitochondrial fission



Vanishing white matter disease, eIF2B and stress



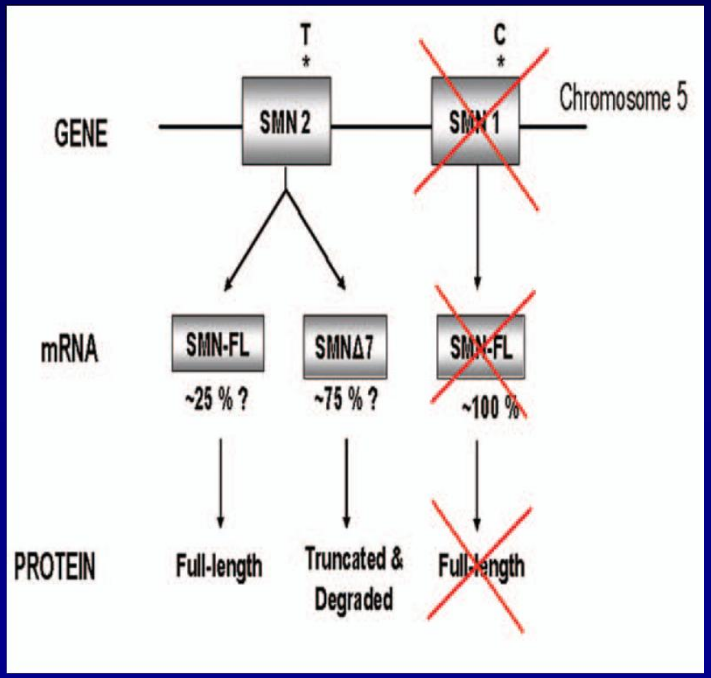


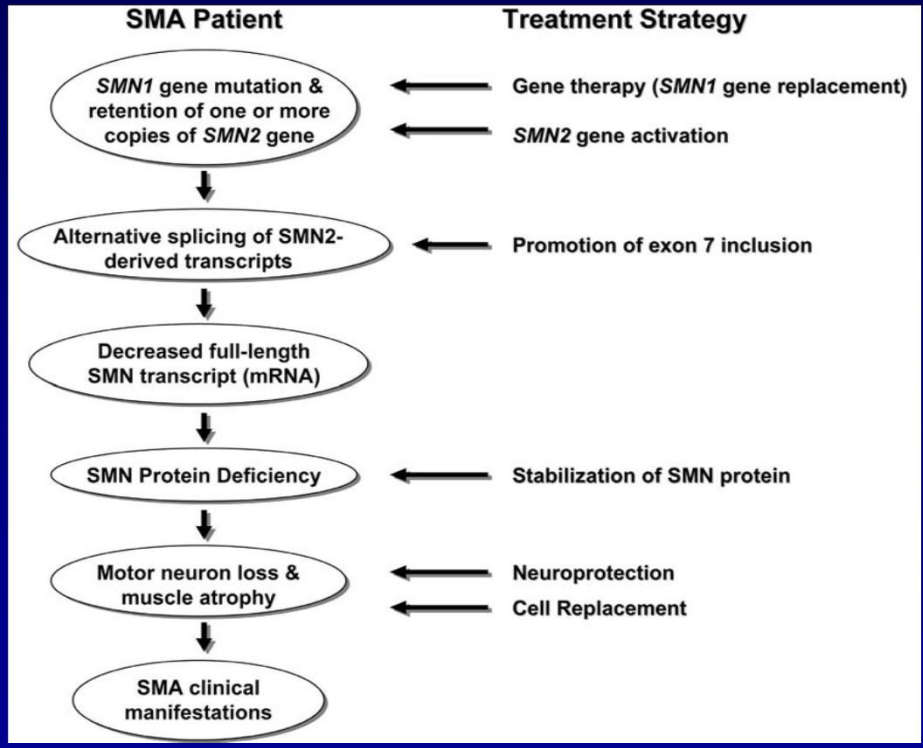
- The responsible gene in this area is EIF2B5, encoding the epsilon-subunit of eukaryotic translation initiation factor (eIF), eIF2B (Leegwater et al, 2001)

Under a variety of stress conditions protein synthesis is decreased. Stress may lead to misfolding and denaturation of proteins, contributing to cell death.

The inhibition of normal RNA translation during stress is thought to enhance cell survival by limiting the accumulation of denaturated proteins.

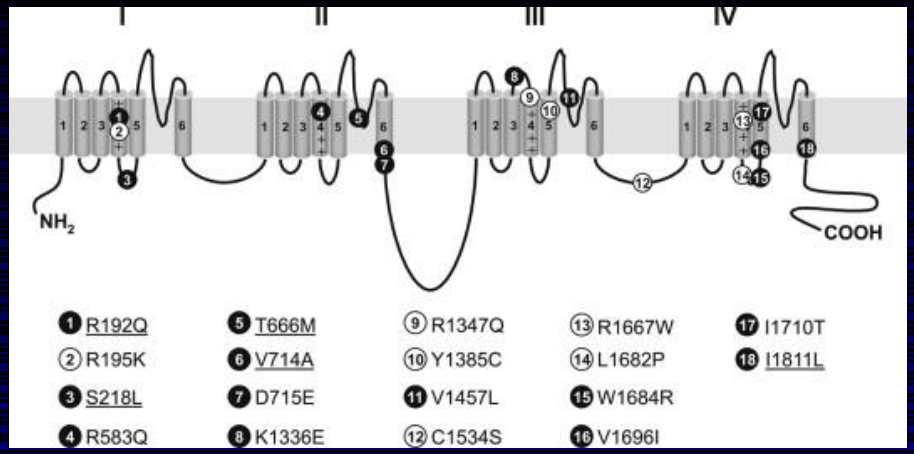
Spinal Muscular Atrophy and SMNp



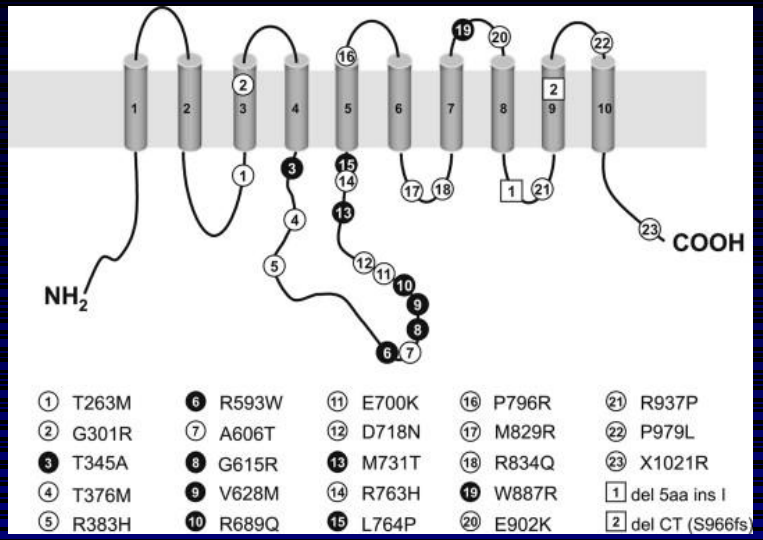


This SMN complex interacts with several other proteins, many of which are components of various **ribonucleoprotein complexes that are involved in distinct aspects of RNA processing**.
The SMN complex may, therefore, play a role in diverse aspects of RNA metabolism, including pre-RNA splicing, transcription, and metabolism of ribosomal RNAs.
Presently, the best-characterized function of the SMN complex is regulating the assembly of a specific class of RNA-protein complexes, the uridine-rich small nuclear ribonucleoproteins.

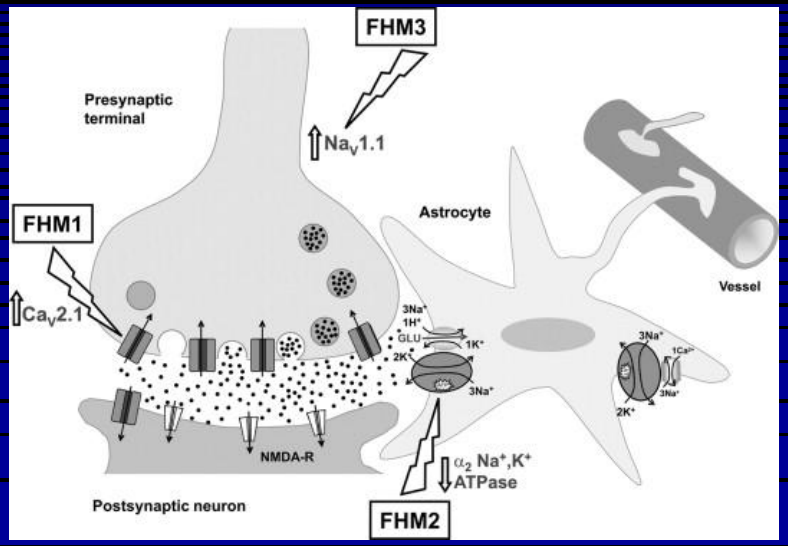
Familial Haemiplegic Migraine, Ca Channel and K-Na ATPase



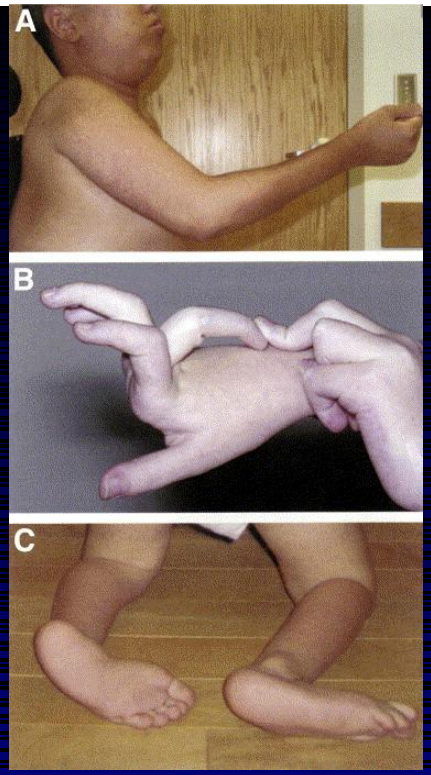
Secondary structure of the Cav2.1 ?1 subunit and location of the familial hemiplegic migraine 1 mutations identified so far

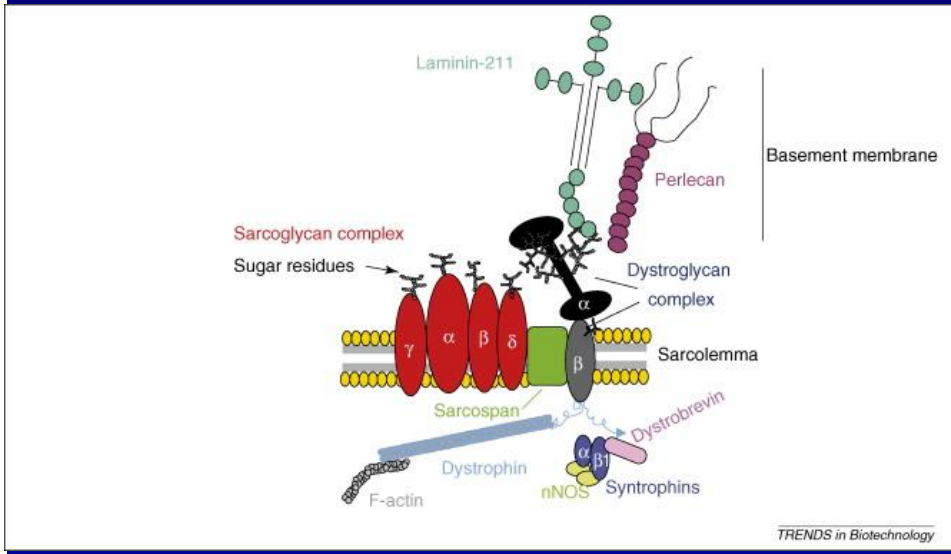


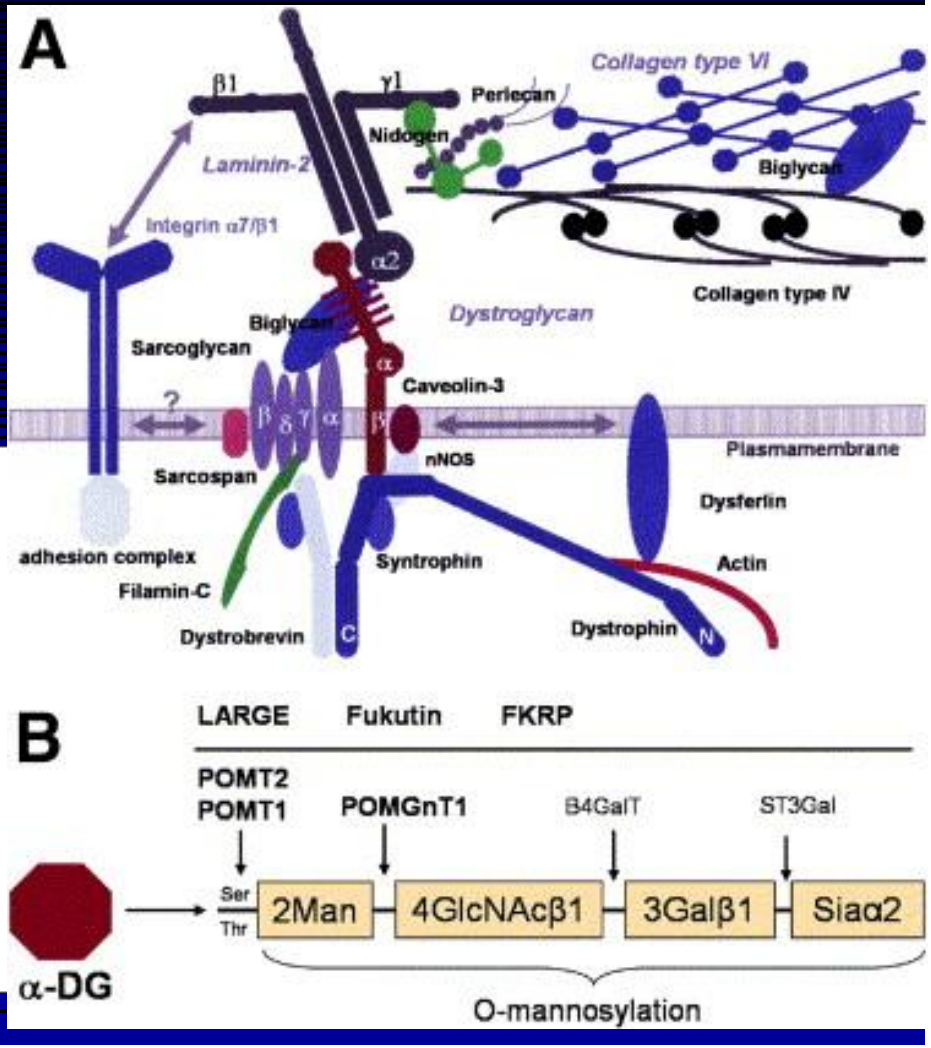
Secondary structure of the Na+,K+-ATPase ?2 subunit and location of the familial hemiplegic migraine 2 mutations



From congenital muscle dystrophies to muscle protein functions



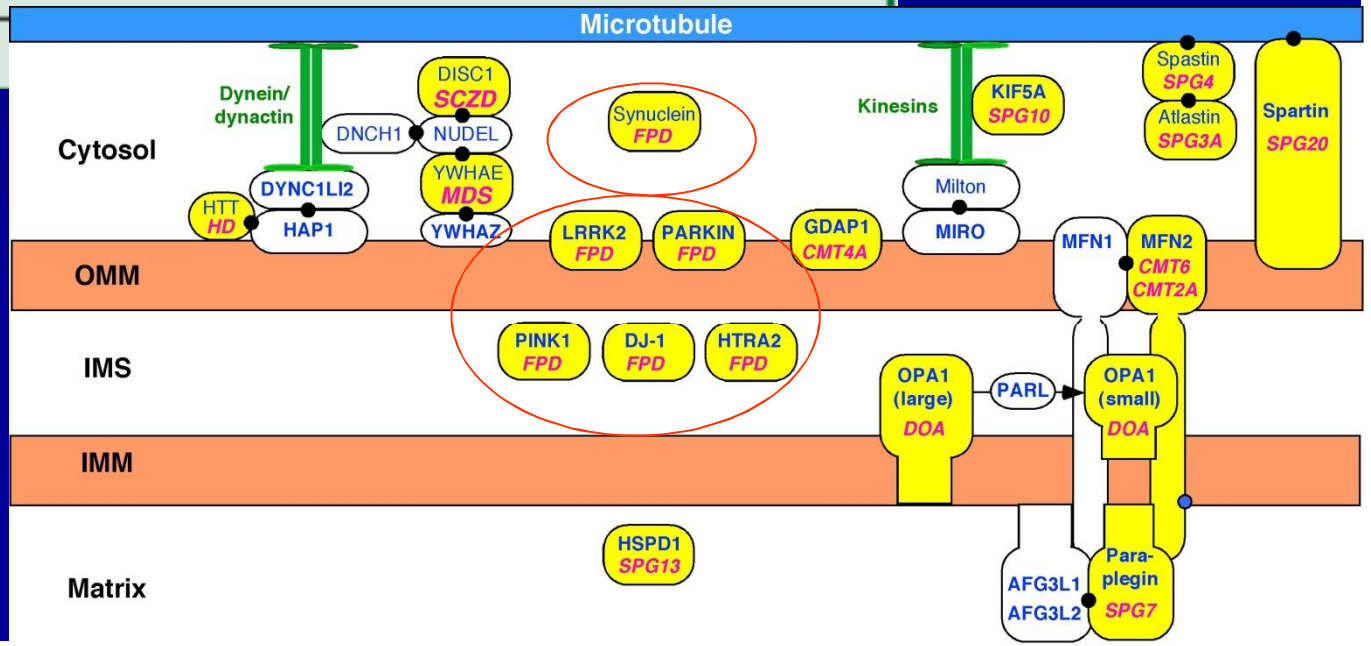




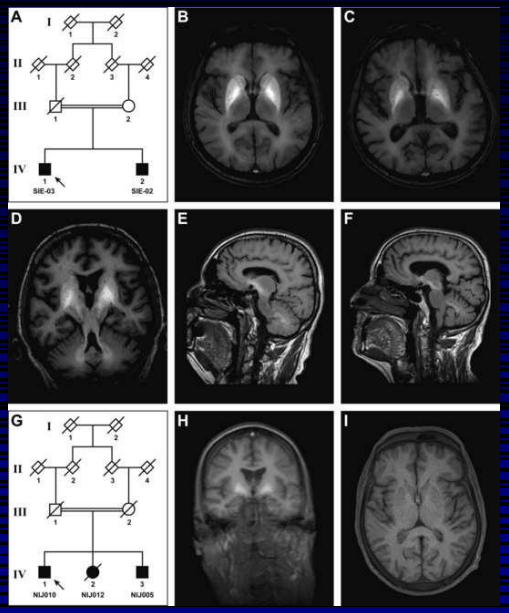
	Mode of inheritance	Locus	Age at onset	Lewy bodies	Gene product
PARK1/4	AD	4q21	40s	Yes	α-Synuclein
PARK2	AR	6q25	20s+	No	Parkin
PARK3	AD	2p13	60s	Yes	..
UCH-L1	AD	4p15	50s	Yes	Ubiquitin thiolesterase
PINK1	AR	1p35	30s	..	PTEN-induced putative kinase 1
PARK7	AR	1p36	30s	..	DJ-1
LRRK2	AD	12p	Variable	Yes/no	Leucine-rich repeat kinase 2
ATP13A2	AR	1p36	Variable	..	ATPase type 13A2
PARK10	AR	1p32	..	..	..
PARK11	..	2q36-q37	..	..	..

AD=autosomal dominant. AR=autosomal recessive.

Table: Genetic causes of parkinsonism



Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease.
Quadri M, Federico A, et al.
Am J Hum Genet. 2012 Mar 9;90(3):467-77.

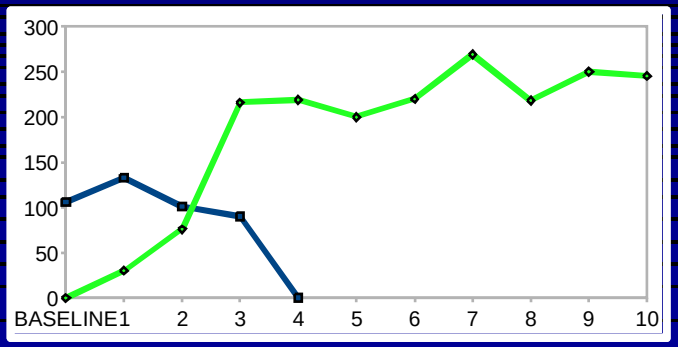


CASE REPORT

Two brothers of 49 and 50 years

LABORATORY TESTS

- High Mn levels on serum and urine
- Polycythemia

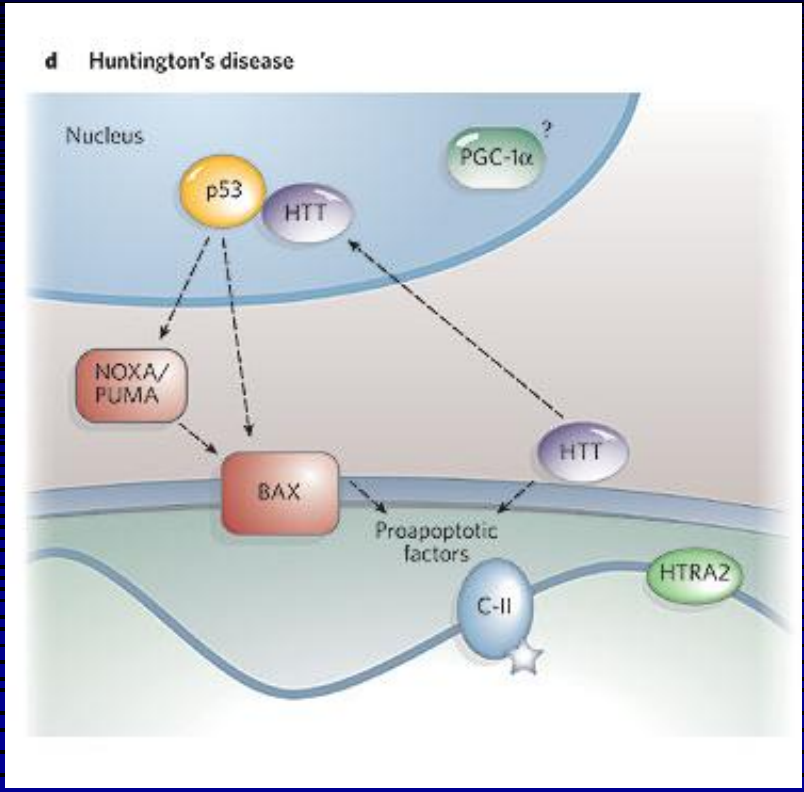


INSTRUMENTAL EXAMINATION

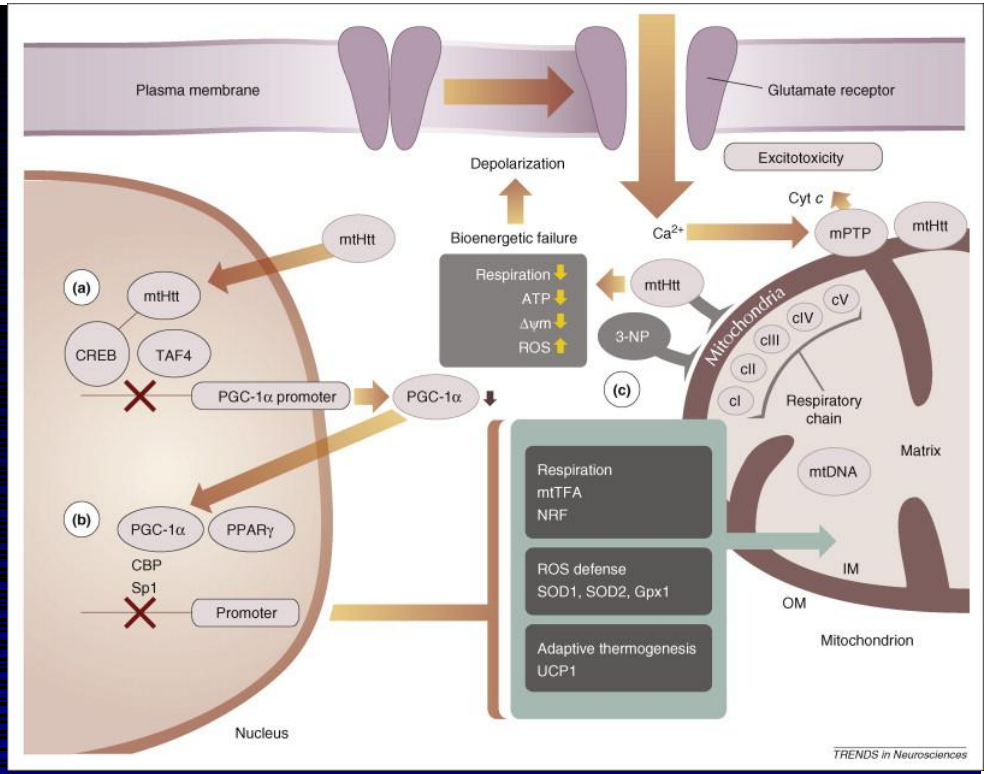
- ***EMG***: sensorimotor axonal polyneuropathy
- ***Liver ultrasound***: moderate steatosic liver (grade 2)
- ***Muscle biopsy***: mild nonspecific abnormalities, Mn accumulation

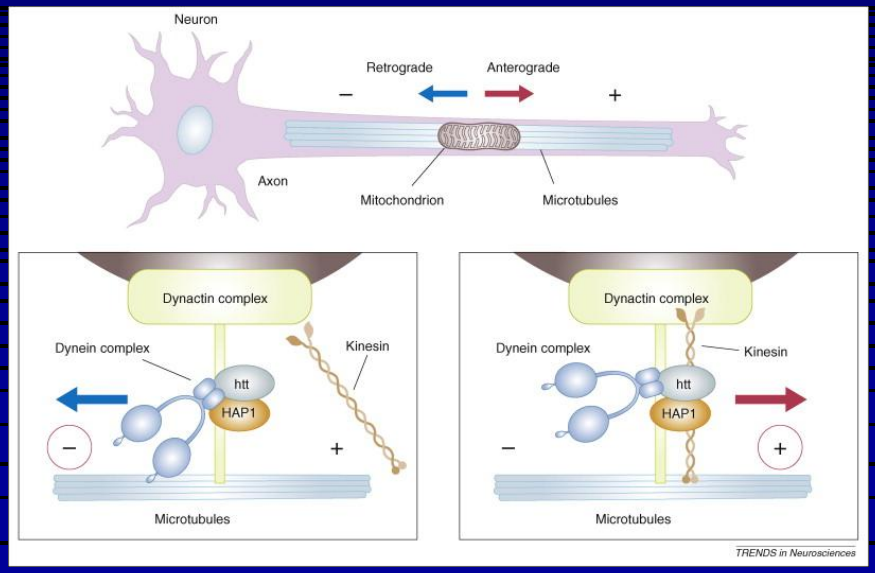
Mitochondria and Hungtington D

- Complex II activity is decreased in the HD brain, and the complex-II inhibitor 3-nitropropionic acid induces striatal degeneration and movement disorder in rodents and primates.
- Overexpression of complex-II subunits reduces cell death in striatal neurons expressing mutant HTT.
- Mutant HTT associates with the OMM and increases sensitivity to calcium-induced cytochrome *c* release. Mutant HTT also translocates to the nucleus, where it binds and increases the level and transcriptional activity of p53.
- p53 activates the pro-apoptotic protein BAX, either directly or by increasing expression of BH3-only Bcl-2 family members NOXA and PUMA.
- In mice, knockout of Pgc-1 or a missense mutation in Htra2 causes involuntary movements and striatal degeneration.



- **Mutant huntingtin (mtHtt) might cause mitochondrial dysfunction by either perturbing transcription of nuclear-encoded mitochondrial proteins or by direct interaction with the organelle and modulation of respiration, mitochondrial membrane potential and Ca(2+) buffering.**
- **In addition, mtHtt might convey its neurotoxicity by evoking defects in mitochondrial dynamics, organelle trafficking and fission and fusion, which, in turn, might result in bioenergetic failure and HD-linked neuronal dysfunction and cell death.**
- **Finally, mitochondria might dictate selective vulnerability of long projection neurons, such as medium spiny neurons, which are particularly affected in HD.**

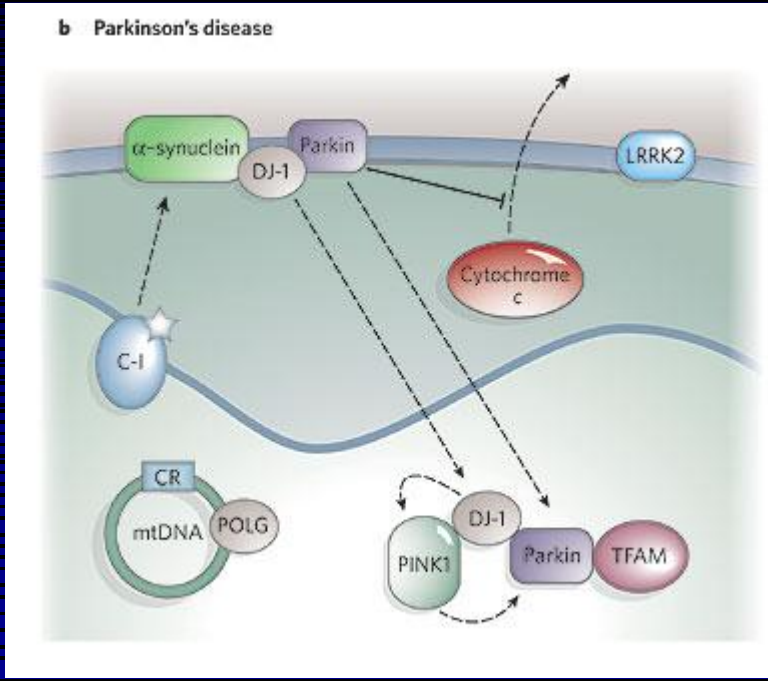




Mutant huntingtin and mitochondrial dysfunction.
Bossy-Wetzel E, Petrilli A, Knott AB.
Trends Neurosci. 2008 Dec;31(12):609-16.

Mitochondria and Parkinson

- **Complex I activity is decreased** in PD, and inhibition of complex I by MPTP or rotenone causes parkinsonism.
- **Mutations in mtDNA-encoded complex I subunits,** 12SrRNA, and POLG also cause parkinsonism.
- **Many genes associated with PD also implicate mitochondria in disease pathogenesis.**
- -Synuclein immunostaining is seen in degenerating mitochondria from mice overexpressing A53T -synuclein.
- -Synuclein overexpression impairs mitochondrial function and enhances the toxicity of MPTP.
- Parkin associates with the OMM and protects against cytochrome *c* release.
- When oxidized, DJ-1 translocates to mitochondria (IMS and matrix), downregulates the PTEN-tumour suppressor (not shown), and protects the cell from oxidative-stress-induced cell death.
- **The mitochondrial kinase PINK1 protects against apoptosis,** an effect that is reduced by PD-related mutations or kinase inactivation.



Parkin and mitochondria

- Darios F, Corti O, Lucking CB, Hampe C, Muriel MP, Abbas N, Gu WJ, Hirsch EC, Rooney T, Ruberg M, Brice A.

  Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. *Hum Mol Genet* 2003;2(5):517-26

- Kuroda Y, Mitsui T, Kunishige M, Matsumoto T.

  Parkin affects mitochondrial function and apoptosis in neuronal and myogenic cells. *Biochem Biophys Res Commun* 2006;348(3):787-793

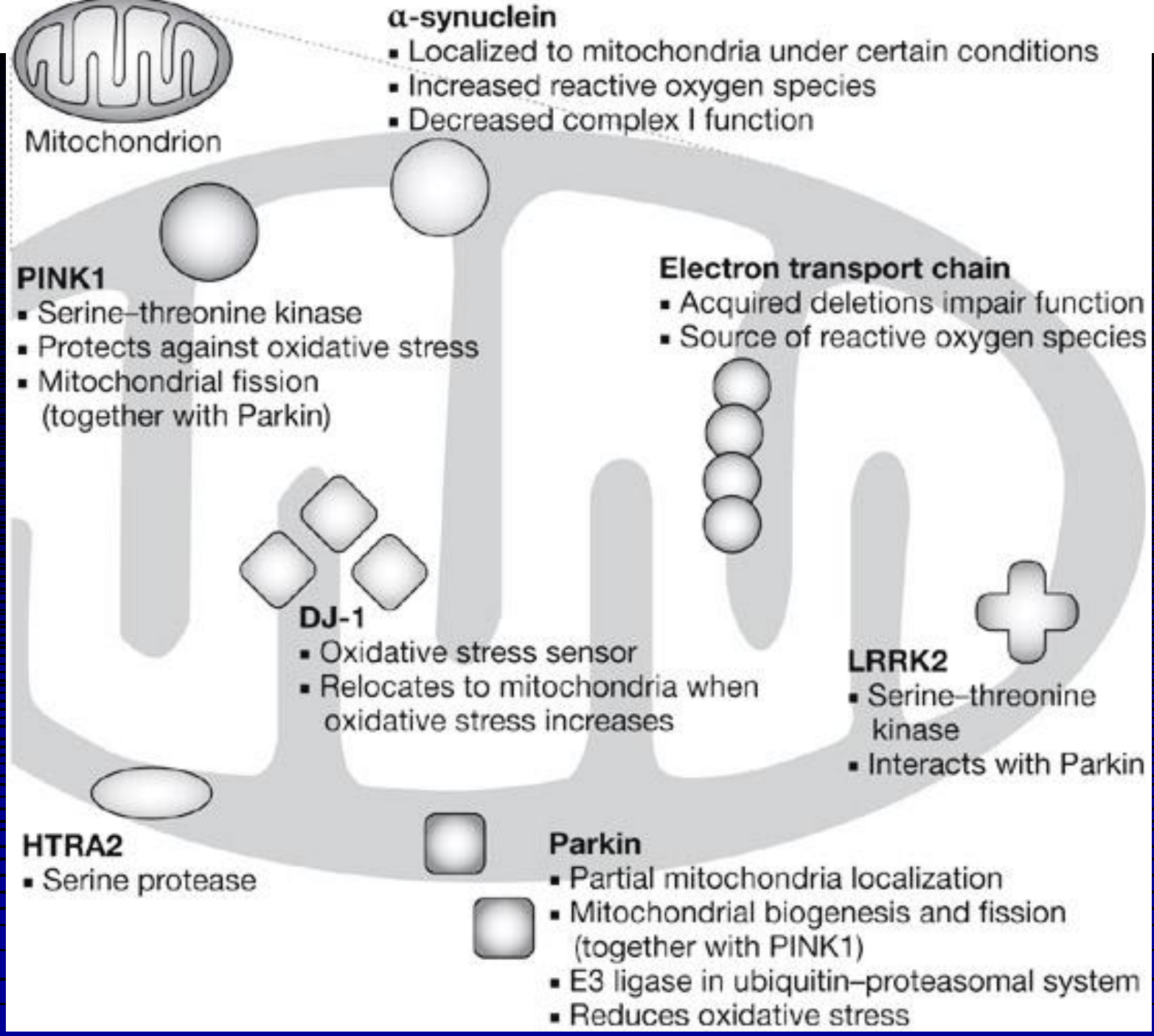
- Palacini JJ, Sagi D, Goldberg MS, Krauss S, Motz C, Wacker M, Klose J, Shen J.

  Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J Biol Chem* 2004;279(18):18614-22

- Greene JC, Whitworth AJ, Kuo I, Andrews LA, Feany MB, Pallanck LJ. Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants. *Proc Nati Acad Sci* U.S.A 2003;100(7):4078-83

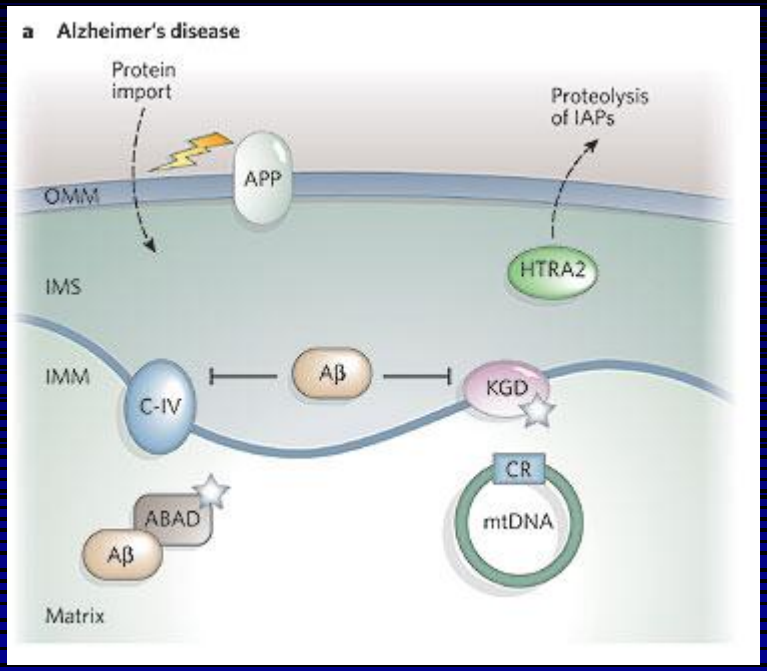
- Stichel CC, Zhu XR, Bader V, Linnartz B, Schmidt S, Lübbert H.

  Mono- and double-mutant mouse models of Parkinson's disease display severe mitochondrial damage. *Hum Mol Genet*. 2007 Oct 15;16(20):3377-93.


Mitochondrion
α-synuclein
▪ Localized to mitochondria under certain conditions
▪ Increased reactive oxygen species
▪ Decreased complex I function
PINK1
▪ Serine–threonine kinase
▪ Protects against oxidative stress
▪ Mitochondrial fission (together with Parkin)
Electron transport chain
▪ Acquired deletions impair function
▪ Source of reactive oxygen species
DJ-1
▪ Oxidative stress sensor
▪ Relocates to mitochondria when oxidative stress increases
LRRK2
▪ Serine–threonine kinase
▪ Interacts with Parkin
HTRA2
▪ Serine protease
Parkin
▪ Partial mitochondria localization
▪ Mitochondrial biogenesis and fission (together with PINK1)
▪ E3 ligase in ubiquitin–proteasomal system
▪ Reduces oxidative stress

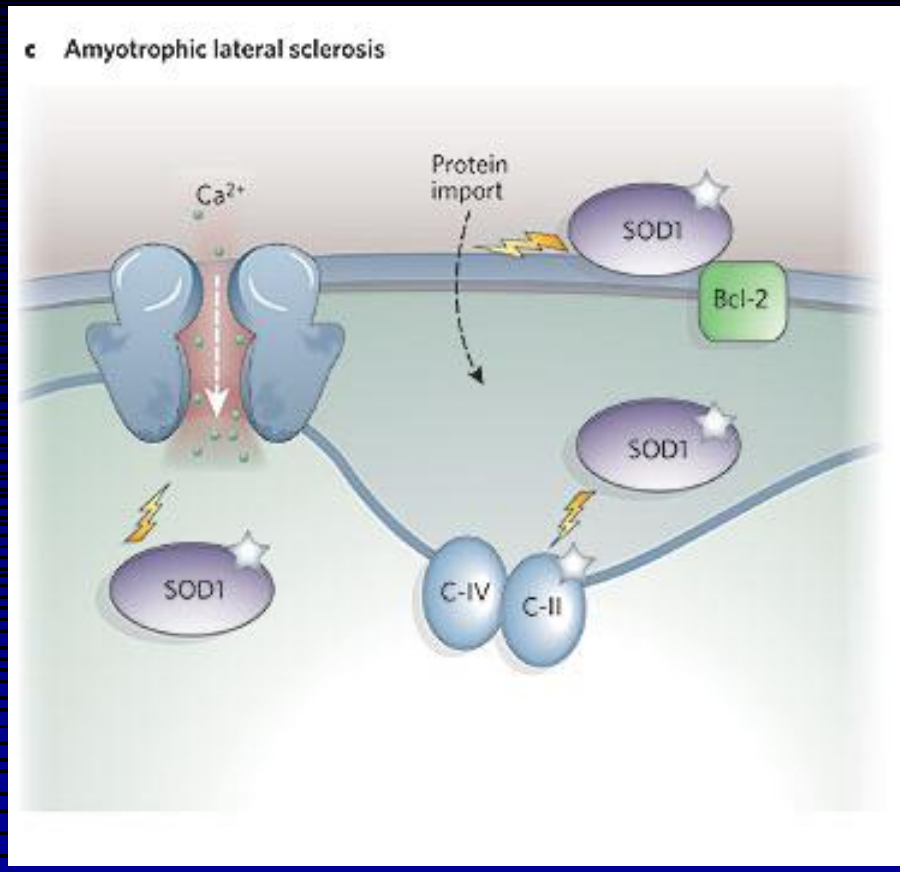
Mitochondria and Alzheimer

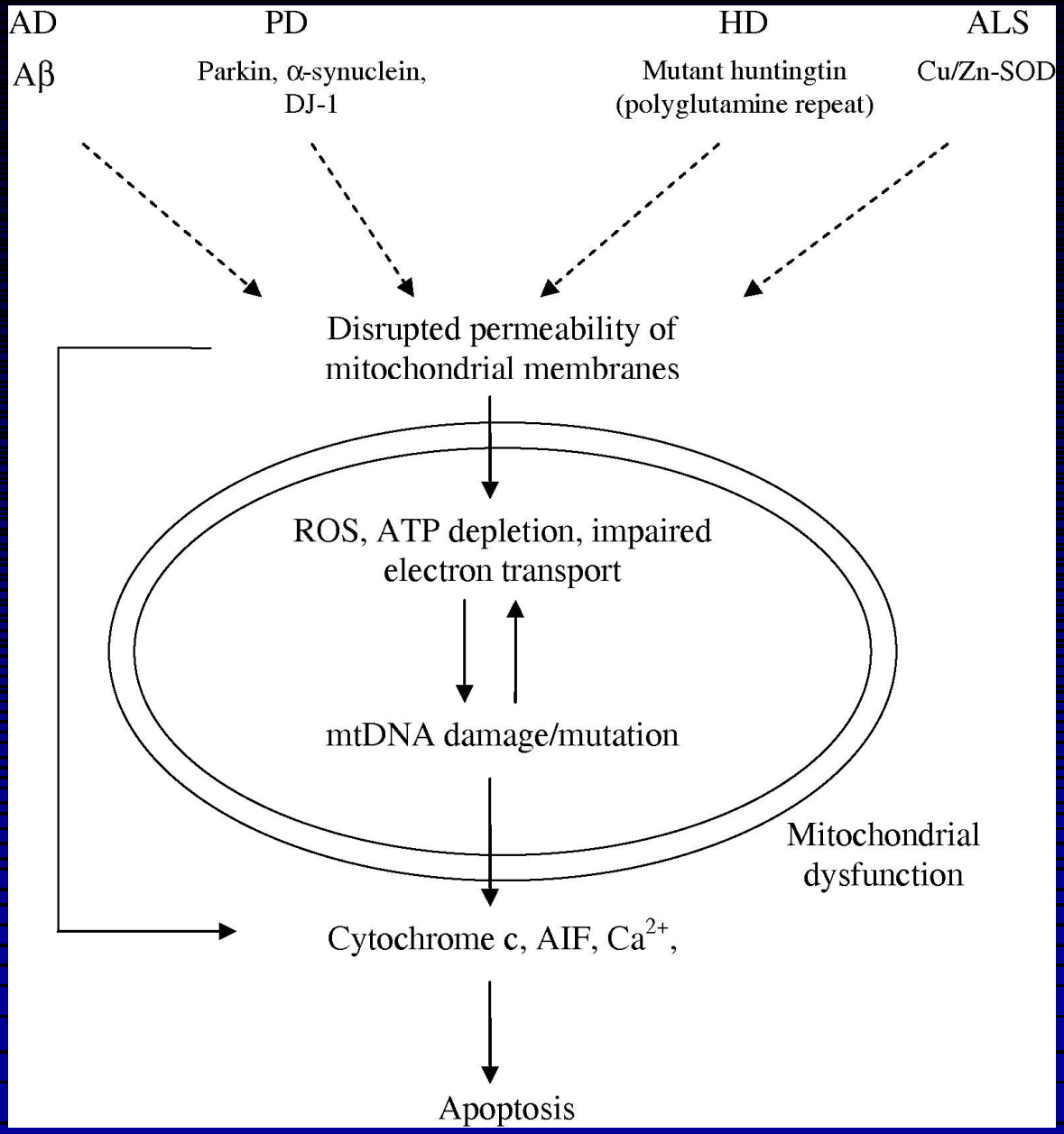
- In AD, mitochondrial ROS generation and inhibition of energy metabolism increase A levels in cells and transgenic mice, and A can interact with mitochondria and cause mitochondrial dysfunction.
- A inhibits complex IV and -ketoglutarate dehydrogenase (KGD), and binds A -binding alcohol dehydrogenase (ABAD). Both KGD and ABAD produce ROS (white stars).
- Amyloid precursor protein (APP) may be targeted to the OMM and interfere with protein import.
- Mitochondria have also been reported to contain active -secretase complexes, which are involved in cleaving APP to form A and contain presenilin 1, which increases the proteolytic activity of HTRA2 towards IAPs.
- AD patients have on average more somatic mutations in the mtDNA control region than control subjects

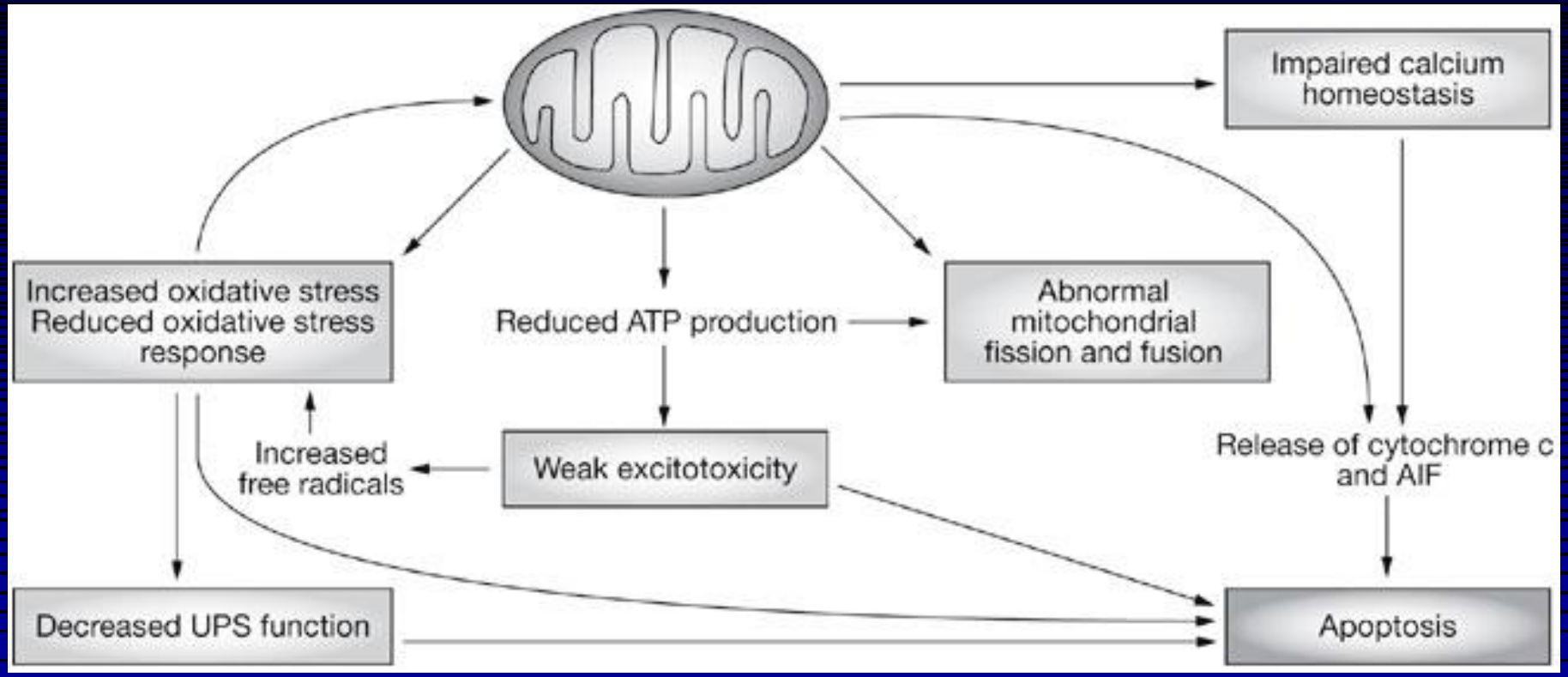


Mitochondria and ALS

- Overexpression of mutant SOD1 in ALS impairs electron-transport-chain activities and decreases mitochondrial calcium-loading capacity.
- SOD1 has been localized to the OMM, IMS and matrix, and targeting of mutant SOD1 to mitochondria causes cytochrome *c* release and apoptosis.
- Mutant SOD1 promotes aberrant mitochondrial ROS production and forms aggregates that may clog the OMM protein importation machinery or bind and sequester the antiapoptotic protein Bcl-2.




AD
Aβ
PD
Parkin, α-synuclein, DJ-1
HD
Mutant huntingtin (polyglutamine repeat)
ALS
Cu/Zn-SOD
Disrupted permeability of mitochondrial membranes
ROS, ATP depletion, impaired electron transport
mtDNA damage/mutation
Mitochondrial dysfunction
Cytochrome c, AIF, Ca^{2+},
Apoptosis

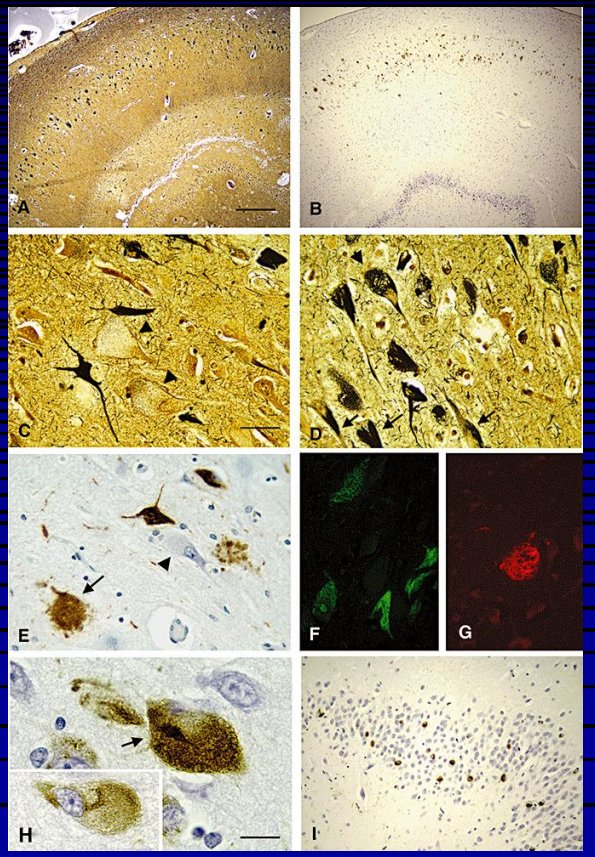

Impaired calcium homeostasis
Increased oxidative stress
Reduced oxidative stress response
Reduced ATP production
Abnormal mitochondrial fission and fusion
Increased free radicals
Weak excitotoxicity
Release of cytochrome c and AIF
Decreased UPS function
Apoptosis

Rare Neurometabolic diseases and Common Neurological disorders

Neurofibrillary tangles in Niemann-Pick type C disease

Love S et al, Brain 118: 119-29, 1995

- The tangles were argyrophillic, fluorescent, strongly reacting with antibody to tau protein; some immunostained for ubiquitin.
- They consist ultrastructurally of paired helical filaments identical to those of AD and are related with the abnormal storage material



Accumulation and aggregation of amyloid beta-protein in late endosomes of Niemann-Pick C cells

Yamazaki T et al

J Biol Chem 276: 4454-60, 2001

Niemann-Pick type C disease in a 68-year-old patient.

Trendelenburg G, Vanier MT, Maza S, Millat G, Bohner G, Munz DL, Zschenderlein R.

J Neurol Neurosurg Psychiatry. 2006 Aug;77(8):997-8.

- The oldest patient affected with the disease so far.
- This 68 year old woman presented with a 15 year history of depression and fluctuating mood, and was treated several times in psychiatric departments during the previous years. At the age of 54 she was unable to work further. **In the past 4 years she had developed a fluctuating, progressive dementia** with reduced impulse, affective instability, dysphagia, cramped hands and dyskinesia.
- blepharospasm, a vertical gaze palsy and choreiform oral buccal movements
- She was bedridden and was not able to communicate, was only intermittently groaning and followed simple requests inconstantly. Her hands were held in a dystonic, flectional position and her upper extremities were moved stereotypically. A positive bilateral Babinski sign was found.
- Molecular genetic analysis showed a new frameshift mutation of the NPC1 gene, K1206fs, on one allele in our patient.

Variation in NPC1, the gene encoding Niemann-Pick C1, a protein involved in intracellular cholesterol transport, is associated with Alzheimer disease and/or aging in the Polish population.

Erickson RP, Larson-Thomé K, Weberg L, Szybinska A, Mossakowska M, Styczynska M, Barcikowska M, Kuznicki J.

Neurosci Lett. 2008 Dec 12;447(2-3):153-7.

- There is abundant evidence that cholesterol metabolism, especially as mediated by the intercellular transporter APOE, is involved in the pathogenesis of sporadic, late-onset Alzheimer disease (SLAD). Identification of other genes involved in SLAD pathogenesis has been hampered since gene association studies, whether individual or genome-wide, experience difficulty in finding appropriate controls in as much as 25% or more of normal adults will develop SLAD.
- Using 152 centenarians as additional controls and 120 "regular", 65-75-year-old controls, an association of genetic variation in NPC1 with SLAD and/or aging has been found. In this preliminary study, we find gradients of two non-synonymous SNP's allele frequencies in NPC1 from centenarians through normal controls to SLAD in this non-stratified Polish population. An intervening intronic SNP is not in Hardy-Weinberg equilibria and differs between centenarians and controls/SLAD. Haplotypes frequencies determined by fastPHASE were somewhat different, and the predicted genotype frequencies were very different between the three groups.
- These findings can also be interpreted as indicating a role for NPC1 in aging, a role also suggested by NPC1's role in Dauer formation (hibernation, a longevity state) in Caenorhabditis elegans.

{gamma}-Secretase-dependent amyloid-{beta} is increased in Niemann-Pick type C: A cross-sectional study.

Mattsson N, Zetterberg H, Bianconi S, Yanjanin NM, Fu R, Månsson JE, Porter FD, Blennow K.

Neurology. 2011 Jan 25;76(4):366-372.

Mutations for Gaucher disease confer high susceptibility to Parkinson disease.

Mitsui J, Mizuta I, Toyoda A, Ashida R, Takahashi Y, Goto J, Fukuda Y, Date H, Iwata A, Yamamoto M, Hattori N, Murata M, Toda T, Tsuji S.

Arch Neurol. 2009 May;66(5):571-6

Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease.

Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, Li A, Holton J, Guerreiro R, Paudel R, Segarane B, Singleton A, Lees A, Hardy J, Houlden H, Revesz T, Wood NW.

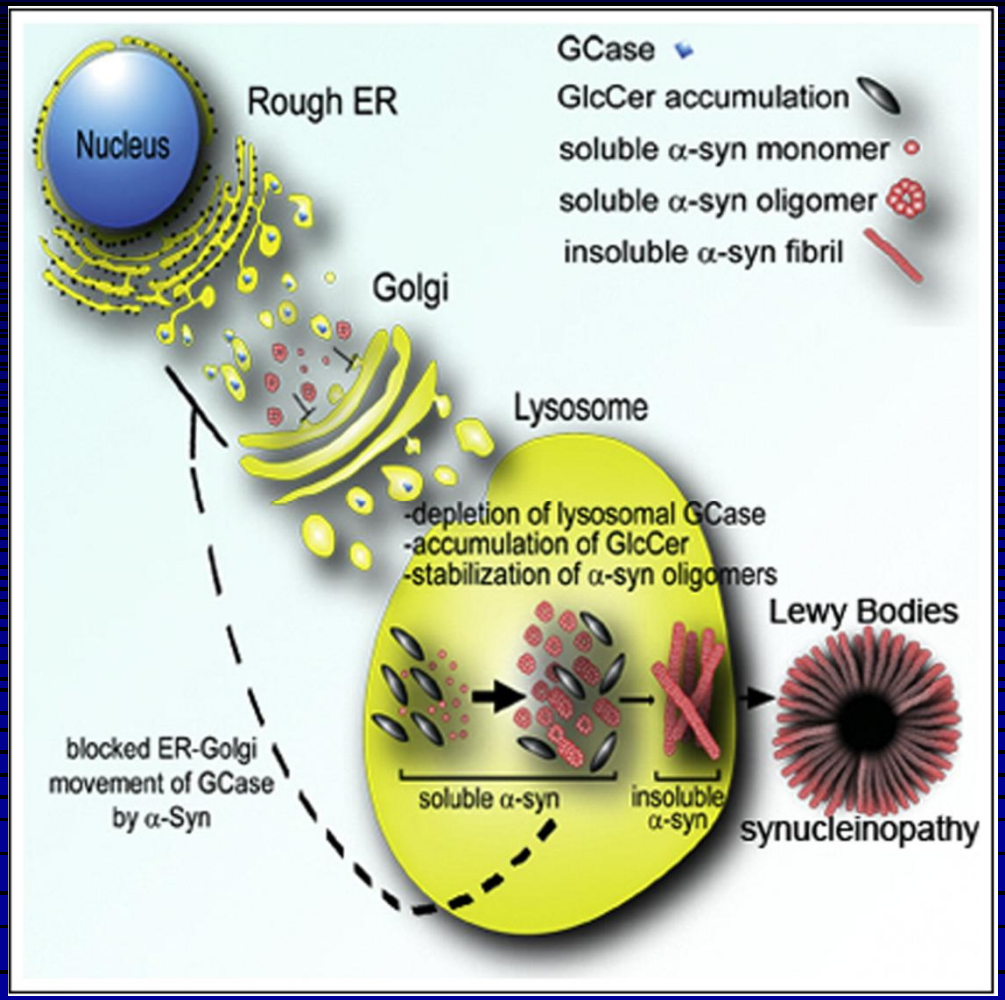
Brain. 2009 Jul;132(Pt 7):1783-94

This study demonstrates that GBA mutations are found in British subjects at a higher frequency than any other known Parkinson's disease gene.

Cell. 2011 Jul 8;146(1):37-52.

Gaucher disease glucocerebrosidase and ?Ñsynuclein form a bidirectional pathogenic loop in synucleinopathies.

Mazzulli JR Xu YH Sun Y Knight AL McLean PJ Caldwell GA Sidransky E Grabowski GA Krainc D



Functional loss of GD-linked glucocerebrosidase (GCase) in primary cultures or human iPS neurons compromises lysosomal protein degradation, causes accumulation of ?Ñsynuclein (?Ñsyn), and results in neurotoxicity through aggregation-dependent mechanisms.

Glucosylceramide (GlcCer), the GCase substrate, directly influenced amyloid formation of purified ?½ syn by stabilizing soluble oligomeric intermediates.

?-syn inhibits the lysosomal activity of normal GCase in neurons and idiopathic PD brain, suggesting that GCase depletion contributes to the pathogenesis of sporadic synucleinopathies.

These findings suggest that the bidirectional effect of ?-syn and GCase forms a positive feedback loop that may lead to a self-propagating disease.

Therefore, improved targeting of GCase to lysosomes may represent a specific therapeutic approach for PD and other synucleinopathies.

The p.L302P mutation in the lysosomal enzyme gene *SMPD1* is a risk factor for Parkinson disease

Ziv Gan-Or et al

Neurology, April 23, 2013 80:1606-1610

General approach to treatments of neurometabolic disorders

- Symptomatic treatments
- Etiopathogenetic treatments

General approach to treatments of neurometabolic disorders

A) Decrease of levels of toxic metabolites

- diet

B) **Removal of toxic substrates**

- Transfusions, plasmapheresis, peritoneal dyalisis
- Drugs

C) Substitution of deficient substance

- Leucocyte and plasma infusions
- Organs Transplantations
- Fibroblasts tranplantations
- Bone marrow transplantation

D) Direct supply of deficient metabolyte

E) Enzymatic induction by coenzymes

F) Enzyme therapy

G) Substrate reduction and chaperones

H) Gene therapy

Ethical and therapeutical issues

"I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients.

Kwon JM, **Steiner RD**.

Neurology. 2011 Aug 9;77(6):522-3.

Making diagnosis of Pompe disease at a presymptomatic stage: to treat or not to treat?

Laloui K, Wary C, Carlier RY, Hogrel JY, Caillaud C, Laforêt P.

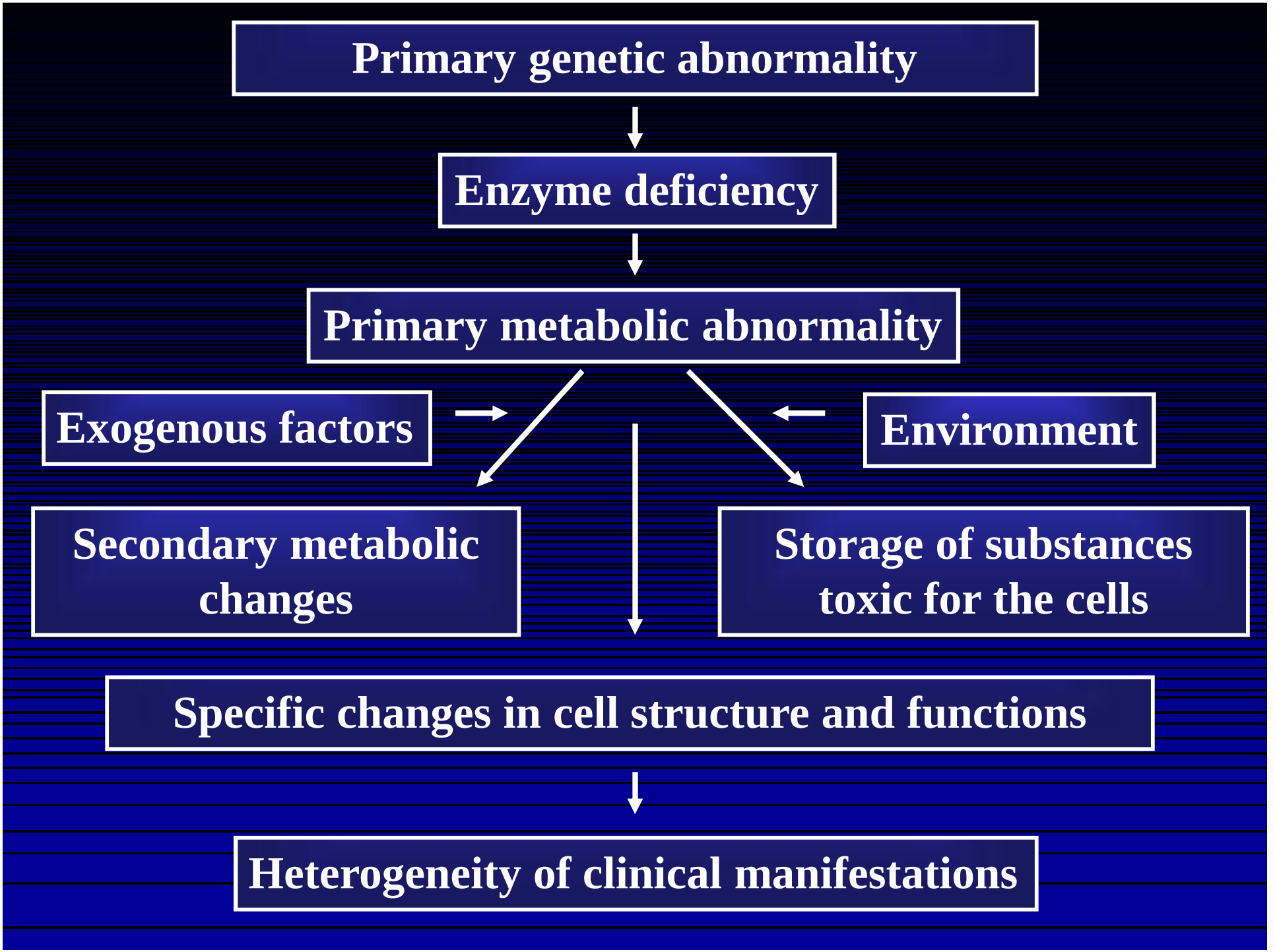
Neurology. 2011 Aug 9;77(6):594-5.

What we learned about the lesson by the late onset neurometabolic deseases as a model for understanding the functions of the nervous system?

1. **Their extreme clinical heterogeneity, characterized by a different vulnerability of neuroaxonal system to a molecular defect**
2. **The possibility of an infantile onset, with a severe and rapidly evolving clinical features, due to the interaction of the primary metabolic disturbance in the biochemical mechanisms of brain maturation and development**
3. **The presence of late onset cases, with a slow evolution suggesting a neuro-axonal abyotrophic process**
4. **Their molecular heterogeneity**

Gene mutations

- Mutations resulting in some residual enzyme activity include missense mutations that do not completely abolish folding, processing and activity of the protein.
- Mutations affecting splicing but located outside the consensus site and producing variable amount of normally and abnormally spliced transcripts result in some residual enzyme activity as do some mutations affecting regulatory regions of the gene (TATA box and others and polyadenulation sites)
- Null alleles may be due to splice-site mutations or deletion.
- Missense mutations originate enzymes frequently fold incorrectly and retained in the endoplasmic reticulum and subsequently degradated.

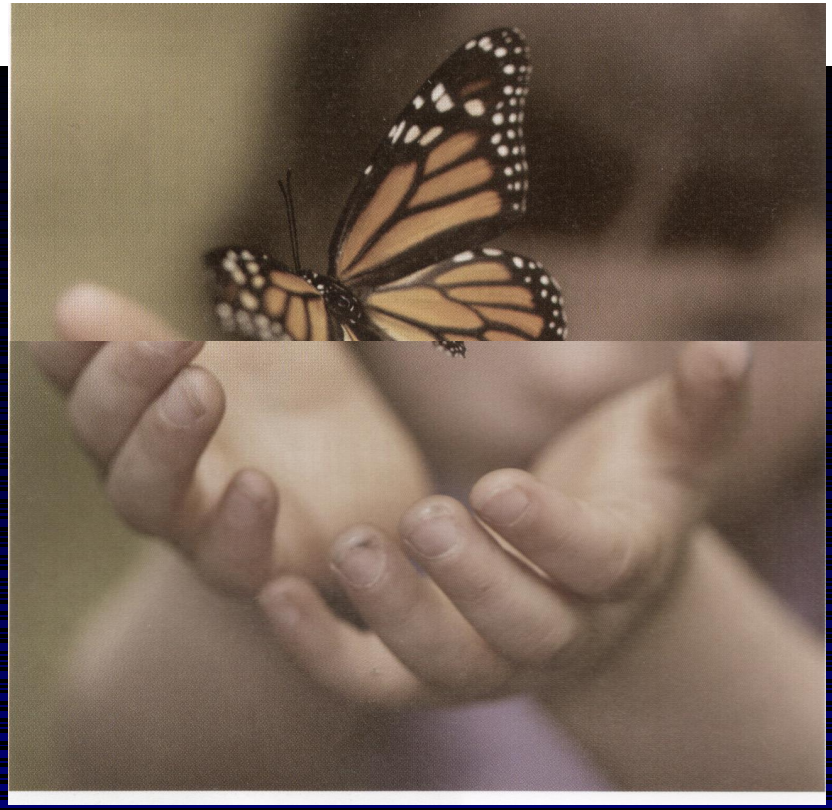

Primary genetic abnormality
Enzyme deficiency
Primary metabolic abnormality
Exogenous factors
Environment
Secondary metabolic changes
Storage of substances toxic for the cells
Specific changes in cell structure and functions
Heterogeneity of clinical manifestations

CONCLUSIONS

Every known neurometabolic condition presenting in childhood may have a less severe clinical presentation with clinical signs only in adult age

In relatioship to the neurologists' interest and attitute to study these clinical manifestations, the phenotypes of late onset neurometabolic diseases will be discovered and the metabolic pathogenesis will be explained.

In any cases, the late onset neurometabolic diseases may be considered an useful model for understanding the pathophysiology of brain functions and dysfunctions



“Nature is nowhere accustommed more openly to display her secret mysteres than in cases where she shows traces after working apart from the beathen path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discoveries of the usual law of nature by careful investigation of causes of rarer forms of diseases. For it has been found, in almost all things, that what they contain of useful or applicable is hardly preceived under we are deprived of them or they become deranged in some way”.

William Harvey, 1647

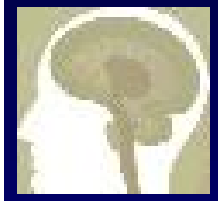
The study of rare diseases: butterfly collecting or an entrèe to understanding common conditions?

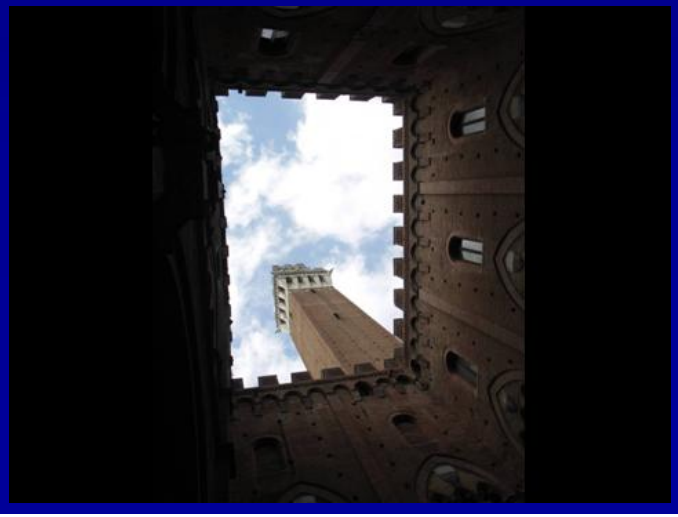
K. Talbot

Pract. Neurol. 7: 210-211, 2007

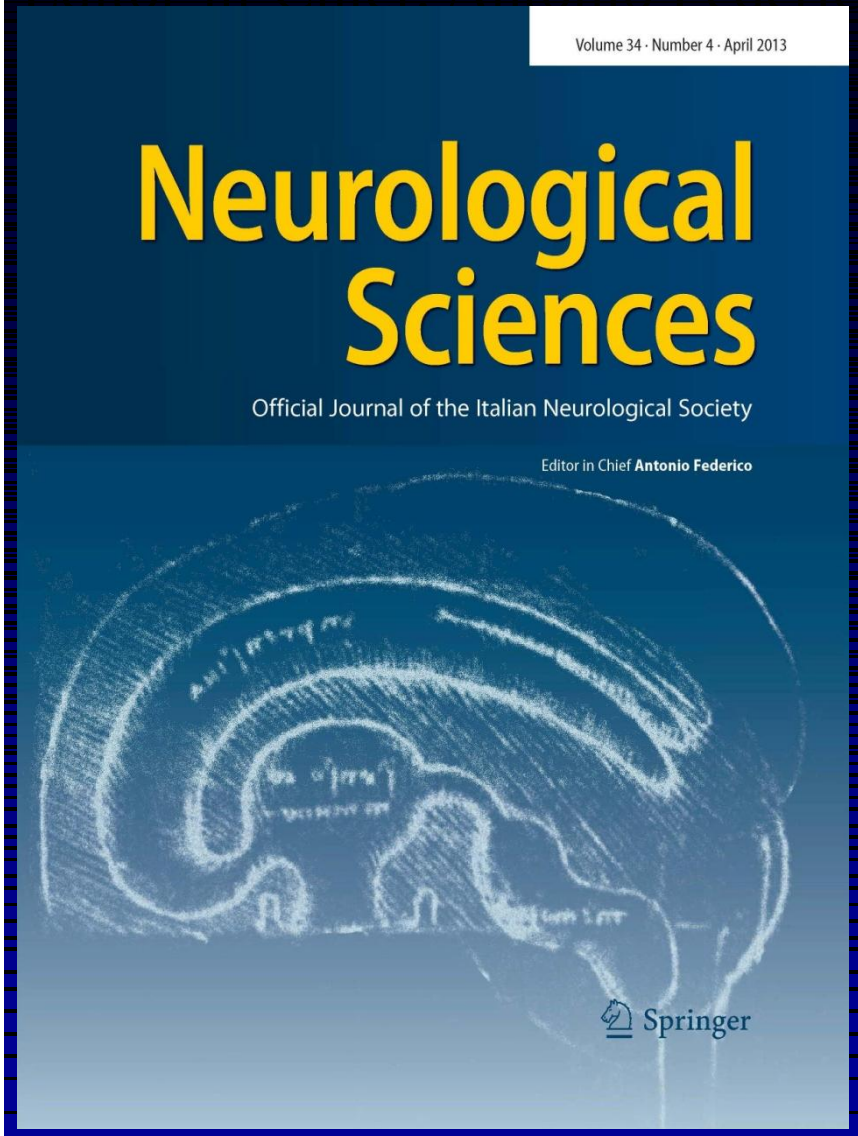
Unit Clinical Neurology and Neurometabolic Diseases

Director: A Federico





Neurological Sciences
Official Journal of the Italian Neurological Society
Editor-in-Chief: Antonio Federico



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Springer Editor