Anémies et présentations hématologiques

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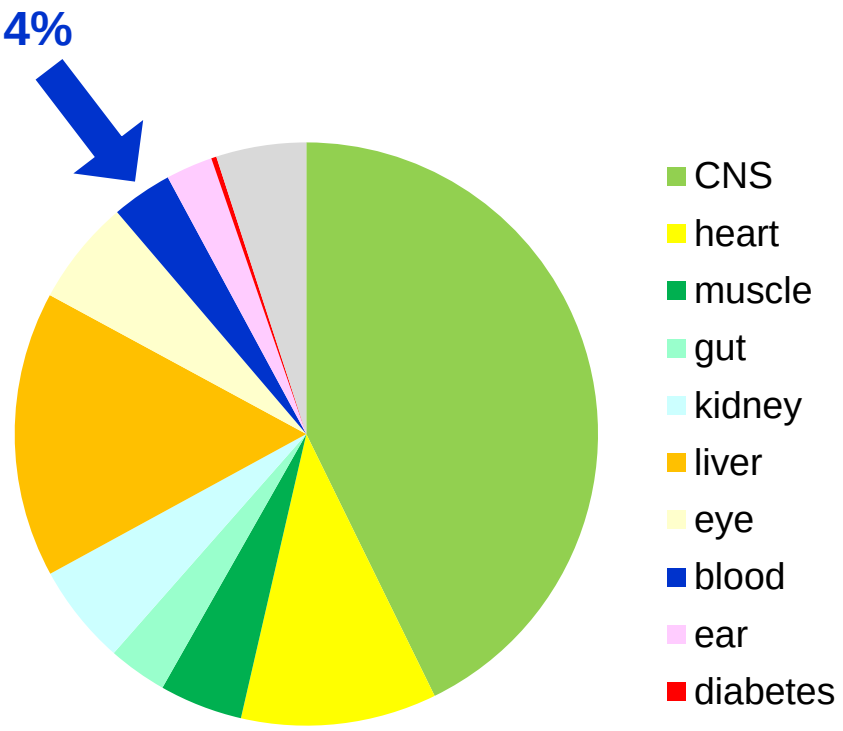
Hematologic manifestations of mitochondrial diseases

- aplastic, macrocytic, or sideroblastic anemia
- leukopenia
- neutropenia
- thrombocytopenia
- pancytopenia

-syndromic or non syndromic
- mtDNA or nuclear gene mutations



Pearson marrow pancreas syndrome

Refractory sideroblastic anemia
Vacuolization of bone marrow precursors
Exocrine pancreatic dysfunction
Hyperlactatemia
Multiple RC deficiency in lymphocytes
heteroplasmic mtDNA deletion

Sporadic

Age of onset < 1 year

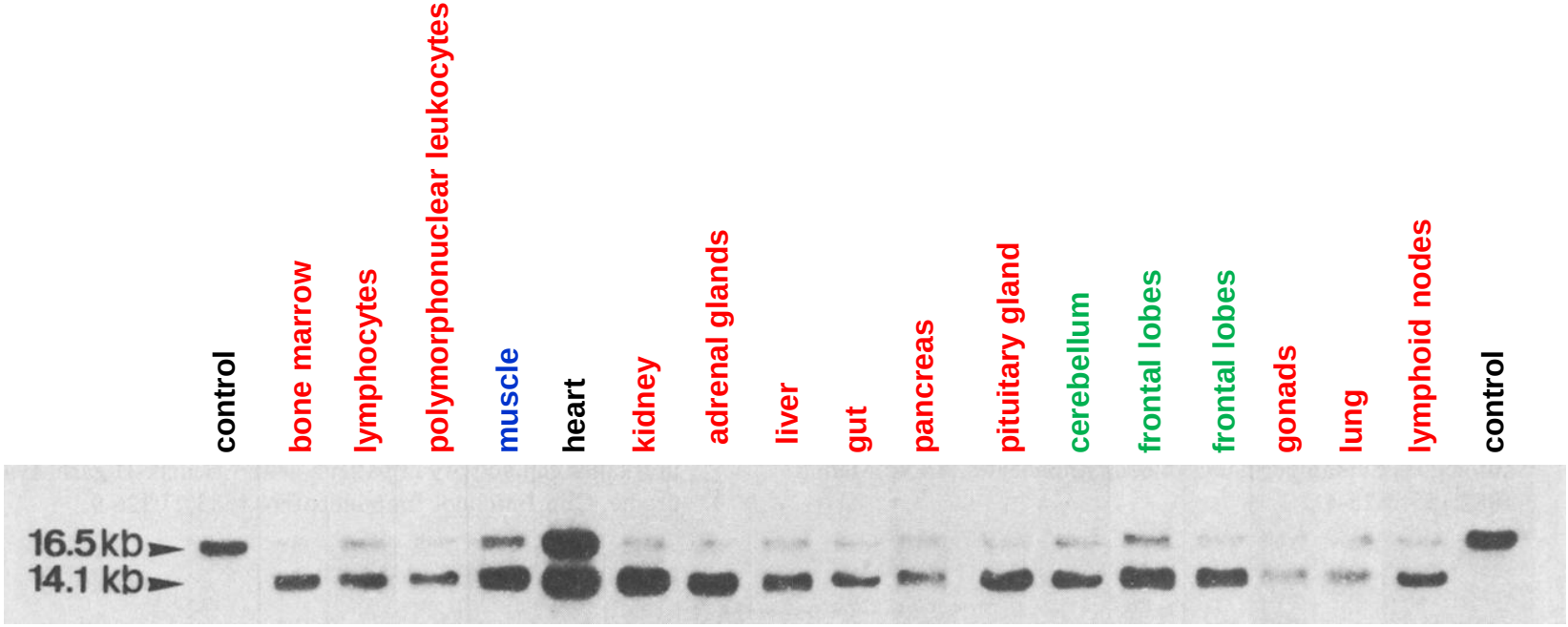
Onset symptom :

Anemia	**50%**
Diarrhea	**50%**

Clinical course

- **50% died of the Pearson syndrome (3 mths - 3 yrs)**
- **50% developed Kearns-Sayre syndrome by the age of 4 yrs**

Tissue heteroplasmy in a patient with Pearson's syndrome



deleted mtDNA amount

90%

80%

60%

40%

(Cormier et al, 1990)

mtDNA deletions in Pearson syndrome

Common deletion

ATP8 — 4978 bp — **ND5**

nt 8469 | *A CCT CCC TCA CCA AAG ……TCA* | nt 13447

5’…AAC TAC CAC CT *A CCT CCC TCA CCA AAG ……TCA* ACC TCC CTC ACC ATT GGC…3’

tRNA^{Gly} — 5902 bp — **tRNA^{Thr}**

nt 9995 | *T TTTAGTATAAATAG ……TGTCCTTGTA* | nt 15897

5’…GAGGGTCTTACTC *T TTTAGTATAAATAG ……TGTCCTTGTA* GTATAAACCTAATAC…3’

ND4 — 2748 bp — **ND5**

nt 11232 | *T CCC CTA CTC AT……AAC CT* | nt 13980

5’…GGC TCC CT *T CCC CTA CTC AT……AAC CT* G CCC CTA CTC C…3’

ND4L — 4191 bp — **CYTb**

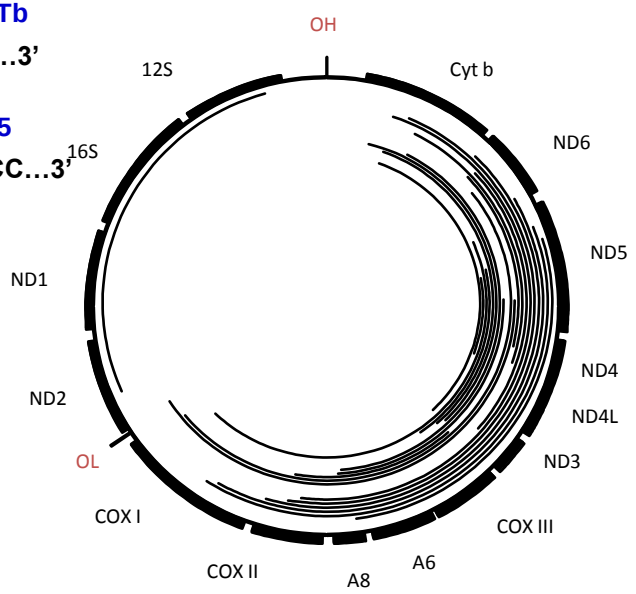
nt 10665 | *TT GCG CCT GCG AA……CTC C* | nt 14856

5’…ATA CTA GTC T *TT GCG CCT GCG AA……CTC C* TT GGC GCC TGC CTG ATC…3’

ND3 — 3563 bp — **ND5**

nt 10190 | *TCC CCC GCC GCG…….AAC AAC ATT* | nt 13753

5’…TC GAC CCT ATA *TCC CCC GCC GCG…….AAC AAC ATT* TCC CCC GCA TCC CCC…3’

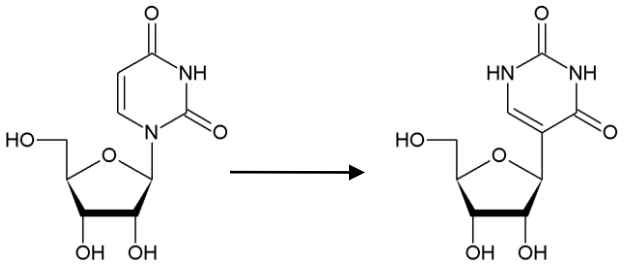


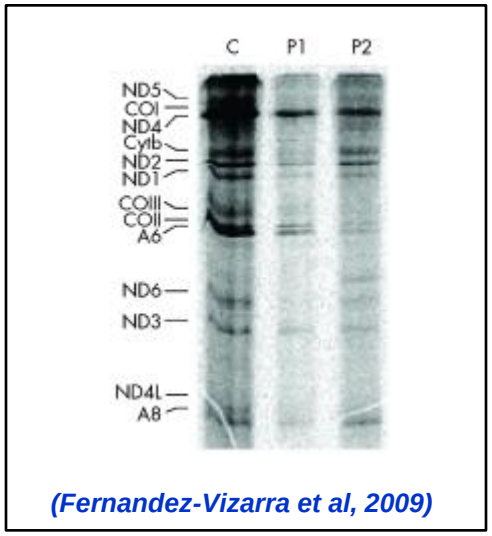
Myopathy, Lactic Acidosis, Sideroblastic Anemia MLASA syndrome

Myopathy, lactic acidosis, and sideroblastic anemia with ringed sideroblasts
Multiple RC deficiency (muscle and fibroblasts)

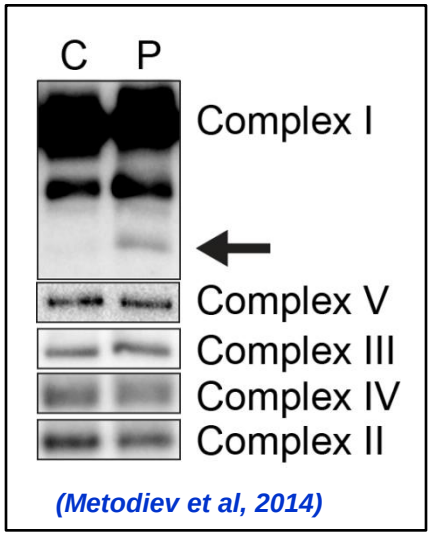
PUS1, tRNA pseudouridylate synthase 1

$tRNA^{Lys}$, $tRNA^{Ser,}$ $tRNA^{Ile}$





(Fernandez-Vizarra et al, 2009)



(Metodiev et al, 2014)

Phenotypic variability

Girl born to consanguineous Turkish parents

1 yr:	sideroblastic anemia, chronic diarrhea
	CI+IV deficiency in muscle
4 yrs:	growth retardation
	no myopathy, very few RRF,
	no metabolic acidosis
	mild intellectual disability
26 yrs:	moderate muscle weakness

Homozygous PUS1 mutation (c.883 C>T, p.Arg295Trp)

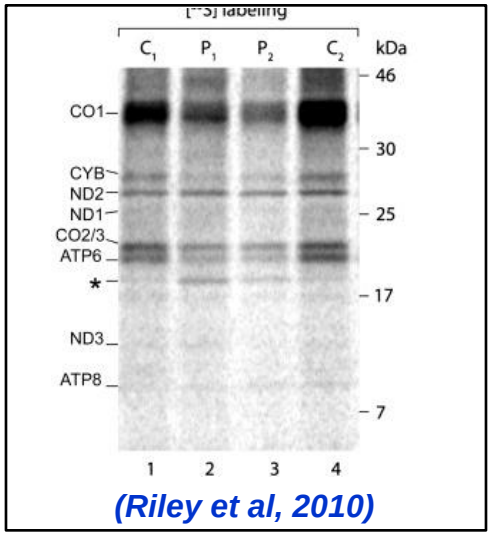
(Metodiev et al, 2014)

Myopathy, Lactic Acidosis, Sideroblastic Anemia
MLASA syndrome

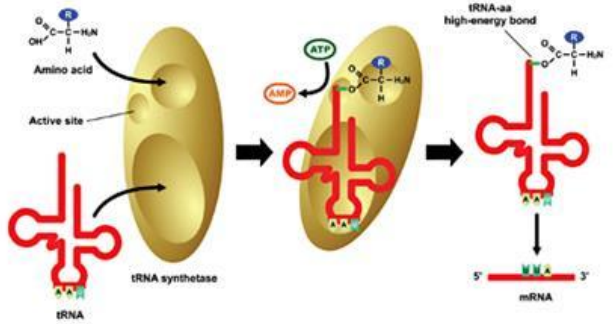
Myopathy, lactic acidosis, and sideroblastic anemia with ringed sideroblasts
Multiple RC deficiency (muscle and fibroblasts)

YARS2, mitochondrial tyrosyl-tRNA synthetase

reduced aminoacylation activity
decreased mitochondrial protein synthesis
mitochondrial respiratory chain dysfunction



(Riley et al, 2010)



Phenotypic variability
- late transfusion dependency
- hypertrophic cardiomyopathy
- delayed motor milestones
-no skeletal myopathy

(Shahni et al, 2013;
Riley et al, 2013)

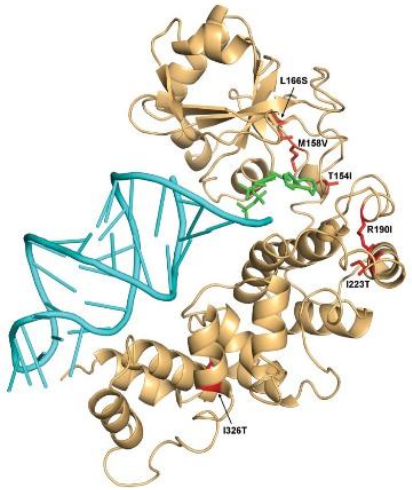
TRNT1 mutations in SIFD

Sideroblastic anemia
Immunodeficiency
Fevers
Developmental delay

sensorineural hearing loss
cardiomyopathy
central nervous system abnormalities

16 patients from 14 families
(Chakraborty et al, Blood 2014)

TRNT1: **CCA-adding enzyme to the 3′ end of all tRNA molecule**
necessary for tRNA aminoacylation
maturation of both cytosolic and mitochondrial tRNAs



2 sibs (Necker)
sideroblastic anemia
failure to thrive
watery diarrhea
metabolic acidosis
normal RC activity in muscle and fibroblasts

ABCB7 mutations in XLSA/A

X-linked sideroblastic anemia and ataxia

Infantile to early childhood onset
Non-progressive cerebellar ataxia
Mild anemia not requiring transfusion with hypochromia and microcytosis

ABCB7 mutations
putative mitochondrial iron transporter
(Allikmets et al, 1999)

Yeast orthologue: Atm1p

Mitochondrial inner membrane
Accumulate high levels of iron in mitochondria
Maturation of cytosolic iron-sulfur (Fe/S) cluster-containing proteins
(Bekri et al, 2000)

Abcb7 mutations directly or indirectly inhibit heme biosynthesis
(Pondarre et al, 2007)

Barth syndrome

X-linked disease
dilated cardiomyopathy
proximal skeletal myopathy
growth retardation
cyclic neutropenia
excess of 3-methylglutaconic acid
multiple RC deficiency in muscle

TAZ, tafazzin mutations
1-acylglycerophosphocholine O-acyltransferase
cardiolipin remodelling

Diagnosis:
- male with cardiomyopathy
- methylgutaconic aciduria
- cardiolipin measurement on fibroblasts
- TAZ sequencing

Mitochondrial proteins and anemia