Klinische Präsentation und Behandlung von Patienten mit Morbus Pearson

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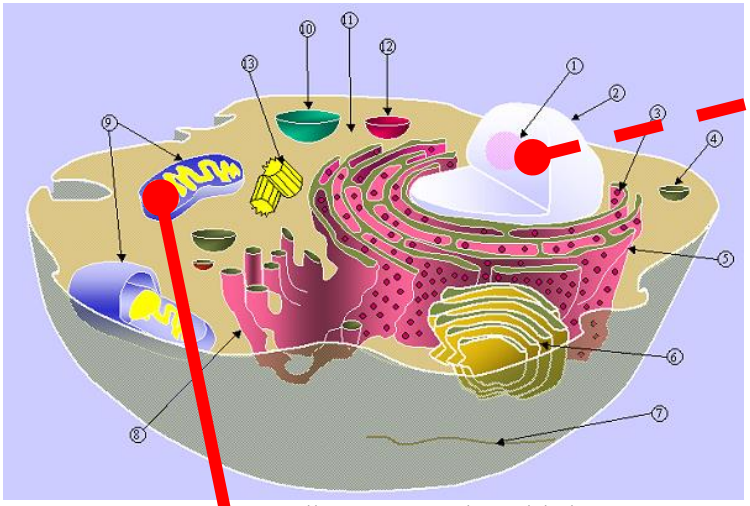
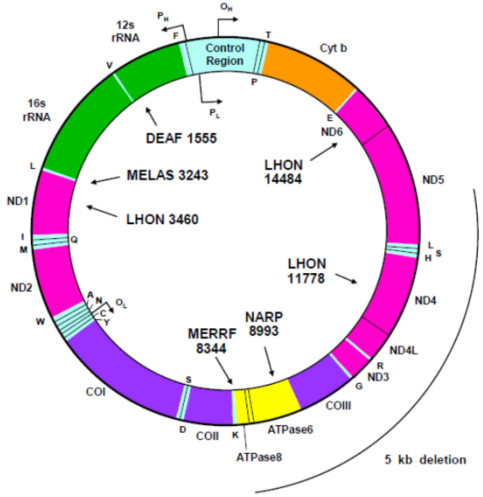
We have two genomes



http://www.pflegewiki.de/images/6/63/Biological_cell.png

Nuclear DNA

47000000 base pairs



Mitochondrial DNA (mtDNA) 16600 base pairs

Total 37 genes

13 essential polypeptides of the respiratory chain complexes

2 ribosomal RNAs

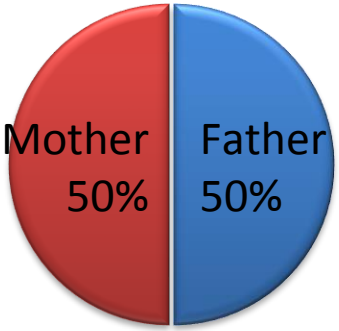
22 transfer RNAs

http://www.mitomap.org/pub/MITOMAP/MitomapFigures/mitomapgenome.pdf

Rules of mitochondrial DNA

- Maternal inheritance

Nuclear DNA

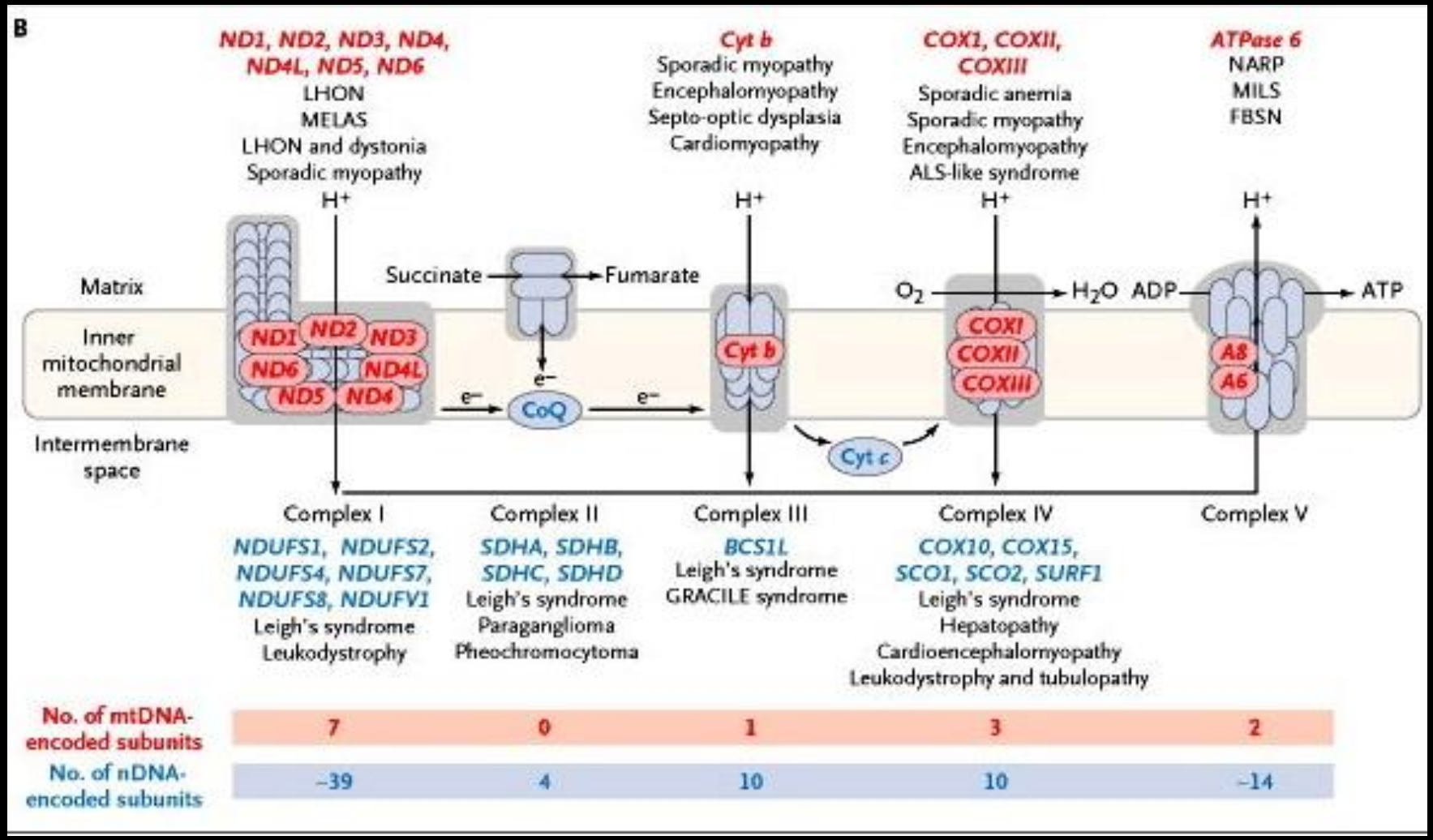


Mitochondrial DNA

Rules of mitochondrial DNA

- Maternal inheritance
- Dual genetic control of mitochondria by both nuclear and mitochondrial DNA

Mitochondrial Respiratory Chain

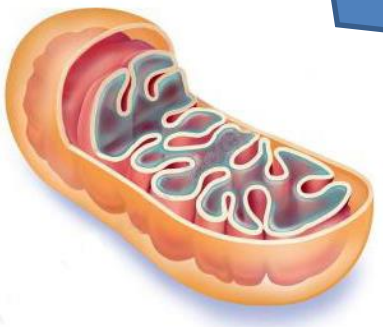


DiMauro S, Schon EA. N Engl J Med 2003;348:2656-2668.

Mitochondria related genes on nuclear DNA

- Some subunits of the respiratory chain complexes
- mtDNA replication, transcription, repair
- Mitochondrial Biogenesis
- Assembly of the OXPHOS complexes
- Synthesis of cofactors
- Translation of the 13 OXPHOS subunits of mitochondrial synthesis

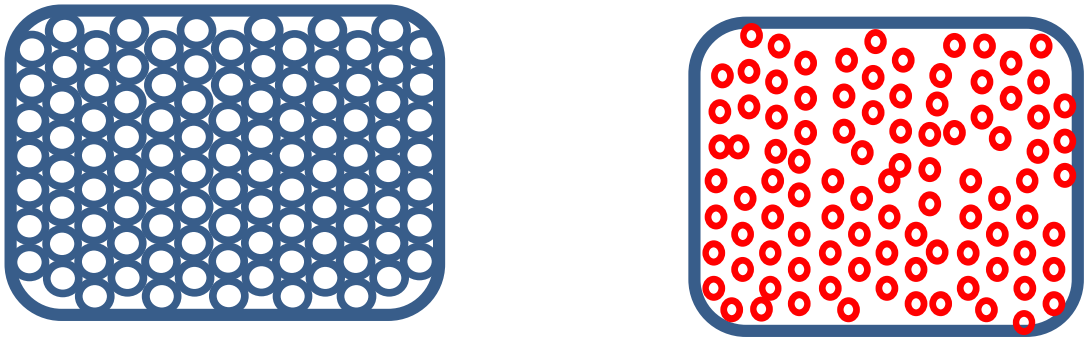
>1400 genes



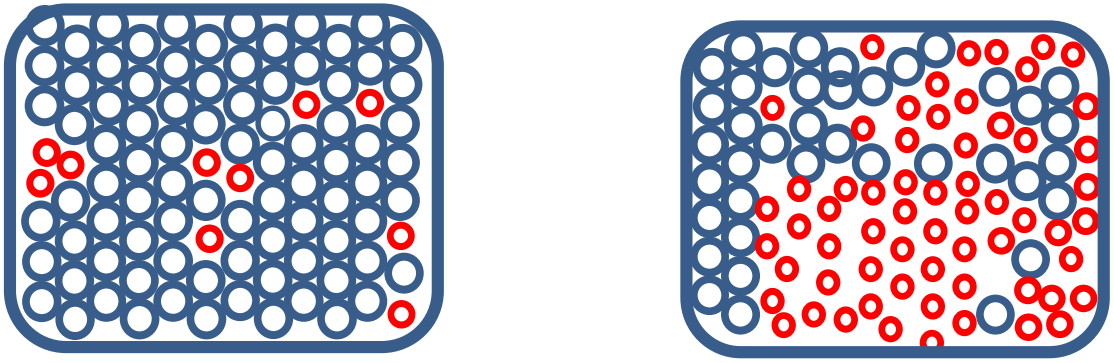
Rules of mitochondrial DNA

- Maternal inheritance
- Dual genetic control of mitochondria by both nuclear and mitochondrial DNA
- Heteroplasmy
- Threshold effect

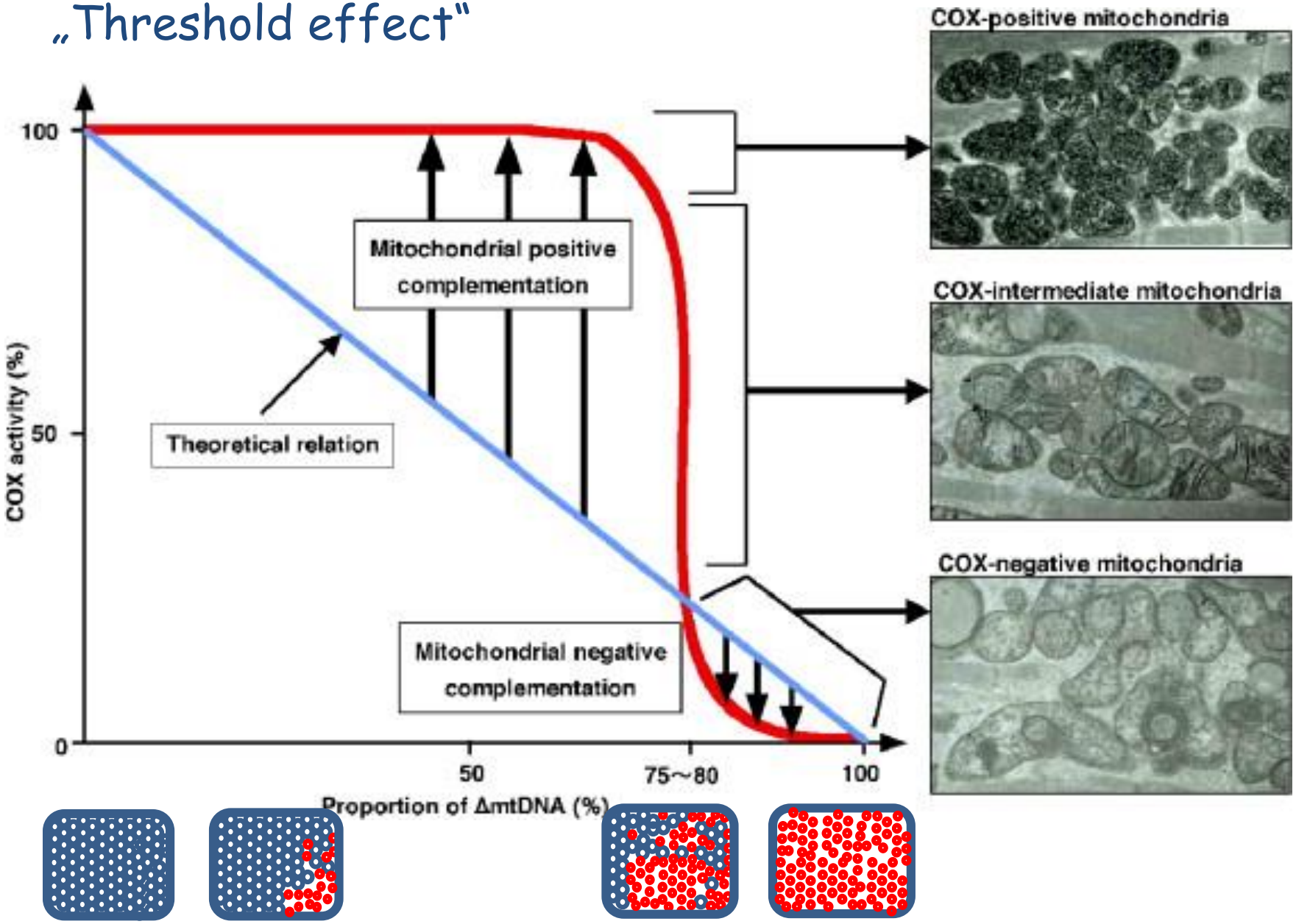
Homoplasmy



Heteroplasmy



„Threshold effect“



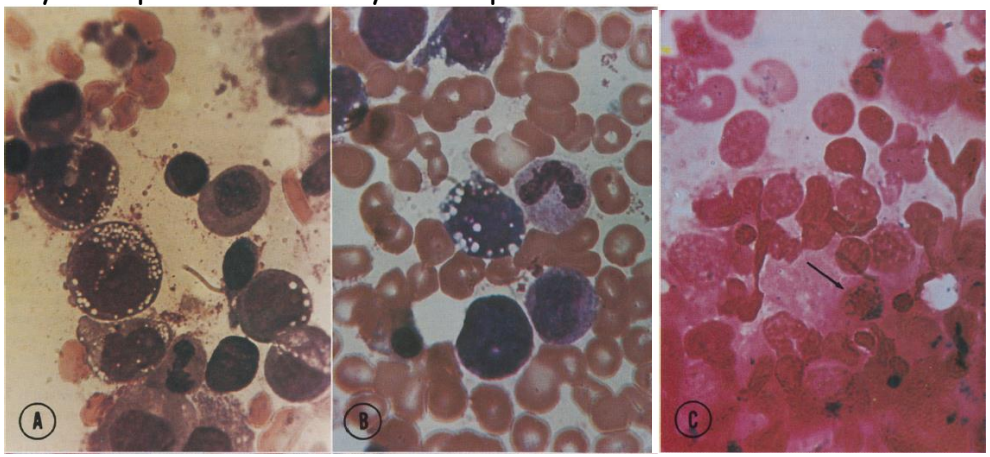
Nakada , et al, The International Journal of Biochemistry & Cell Biology, 2009

First report by Howard Pearson

A new syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction

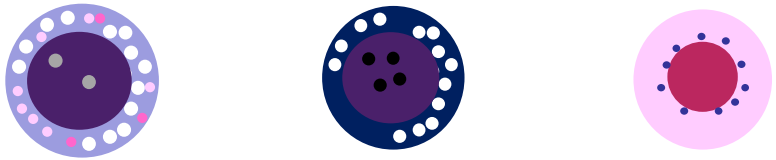
Pearson, Journal of Pediatrics, 1979

myeloid precursors erythroid precursors



Vacuolization

Ringed sideroblasts



4 patients age 0-16 months

All patients had neutropenia

3 patients had thrombocytopenia

Two patients died:

- acidosis + hepatic failure at 20 months
- sepsis at 26 months

Two patients had spontaneous improvement of anemia

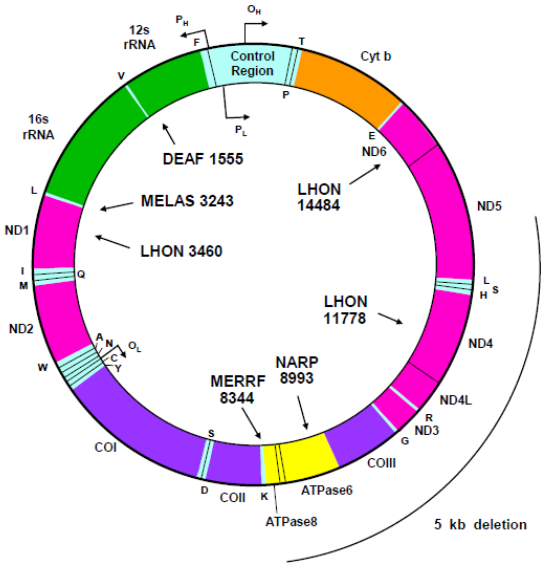
Deletion of Blood Mitochondrial DNA in Pancytopenia

Rötig, et al Lancet 1988

Site-Specific Deletions of the Mitochondrial Genome in the Pearson Marrow–Pancreas Syndrome

AGNÈS RÖTIG, VALÉRIE CORMIER, FRANCE KOLL, CHARLES E. MIZE,* JEAN-MARIE SAUDUBRAY, ANJO VEERMAN,† HOWARD A. PEARSON,‡ AND ARNOLD MUNNICH

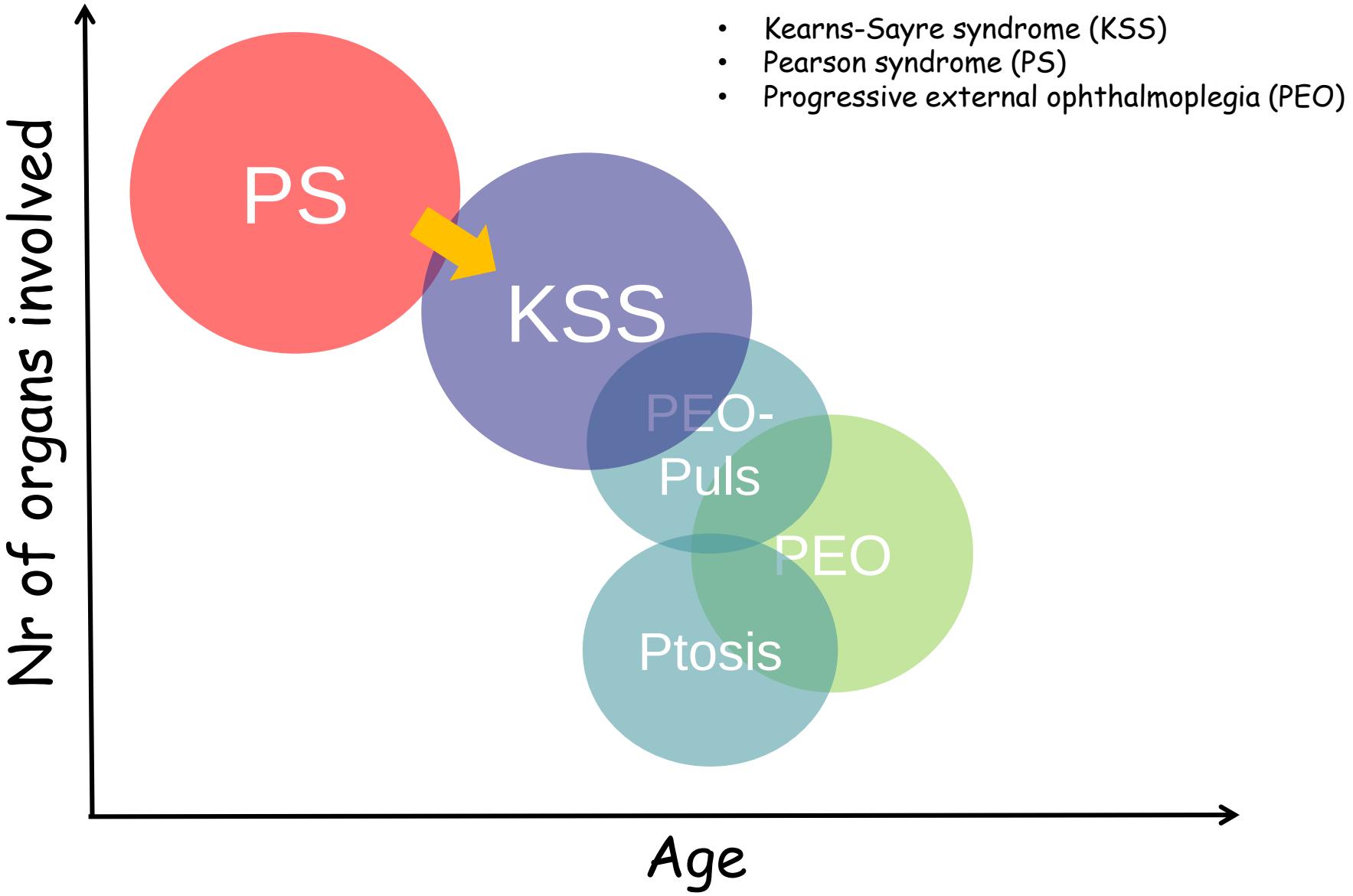
Rötig, et al Genomics 1991



m.8470_13446del4977
„common deletion"

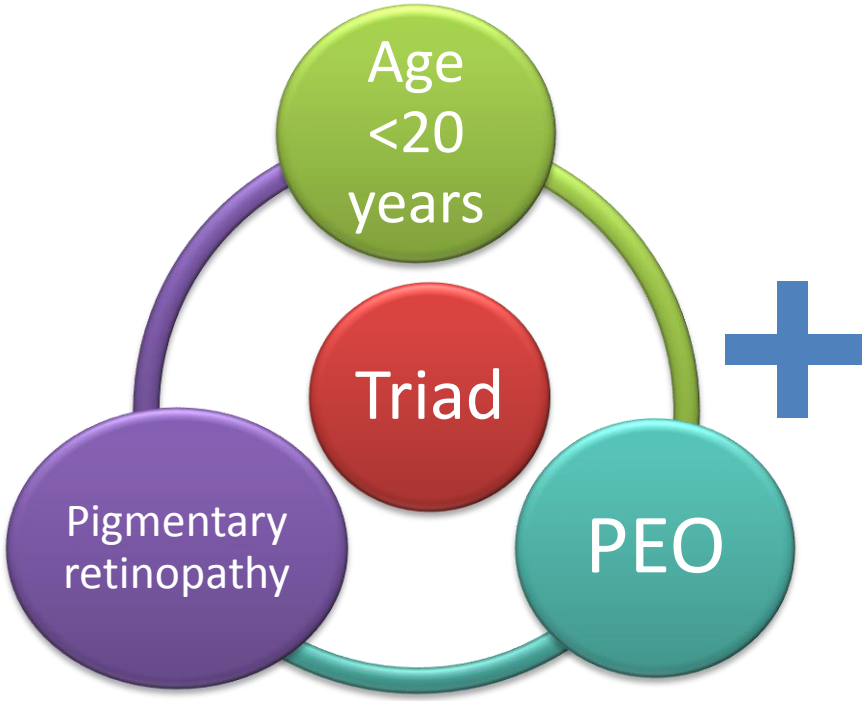
http://www.mitomap.org/pub/MITOMAP/MitomapFigures/mitomapgenome.pdf

Pearson syndrome belongs to the spectrum of diseases with single large mitochondrial DNA deletion



- Kearns-Sayre syndrome (KSS)
- Pearson syndrome (PS)
- Progressive external ophthalmoplegia (PEO)

Kearns-Sayre syndrome (KSS)



at least one of the followings

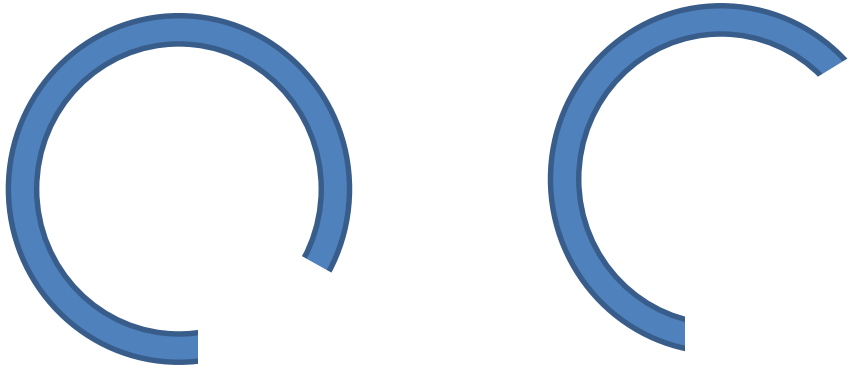
- ☑ Cardiac conduction block
- ☑ Elevated CSF protein concentration (>100 mg/dL)
- ☑ Cerebellar ataxia

CSF: cerebrospinal fluid protein
PEO (progressive external ophthalmoplegia)

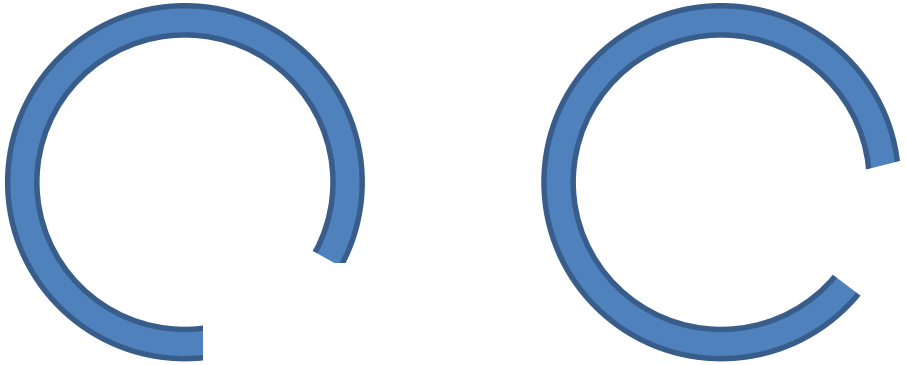
Why does same mitochondrial DNA deletion cause different diseases (PS, KSS, PEO)?

Size of deletion?

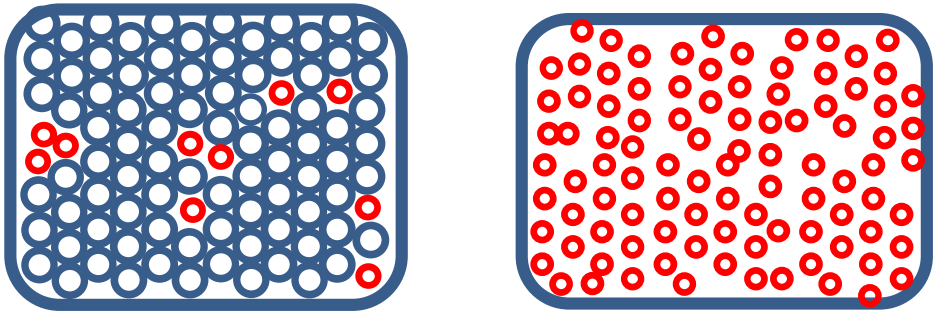
two to ten kb



Place of deletion?



Load of mutants? (heteroplasmy status)



High % of deleted mtDNA in Pearson syndrome

Table 4. Percentages of deleted mtDNA of the total amount of mtDNA per tissue

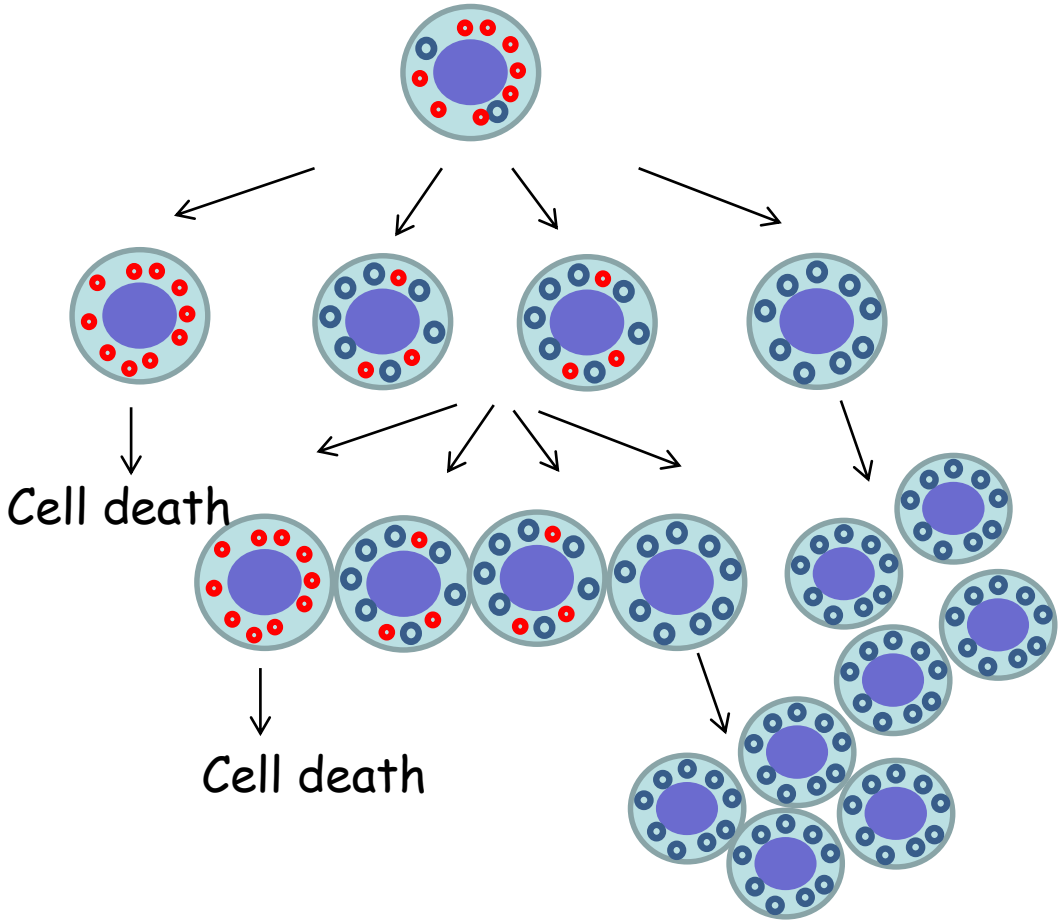
Tissue	% deleted mtDNA		Tissue affected	
	Present patient*	Lit.‡	Present patient†	Lit.§
Lung	76	90	−	−
Pancreas	88	90	−	+
Liver	>99	90	±	+
Small intestine	81	90	+	+
Large intestine	64			
Spleen	89			
Musculus psoas	67			
Musculus intercostalis	56			
Musculus quadriceps	82	40–60	+	+
Musculus diaphragm	66			
Kidney	94	90	−	+
Blood	91	90	+	+
Heart muscle	58	40–60	−	−

*The percentage of deleted mtDNA and †the involvement of the various tissues of our Pearson patient were compared with ‡the values and §biochemical and clinical data reported by Cormier *et al.* [7].

De Vries 1992

Why does anemia spontaneously improve in PS?

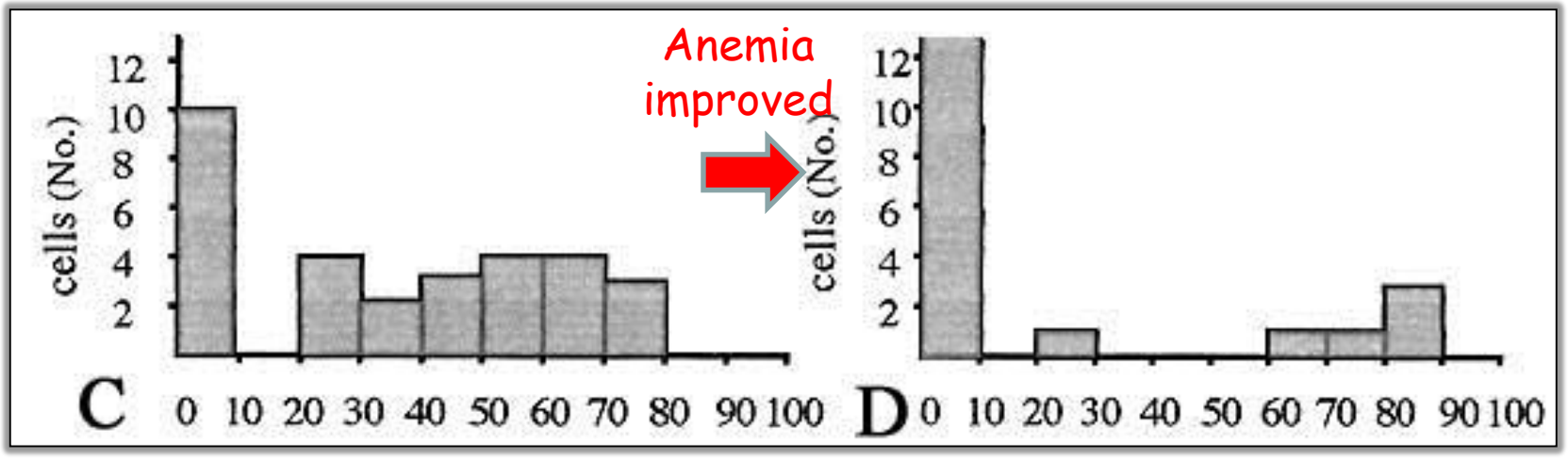
Hypothesis: depletion of cells with high proportion of mtDNA in highly proliferative tissues

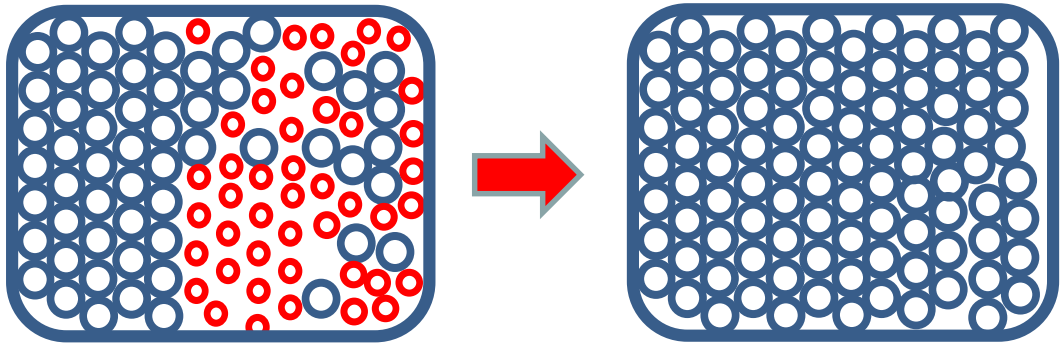


Heteroplasmic status in peripheral blood cells in PS patient

Pt 2: 7 months after onset

Pt 2: 13 months after onset

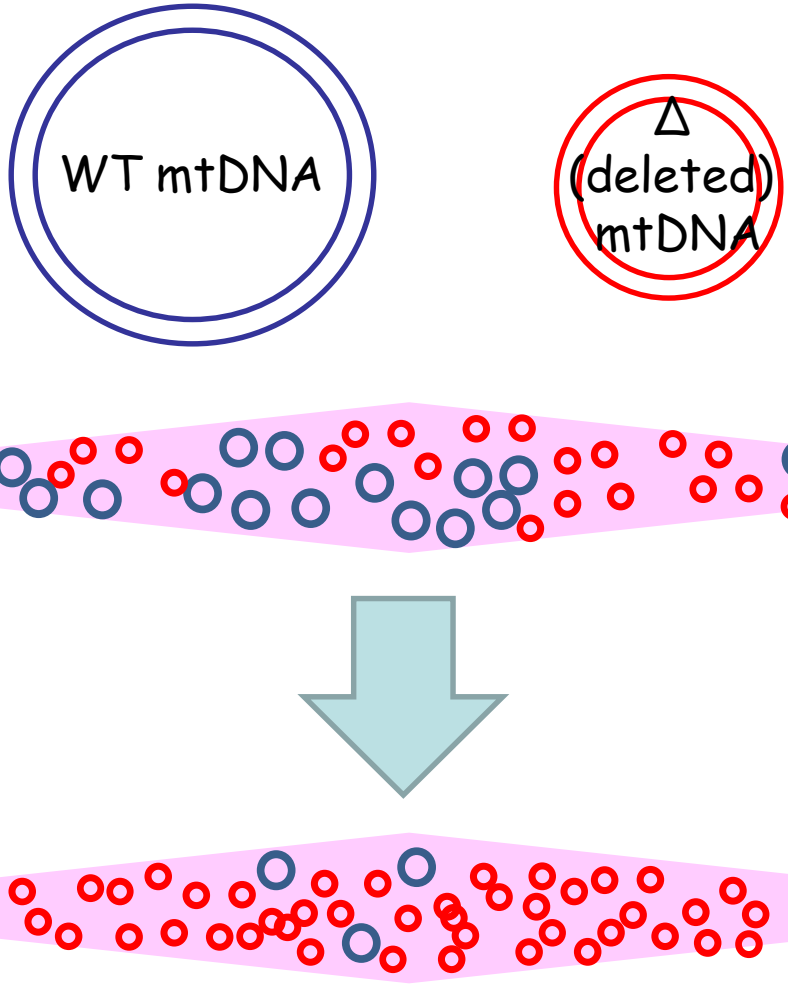




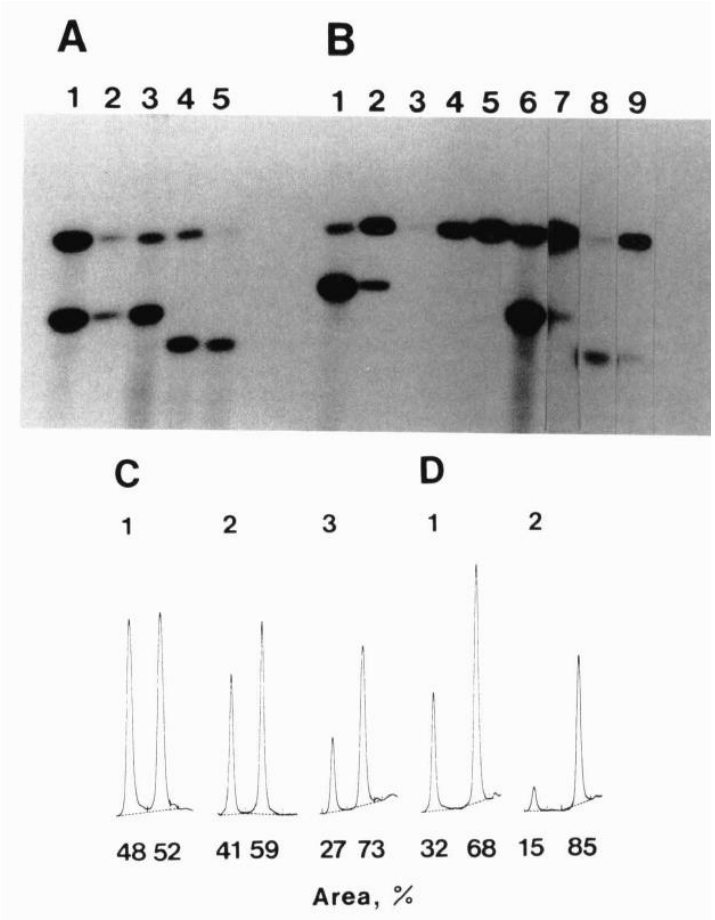
Midified of Yanagihara, The Journal of Pediatrics, 2001
Fluorescence in situ hybridization analysis of peripheral blood cells in Pearson marrow-pancreas syndrome

Why do same patients with PS develop KSS later?

Hypothesis: replication advantage of ΔmtDNA results in accumulation of ΔmtDNA in post-mitotic cell



Increased proportion of ΔmtDNA in muscles in patients with KSS



% ΔmtDNA in muscles

Case 1

Disease Progress

52% 14y → 59% 16y → 80% 17y

Case 2

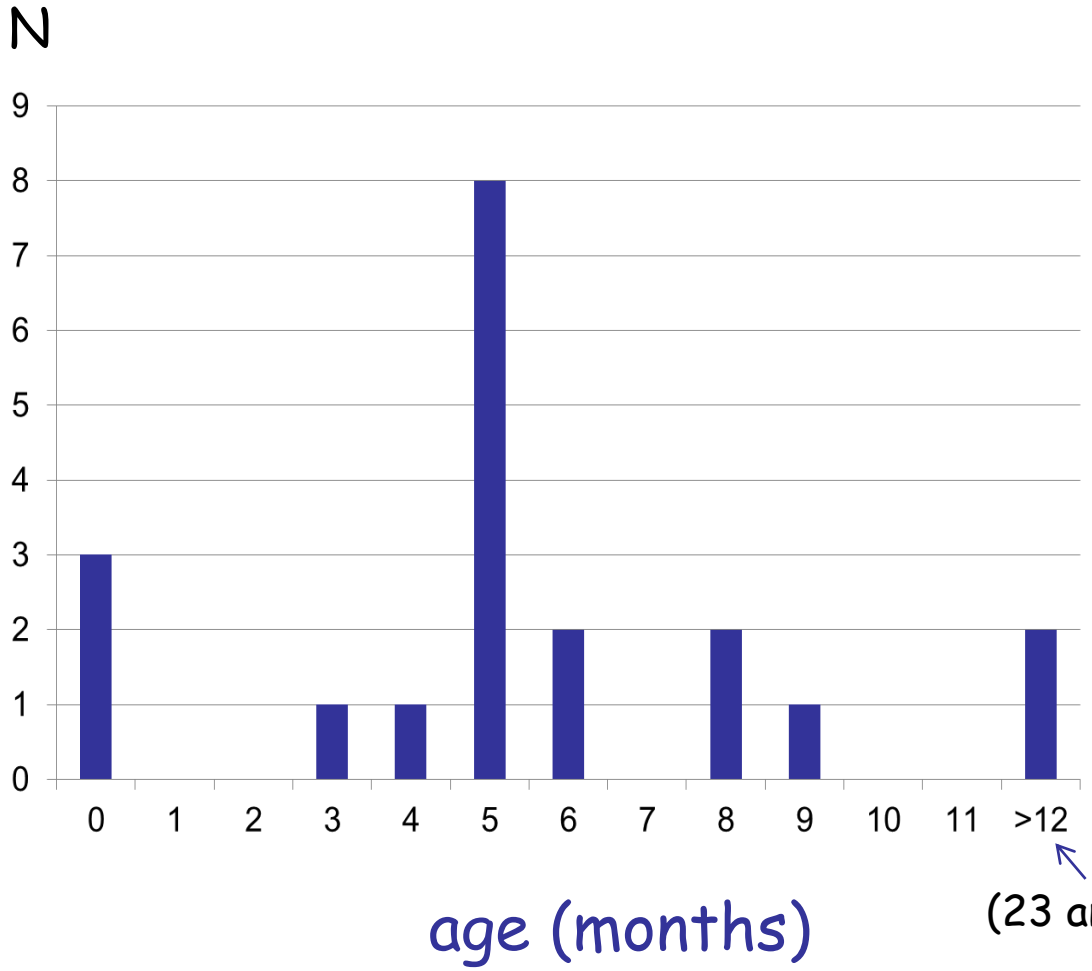
Disease Progress

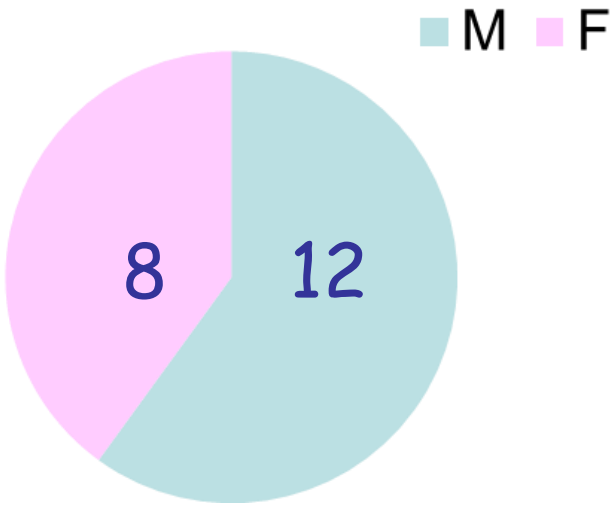
60% 14y → 82% 19y

Larsson 1990 Pediatric Reseach

20 Patients with PS diagnosed in Germany

Age at onset and sex





Clinical symptoms at diagnosis

- Anemia n=20 -> no other symptoms in 12 pts
- Failure to thrive (n=5)
- Diarrhea due to pancreas insufficiency (n=1)
- Malformation (n=1)
- Mild muscle hypotonia (n=3)

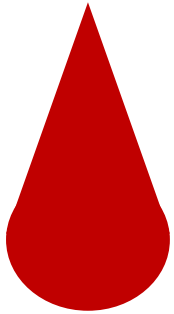
No family history (sporadic) (n=20/20)

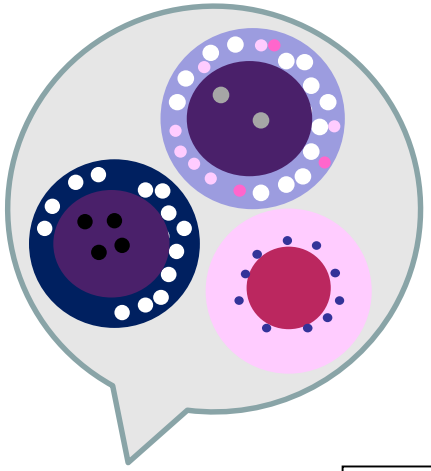
Diagnostic Steps

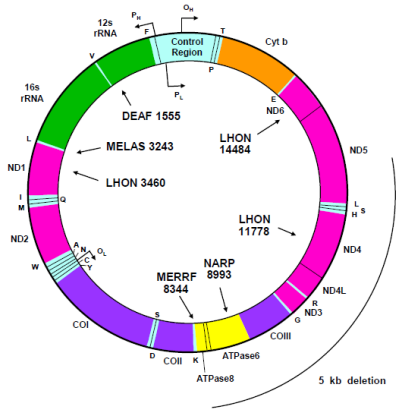
Blood test

Bone marrow
+ iron staining

Genetic test
Mitochondria DNA
Long range PCR, southern blot







- CBC with a reticulocyte count and MCV
- HbF
- Blood gas
- Lactic acid/pyruvate

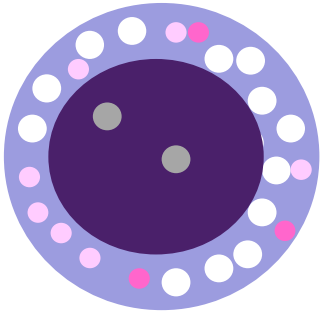
- Liver function
- Pancreas enzyme
- Urine (tubulopathy)
- EKG/cardiac ultrasound
- Ultrasound abdomen

Laboratory Findings at Diagnosis (n=20)

Median Hb (g/dl, range)	5.9 (2.2-9.8)
Median neutrophil count (G/L, range)	0.9 (0.1-2.4) (normal: n=5)
Median platelet count (G/L, range)	116 (31-300) (normal: n=5)
MCV (normal/ elevated /uk)	4/12/4
Hb F (normal/ elevated) (n=9)	1/8
Lactic acid (normal/ elevated) (n=15)	3/12

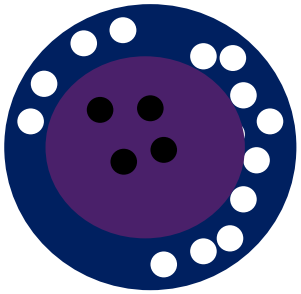
Bone Marrow Features

Vacuoles
in myelocytes



20/20 (100%)

Vacuoles
in erythroblasts

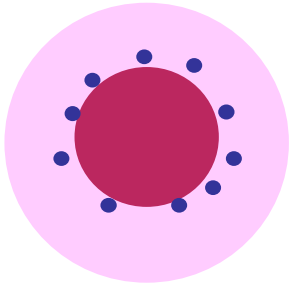


20/20 (100%)

Othere features

- Micromegakaryocytes 4/20 (25%)
- Hypoplastic erythropoesis
- Macrocytosis of erythroblasts
- Left shift of
- erythro-/myelopoiesis

Ringed sideroblasts



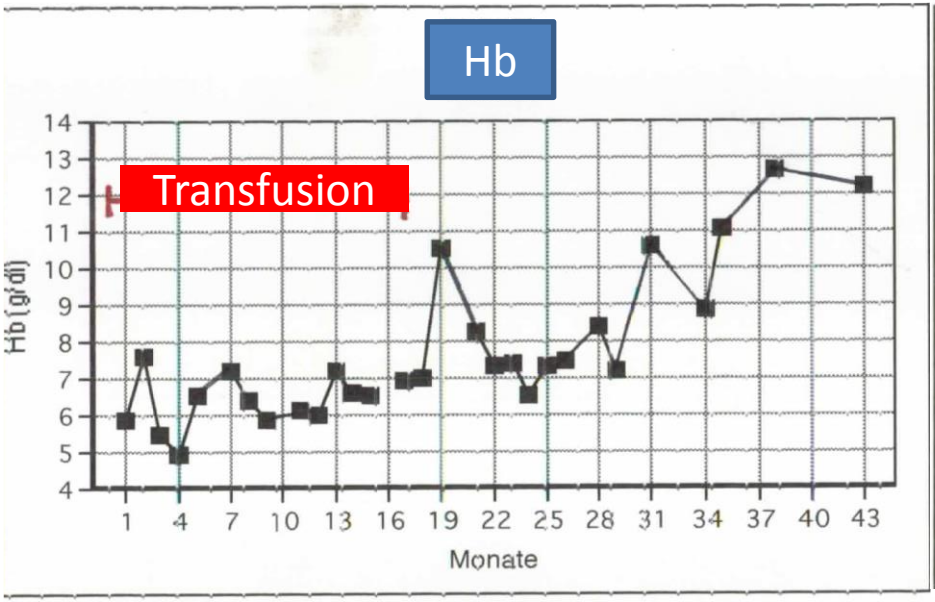
13/19 (68%)

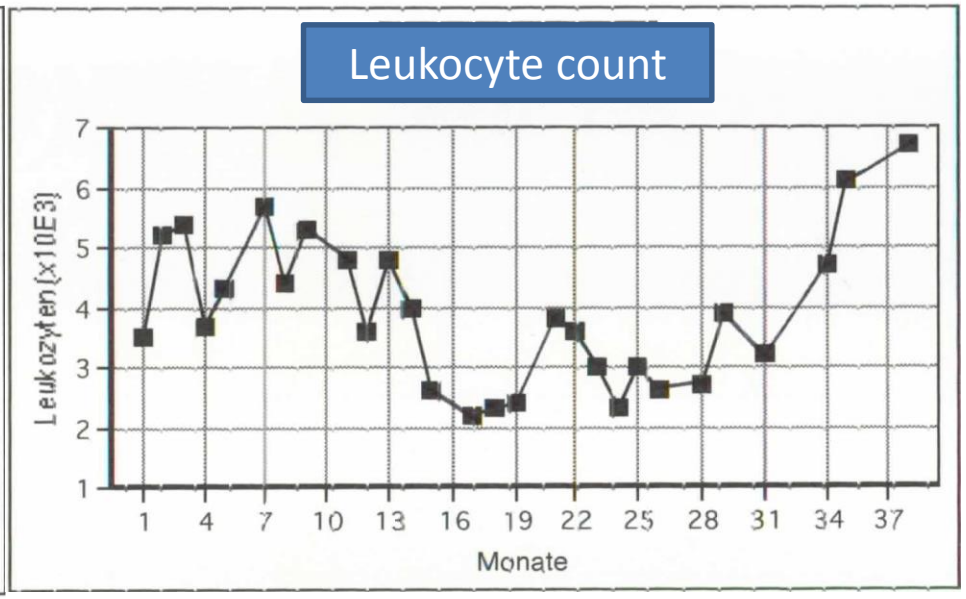
mtDNA Analysis

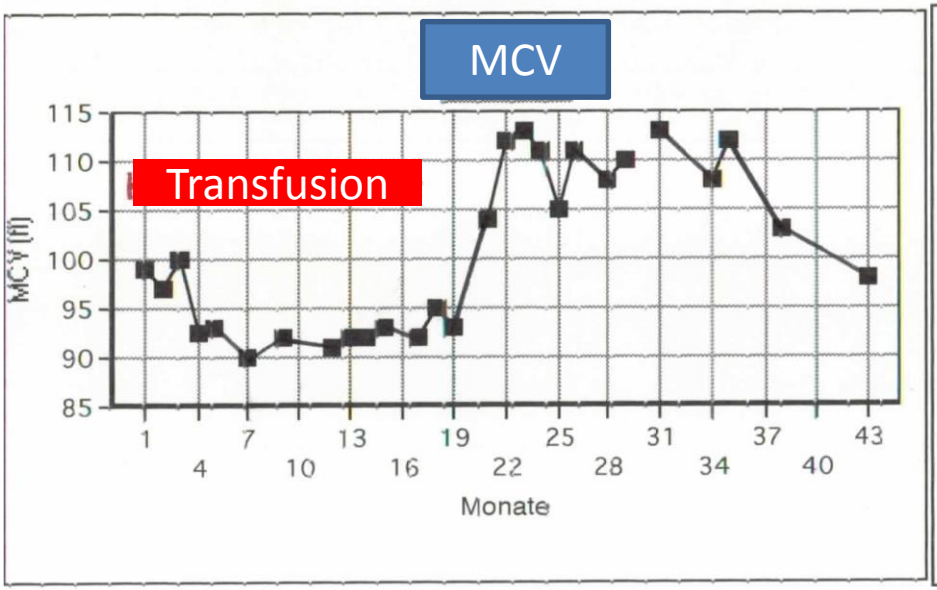
Samples: blood cells
Methods: Southern blot + long PCR

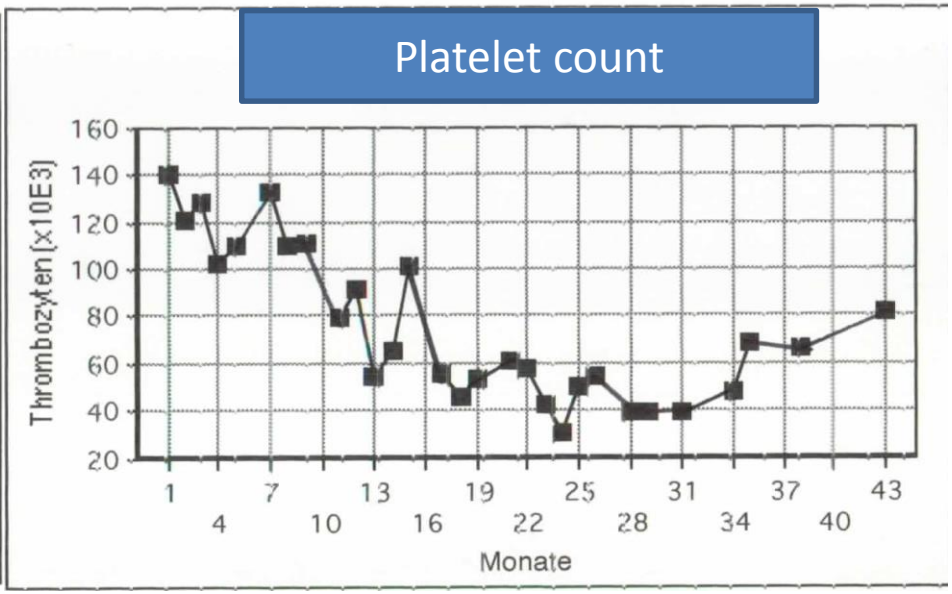
Detection of mtDNA deletion	20/20, 1 had also duplication
Size of deletion (n=16)	3500-6500 bp
% of deleted mtDNA (n=9) 50% 70-80% 80-90% >90%	 1 5 2 2

Hematological Improvement

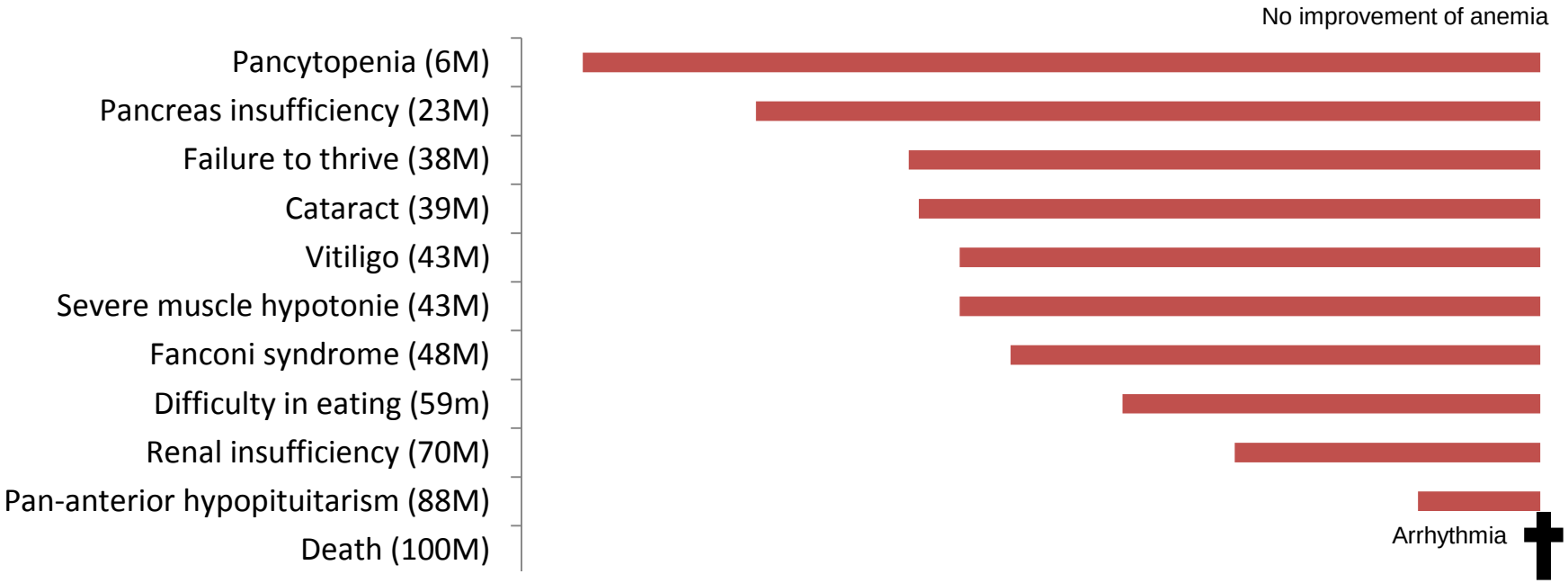


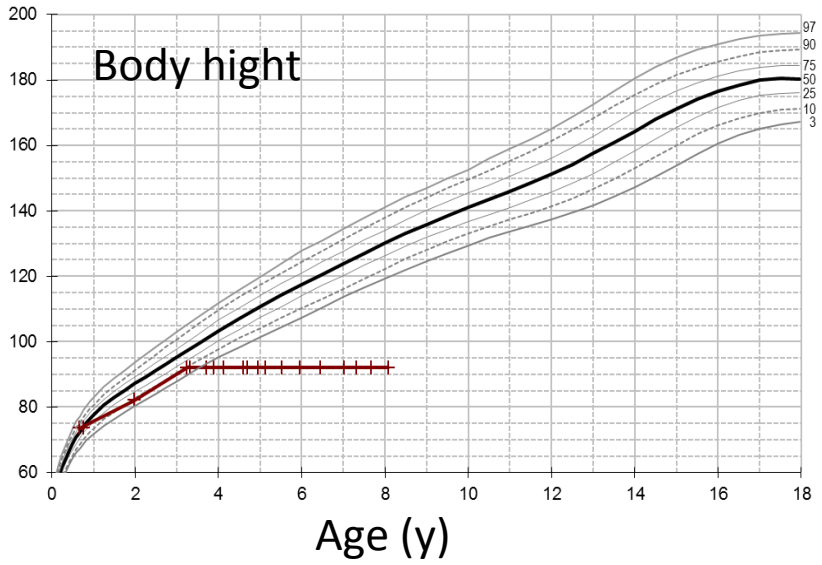


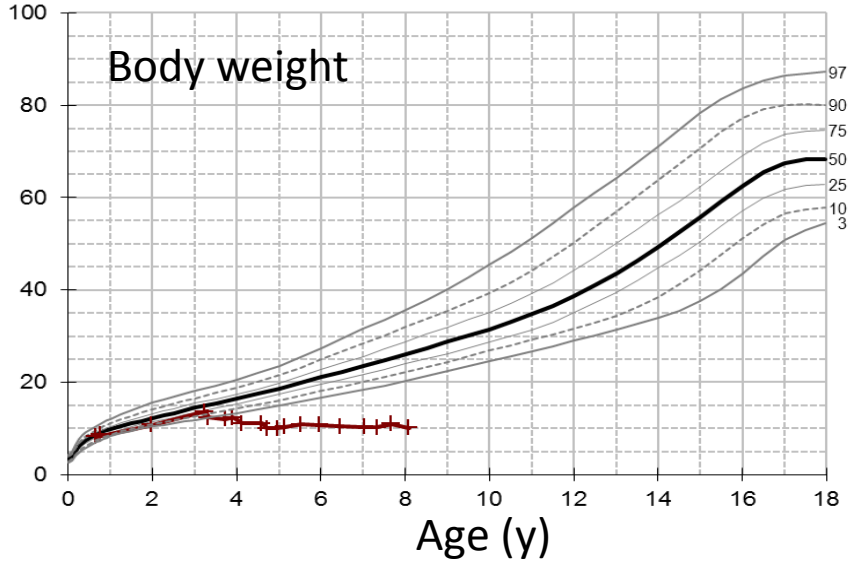




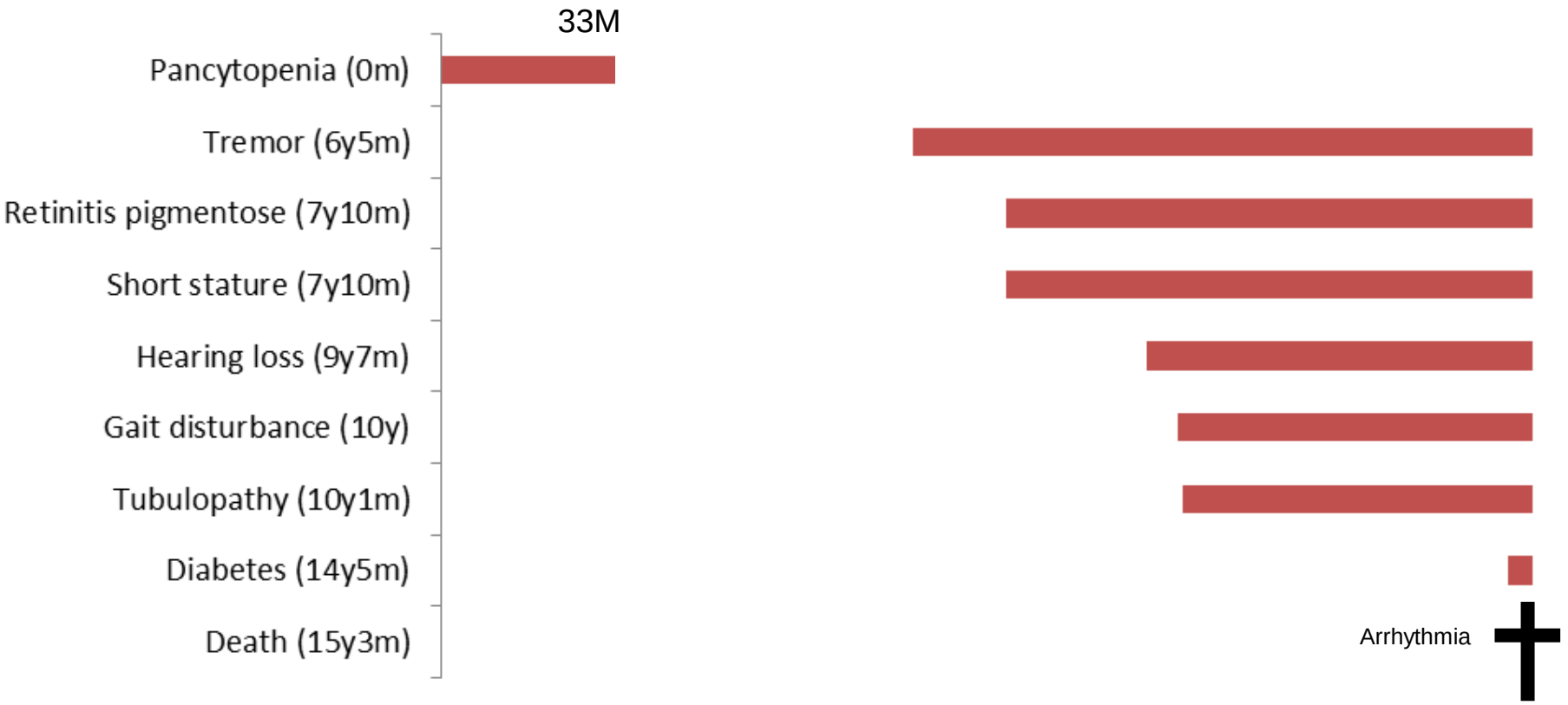
Clinical Course of a Patient with PS







Clinical Course of the Longest Survivor

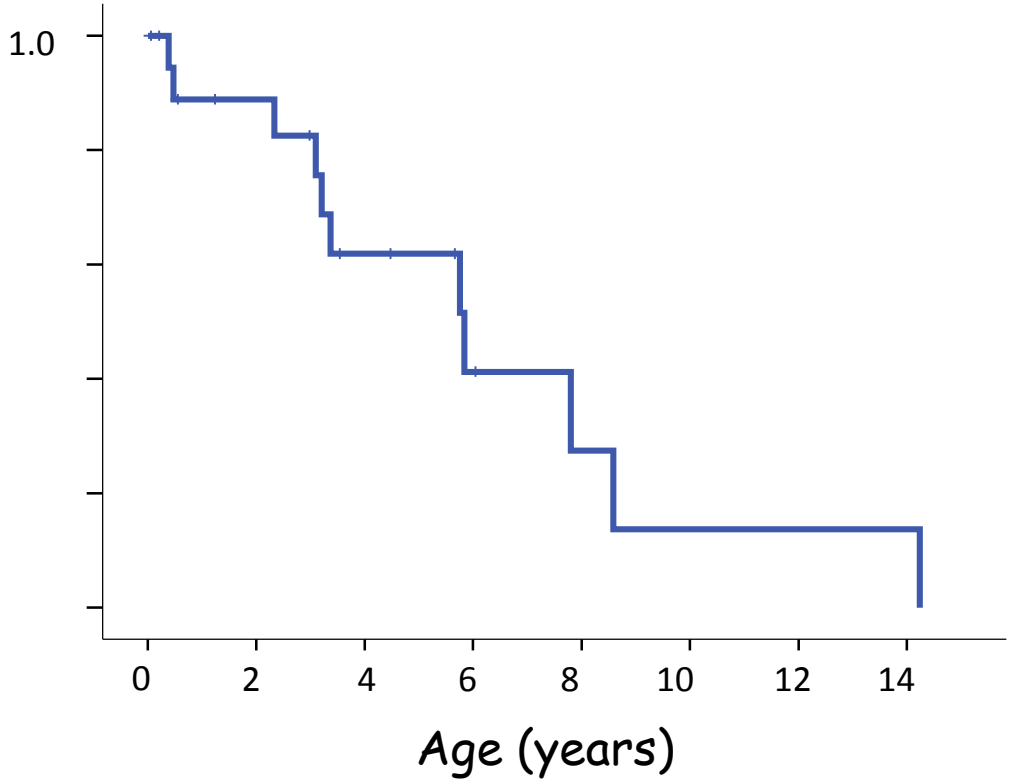


Complications during the follow-up (n=20)

Med FU 48 mo (7 - 183mo)

Symptoms/Organ failures	n	Median age at presentation (range, months)
Pancreas insufficiency	6	13 (10-30)
Diabetes	1	19
Ophthalmoplegia	1	19
Liver dysfunction	4	21 (13-30)
Failure to thrive/short stature	13	22 (7-92)
Muscle hypotonia	7	31 (7-77)
Tubulopathy/Fanconi syndrome	5	32 (21-121)
Cataract	3	30, 39, 72
Endocrine dysfunctions (other than diabetes)	4	63 (26-96)
Arrhythmia/cardiac disease	5	66 (31-183)
Ataxia	2	31, 147
Encephalopathy	1	74
Retinitis pigmentosa	1	92
Hearing loss	1	115

Survival of Patients with PS (n=20)



Cause of death (n=10)

- Acute metabolic acidosis (n=4) (with pneumonia: n=1)
- Arrhythmia (n=2)
- Hepatic/renal failures (n=1)
- Pneumonia (n=1)
- Cerebral infarction/ Leigh disease (n=1)
- Unknown (n=1)

Med FU 48 m (7 - 183m)

10 patients are alive : median age of 45 m (7 - 96 m)

10 patients died: median age of 49 m (14 - 183m)

Symptomatic Therapy in Pearson Syndrome

AV-block
->pacing machine

Ptosis, cataracts
->operation

Physiotherapy

Fanconi syndrome
->substitution of electrolytes

Hormone deficiency
->substitution

Pancreas insufficiency
-> substitution of enzyme
Diabetes mellitus
->insulin

Dysphagia/ failure to thrive
-> PEG-tube/ parenteral feeding

Pancytopenia
->transfusions/G-CSF

Hearing loss
-> cochlear implant

Pharmacological Therapy

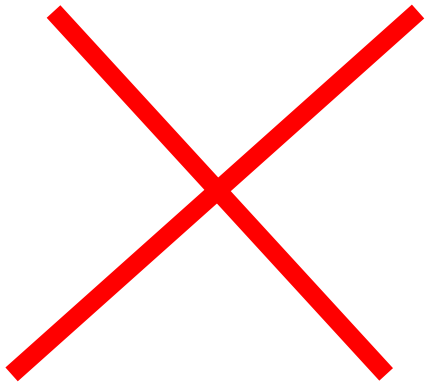
- "Cocktail" of some respiratory chain cofactors, vitamins and antioxidant*

  eg. Coenzyme Q10*, riboflabin (B2), thiamine (B6), vitamin C, vitamin K, biotin, carnitine*, creatine*, vitamin E*, succinate, EPI-743, Idebenone

- Drugs that reduce lactic acid accumulation (dichloroacetate)

Avoid drugs which may interfere with respiratory chain function

valproic acid



tetracyclines

chloramphenicol

Research of Novel Treatments

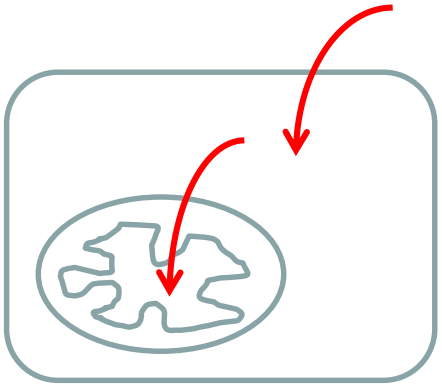
Gene therapy

Nuclear DNA

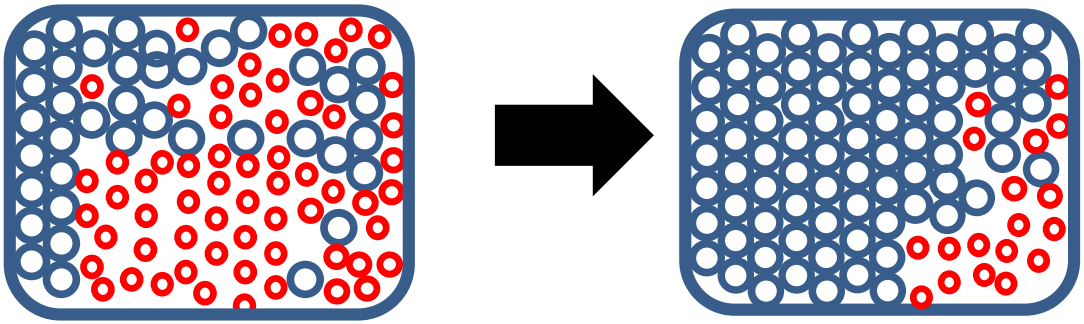
Different approaches

Mitochondrial DNA

More challenging



Gene shifting



pharmacological approaches
dietary manipulation
exercise therapy

Acknowledgement

University Medical Center Ulm

Holger Cario

University of Erlangen

Markus Metzler

Heinrich Heine University, Duesseldorf

Michaela Kuhlen, Arndt Borkhardt

Aachen University Medical School

Udo Kontny

Nagoya University, Japan

Kyogo Suzuki

Olgahospital, Stuttgart

Ute Groß-Wieltsch, Stefan Bielack

University of Freiburg

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