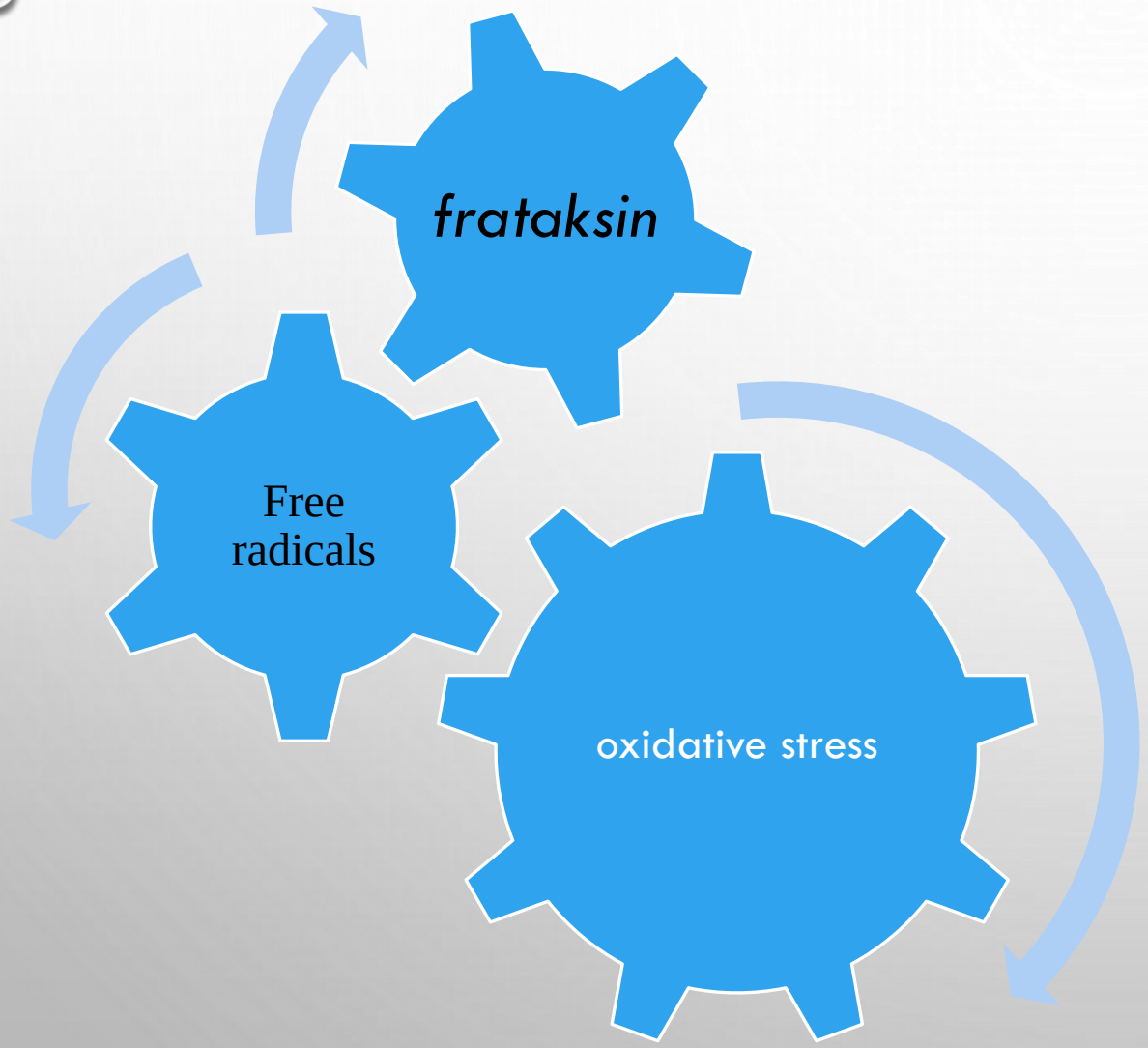
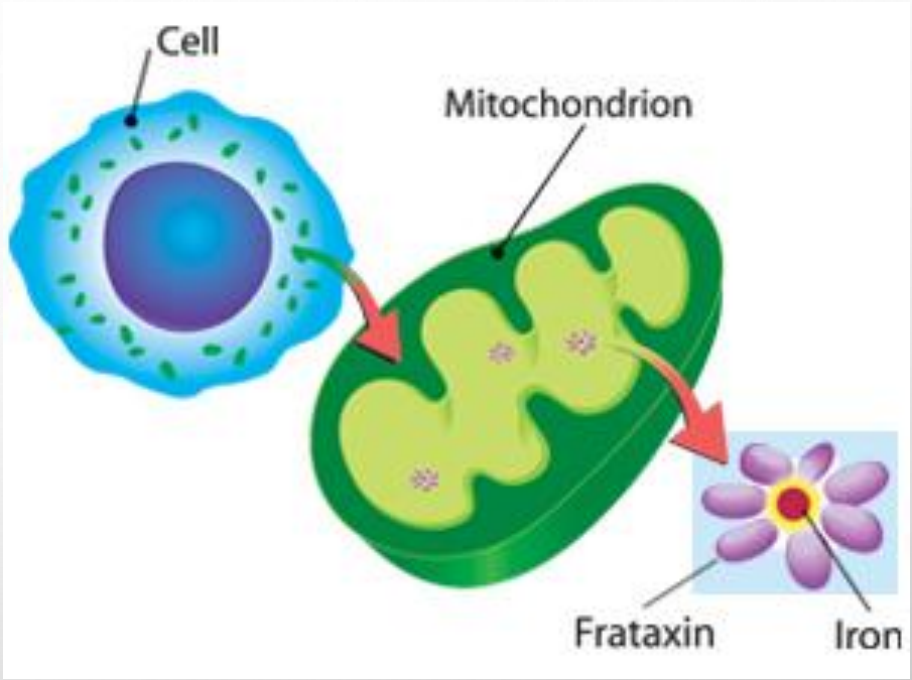
MOLECULAR BASIS OF MITOCHONDRIAL DISEASE

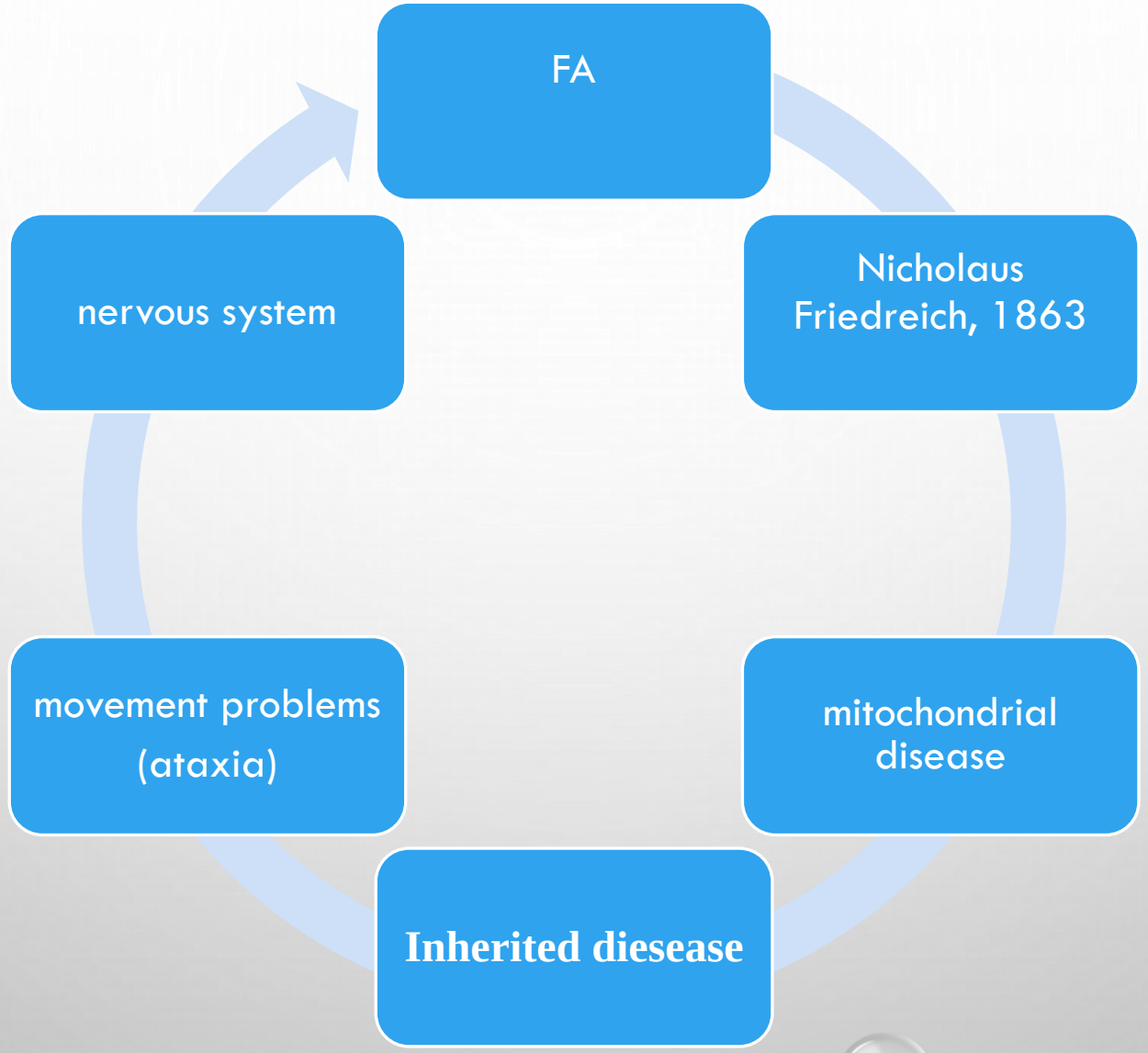
VELICKOVA, N.

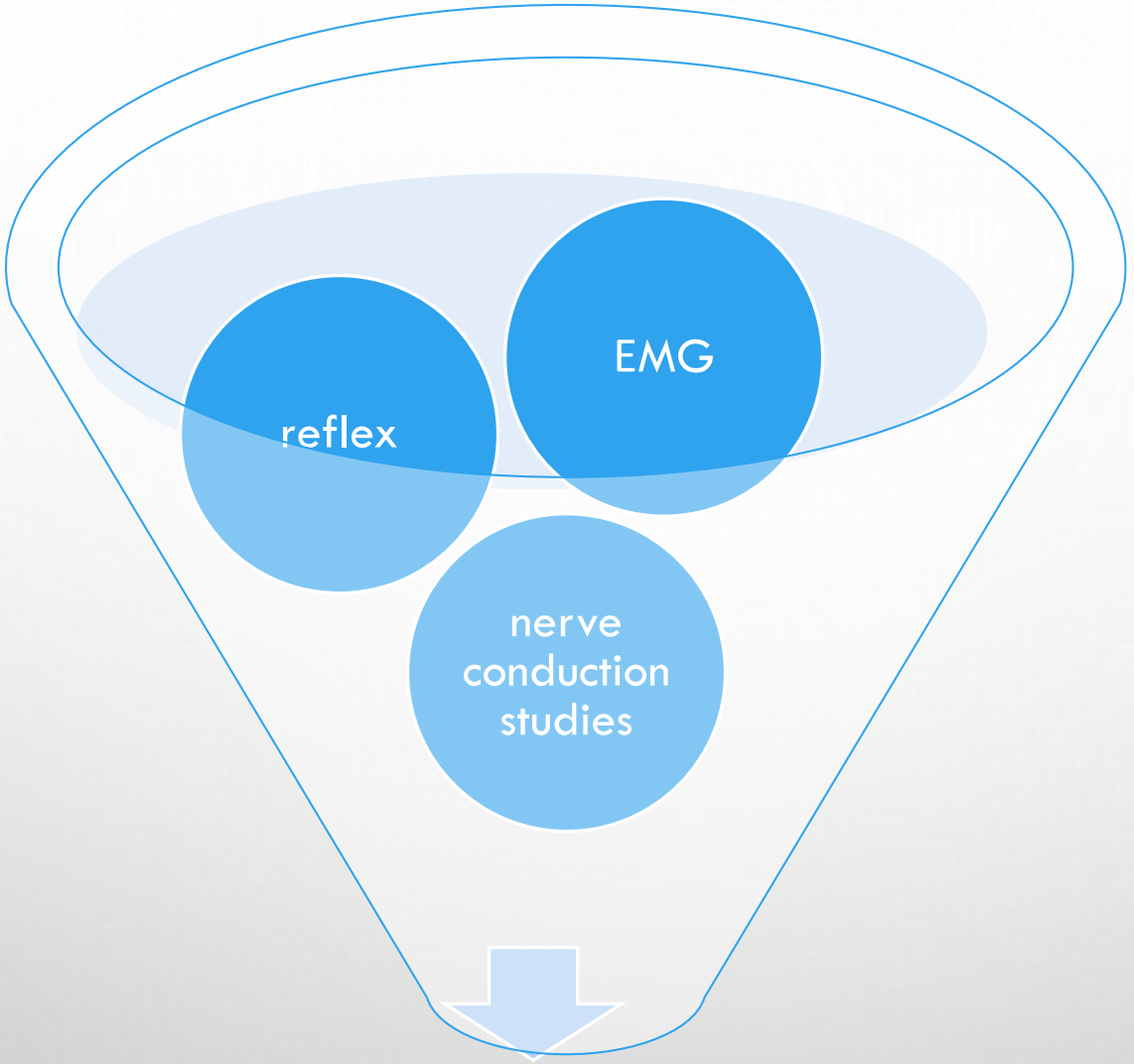
FACULTY OF MEDICAL SCIENCES

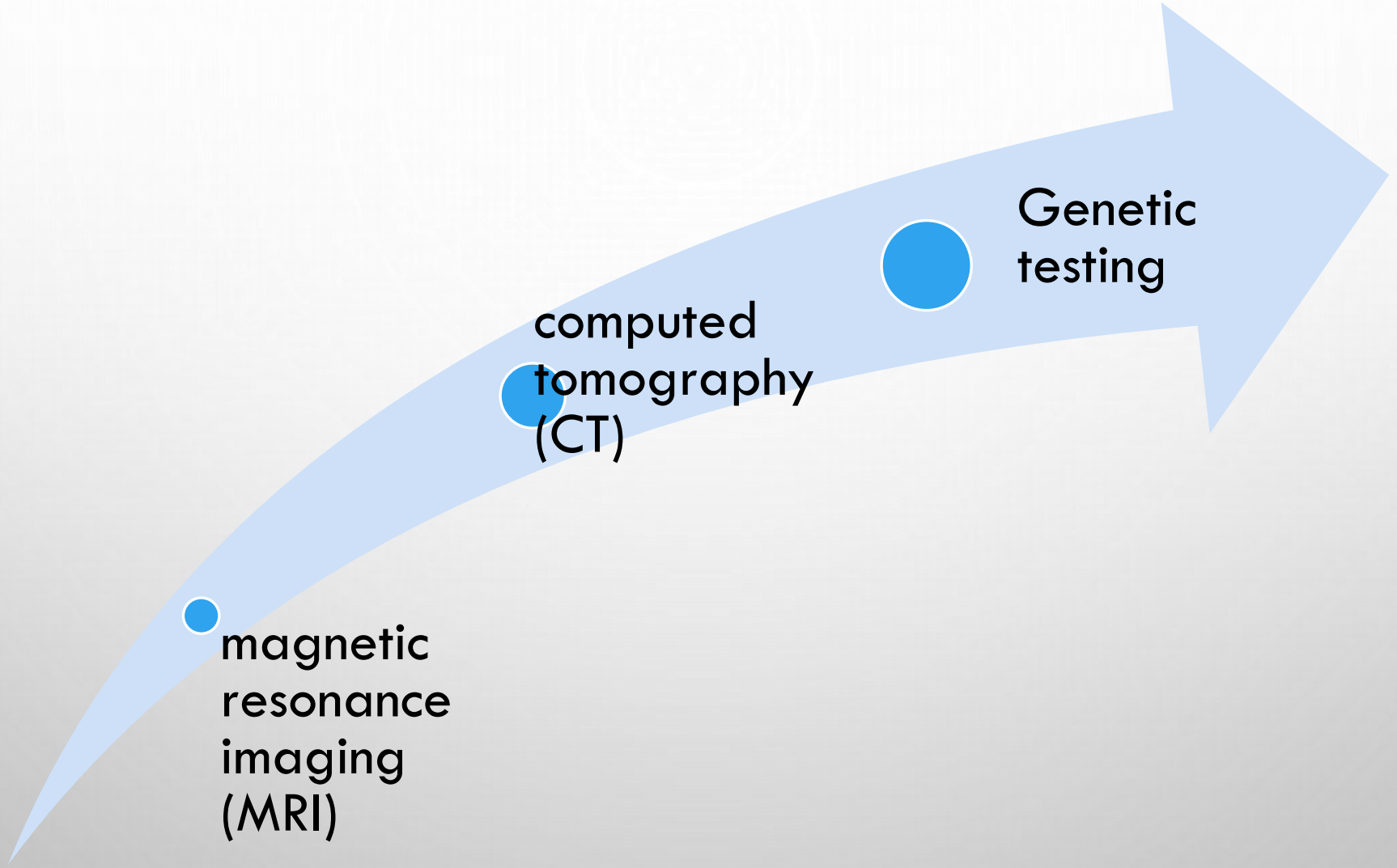
UNIVERSITY “GOCE DELCEV” - STIP, R.MACEDONIA

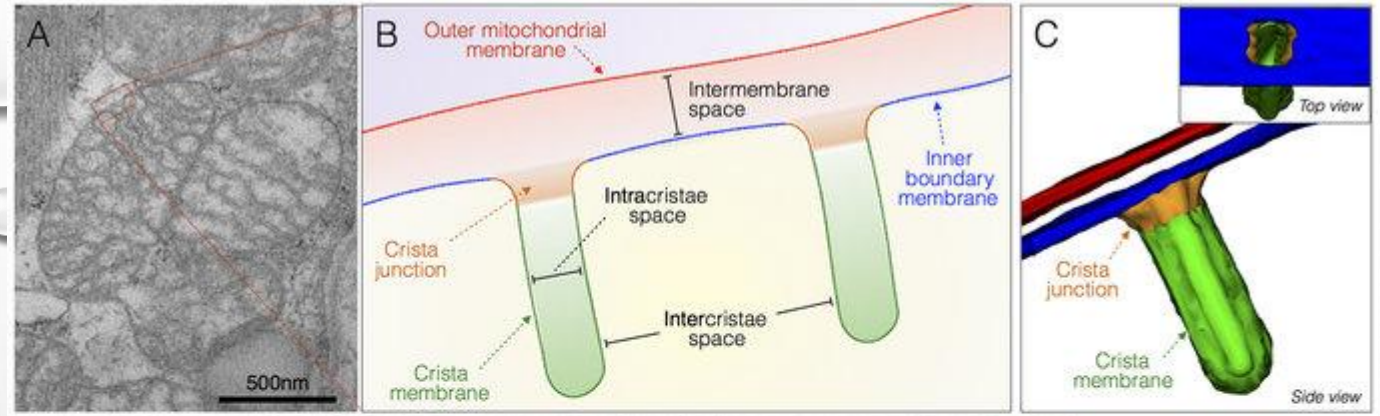

frataksin
Free radicals
oxidative stress

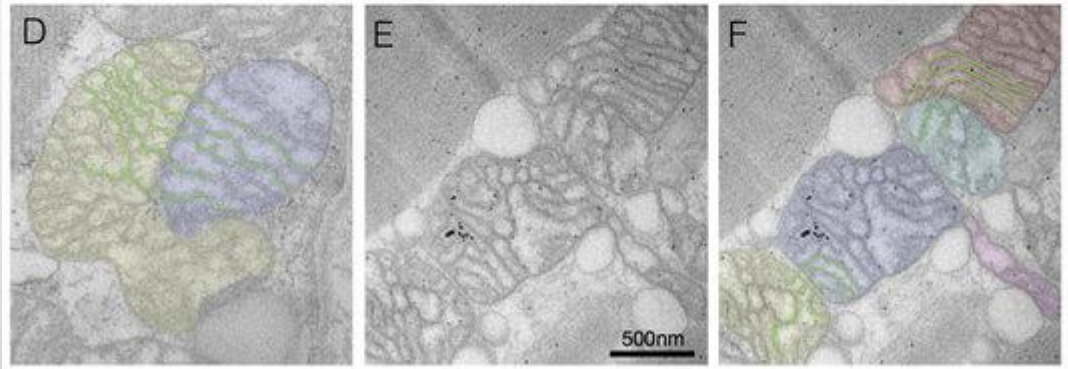

Cell
Mitochondrion
Frataxin
Iron

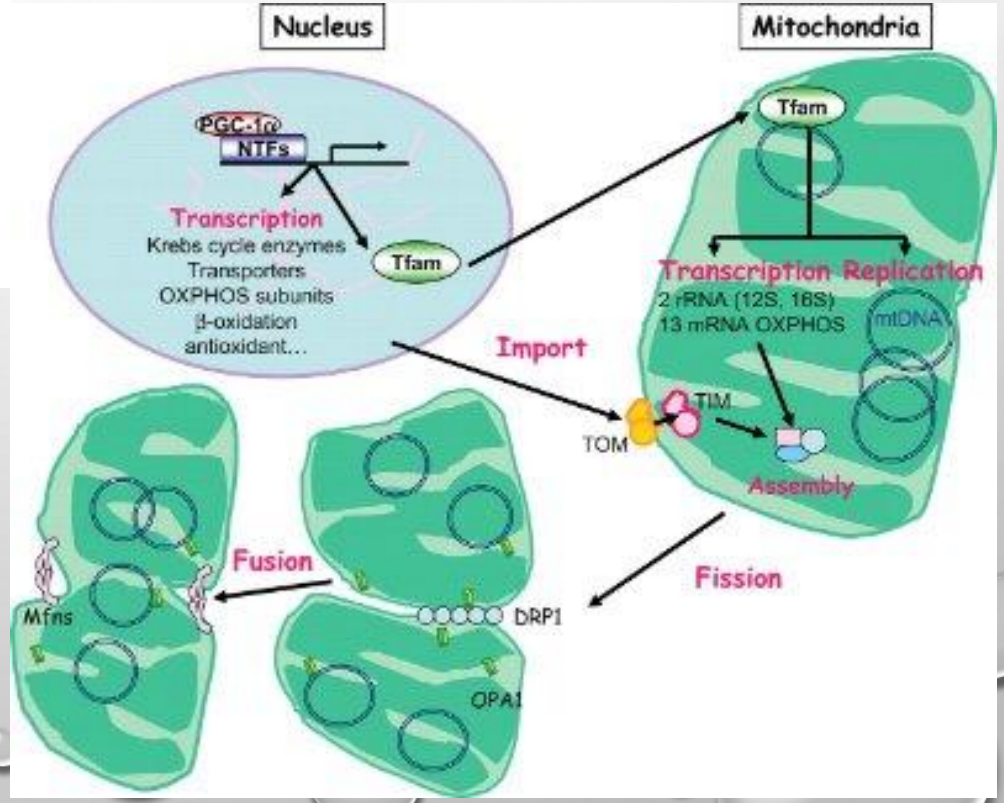

FA
Nicholaus Friedreich, 1863
mitochondrial disease
Inherited diesease
movement problems (ataxia)
nervous system


EMG
reflex
nerve conduction studies


magnetic resonance imaging (MRI)
computed tomography (CT)
Genetic testing


A
500nm
B
Outer mitochondrial membrane
Intermembrane space
Inner boundary membrane
Intracristae space
Crista junction
Intercristae space
Crista membrane
C
Top view
Crista junction
Crista membrane
Side view


D
E
500nm
F


Nucleus
Mitochondria
PGC-1α
NTFs
Transcription
Krebs cycle enzymes
Transporters
OXPHOS subunits
β-oxidation
antioxidant...
Tfam
Tfam
Transcription Replication
2 rRNA (12S, 16S)
13 mRNA OXPHOS
mtDNA
Import
TIM
TOM
Assembly
Fusion
Fission
Mfns
DRP1
OPA1

:GAA”

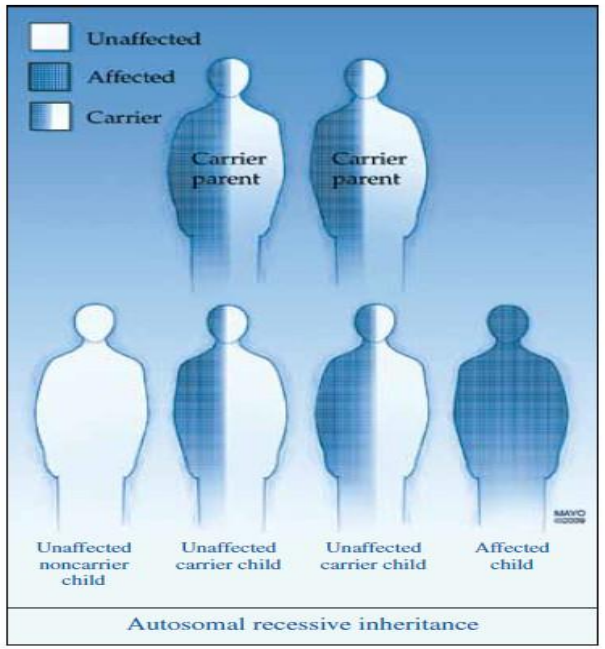


Figure 2. In an autosomal recessive disorder, 2 mutated genes are inherited, 1 from each parent. This type of disorder is usually passed on by 2 carriers. The carriers' health is rarely affected, but they have 1 mutated gene (recessive gene) and 1 normal gene (dominant gene) for the condition. Two carriers have a 25 percent chance of having an unaffected child with 2 normal genes, a 50 percent chance of having an unaffected child who also is a carrier, and a 25 percent chance of having an affected child with 2 recessive genes.

autosomal recessive disease

FXN gene, 9 chromosome

1:50.000 САД

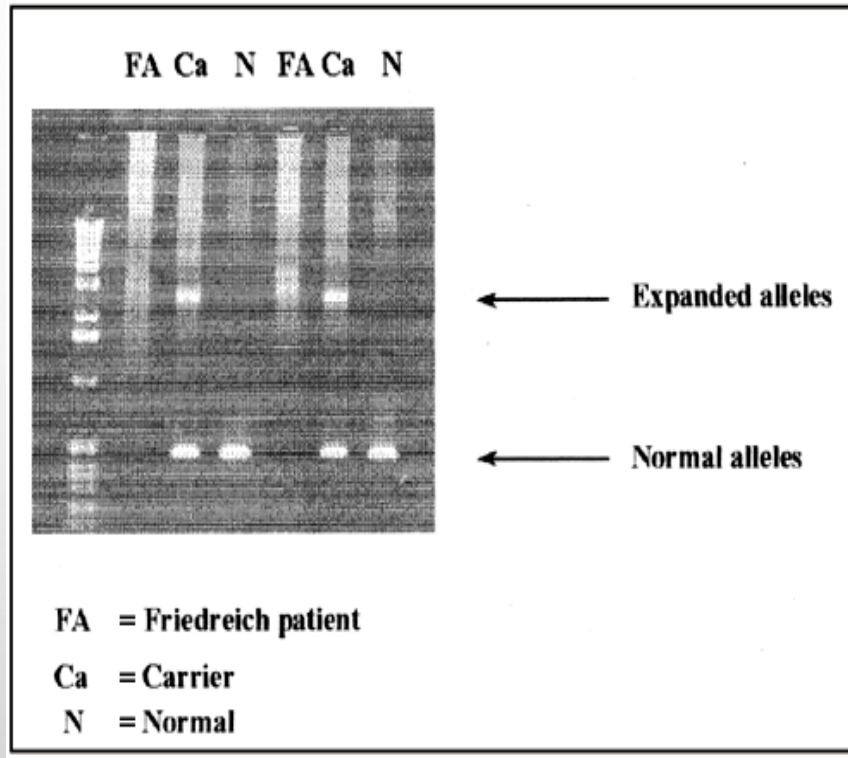
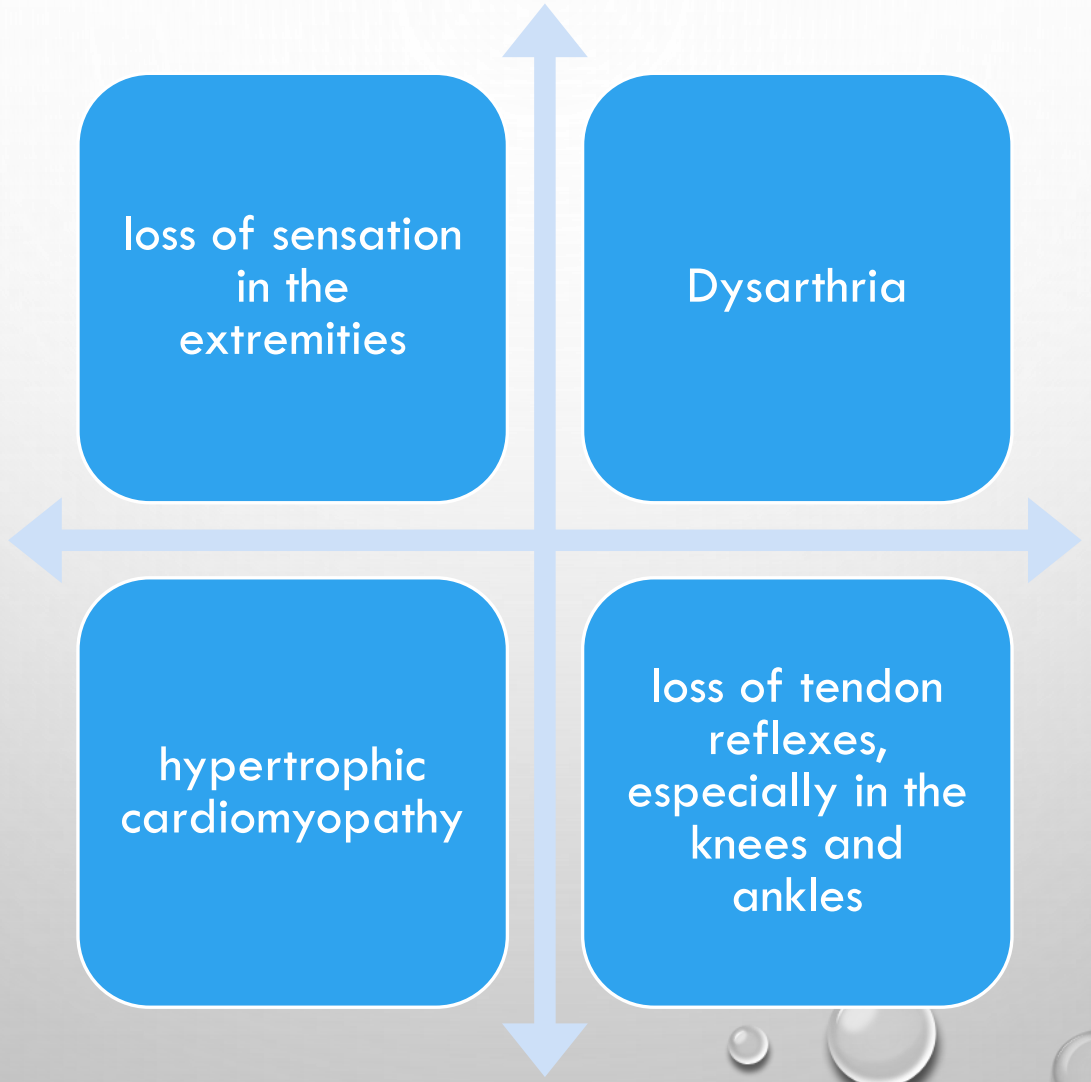


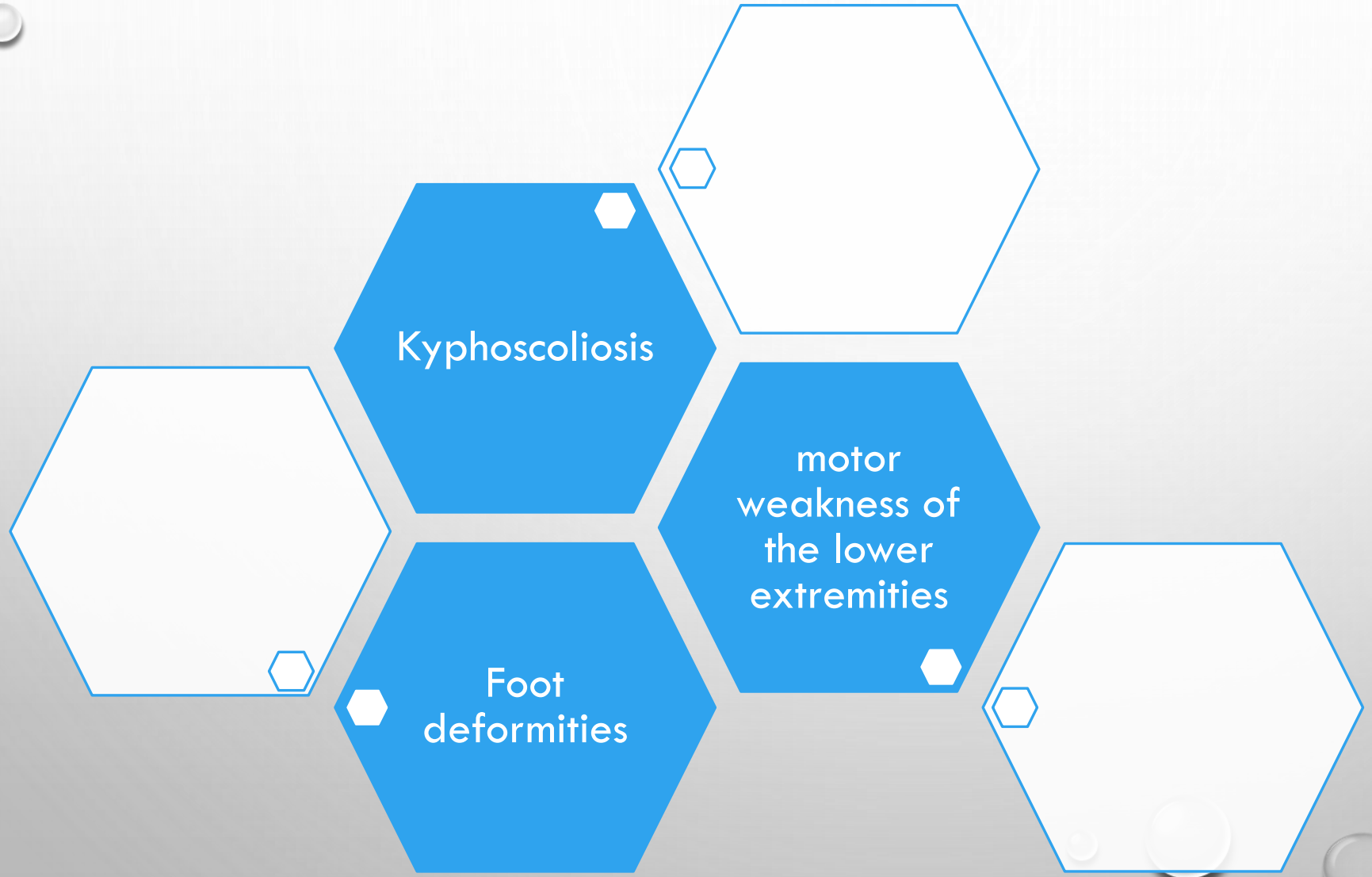
Figure 1 - Gel images of GAA expansion of Friedreich's ataxia patients, heterozygotes, and norma controls.

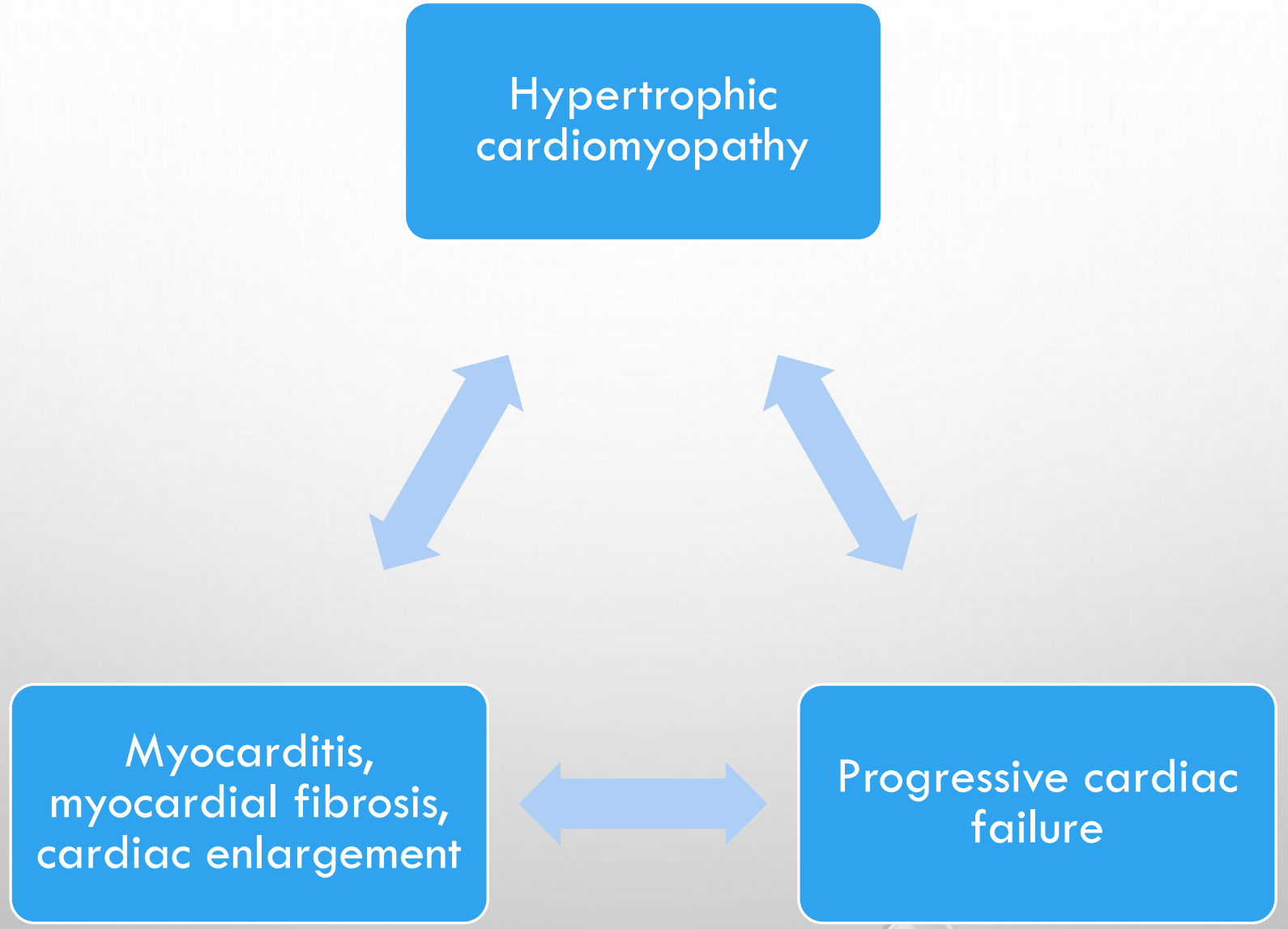
SIGNS AND SYMPTOMS

- THE AGES OF 5 AND 15 YEARS
- ATAXIA
- HEART DISEASE
- SPINAL CORD AND PERIPHERAL NERVES DEGENERATE
- CEREBELLUM (AWKWARD, UNSTEADY MOVEMENTS AND IMPAIRED SENSORY FUNCTIONS)

Include loss of tendon reflexes, especially in the knees and ankles

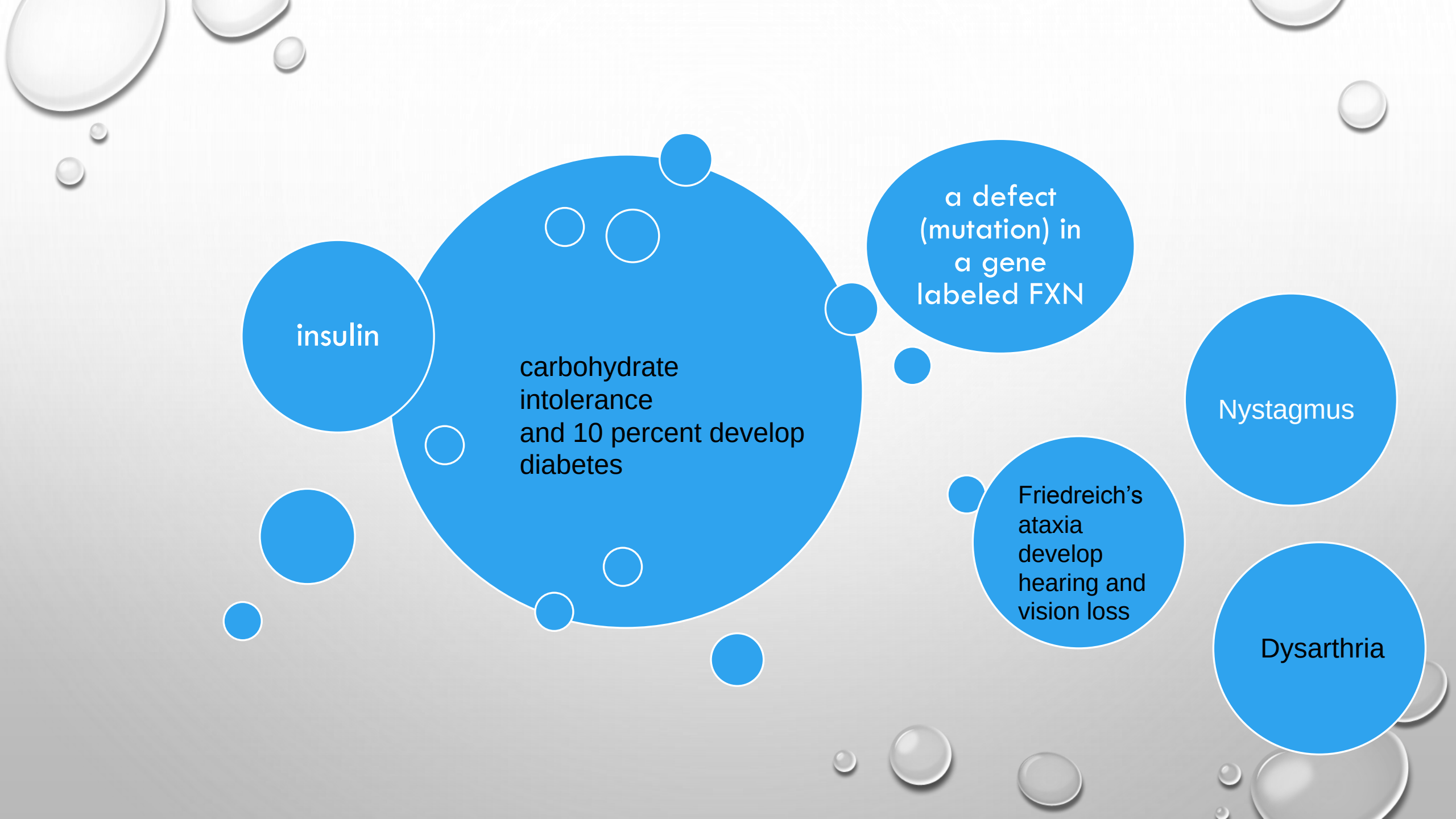

loss of sensation in the extremities
Dysarthria
hypertrophic cardiomyopathy
loss of tendon reflexes, especially in the knees and ankles


Kyphoscoliosis
motor weakness of the lower extremities
Foot deformities


Hypertrophic cardiomyopathy
Myocarditis, myocardial fibrosis, cardiac enlargement
Progressive cardiac failure

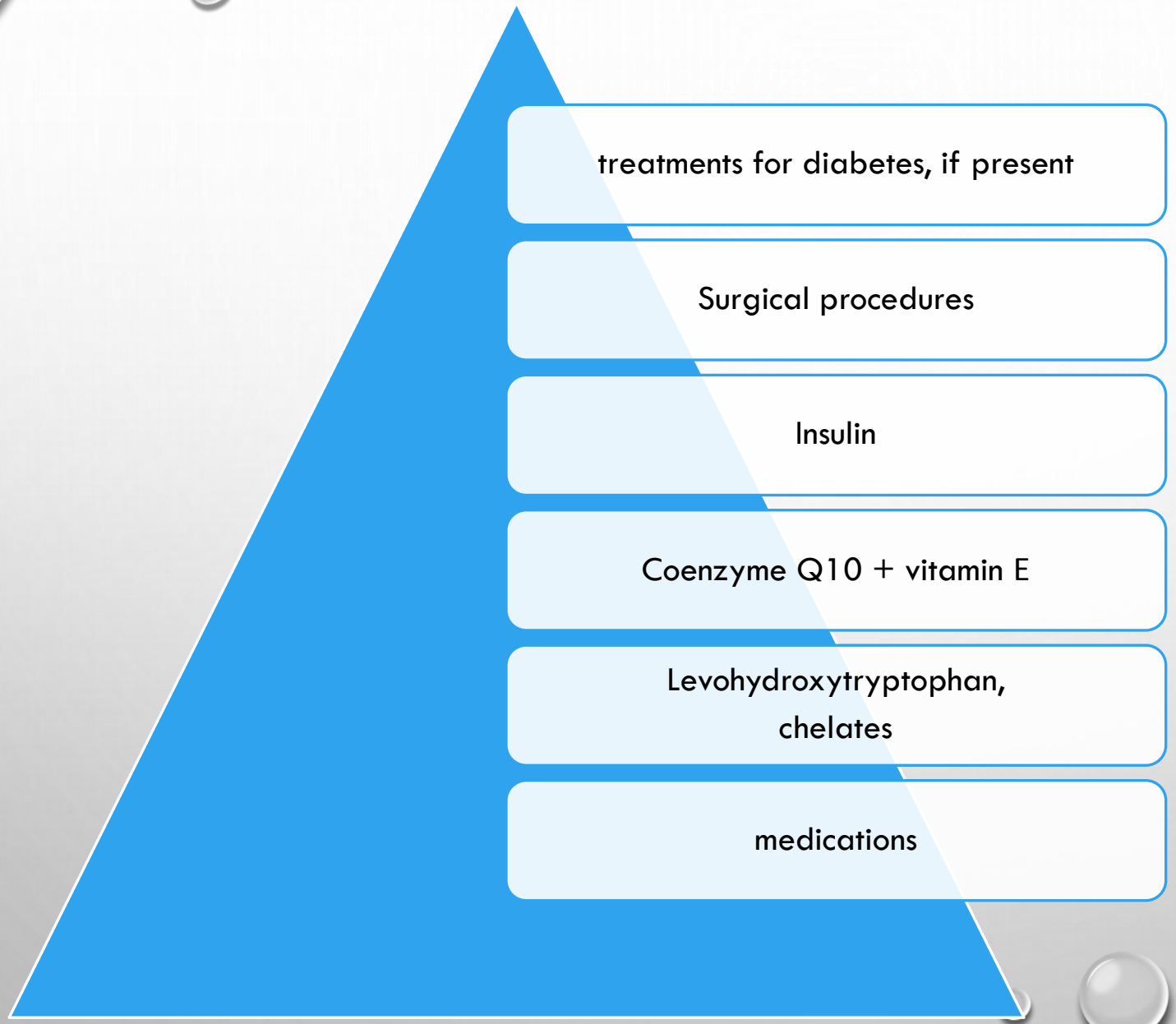
loss of vibratory and position senses from the onset, initially affecting the feet and hands

Progressive limb and gait ataxia


insulin
carbohydrate intolerance and 10 percent develop diabetes
a defect (mutation) in a gene labeled FXN
Nystagmus
Friedreich's ataxia develop hearing and vision loss
Dysarthria

between the ages of 5 and 15 years → rare occasions as late as age 75 → **cured or treated** → Physical therapy

TREATMENTS


treatments for diabetes, if present
Surgical procedures
Insulin
Coenzyme Q10 + vitamin E
Levohydroxytryptophan, chelates
medications

GENE THERAPY

Study of beta cells and neurons indicate incretin analogs as potential therapeutics for Friedreich's ataxia.

Massimo Pandolfo4, Mariana Igoillo-Esteve5, Amélie Hu3, Ewa Gurgul-Convey1, Laila Romagueira Bichara Dos Santos2, Jonas Jean-Christophe2, Decio Eizirik5 and Miriam Cnop5

Published online before print April 8, 2015, Neurology April 6, 2015 vol. 84 no. 14 Supplement

INCREASE FRATAXIN LEVELS THROUGH DRUG TREATMENTS, GENETIC ENGINEERING AND PROTEIN DELIVERY SYSTEMS

A Potential New Therapeutic Approach for Friedreich Ataxia: Induction of Frataxin Expression With TALE Proteins

Open

Pierre Chapdelaine[1,2], Zoé Coulombe[1,2], Amina Chikh[1,2], Catherine Gérard[1,2]and Jacques P Tremblay[1,2]

- The Friedreich's Ataxia Research Alliance (FARA)
- http://www.curefa.org/index.php
- http://www.fara.org.au/