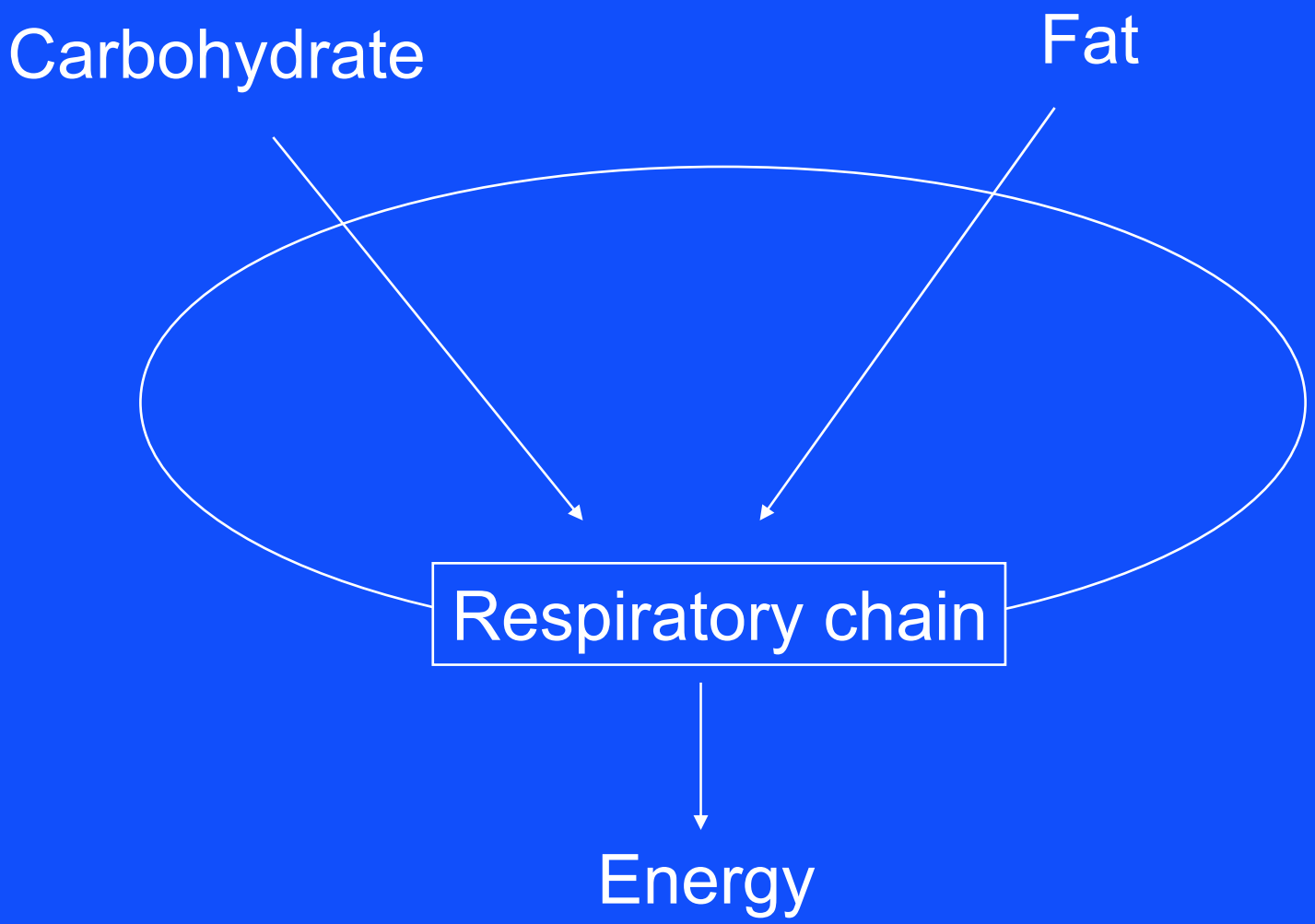
Presentation and investigation of mitochondrial disease in children

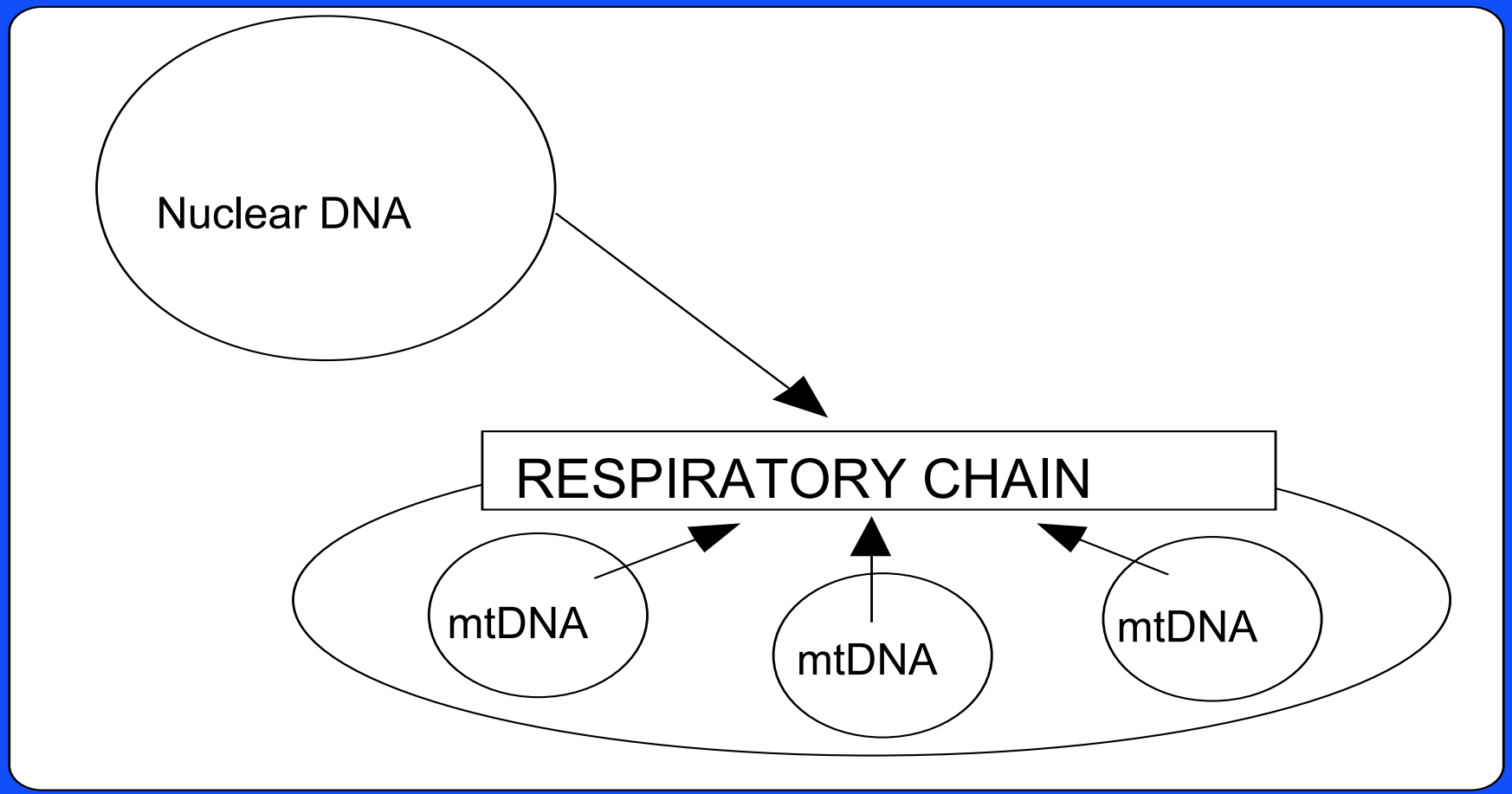
Andrew Morris

Willink Unit, Manchester

Mitochondrial function



Mitochondria are the product of 2 genomes



Clinical Features

Respiratory chain disease can present

- In any system
- At any age
- With any pattern of inheritance

J-M Saudubray

Clinical clues to mitochondrial disease

- Recognised syndromes

  e.g. Pearson – anaemia, pancreatic insufficiency

- Multisystem disease

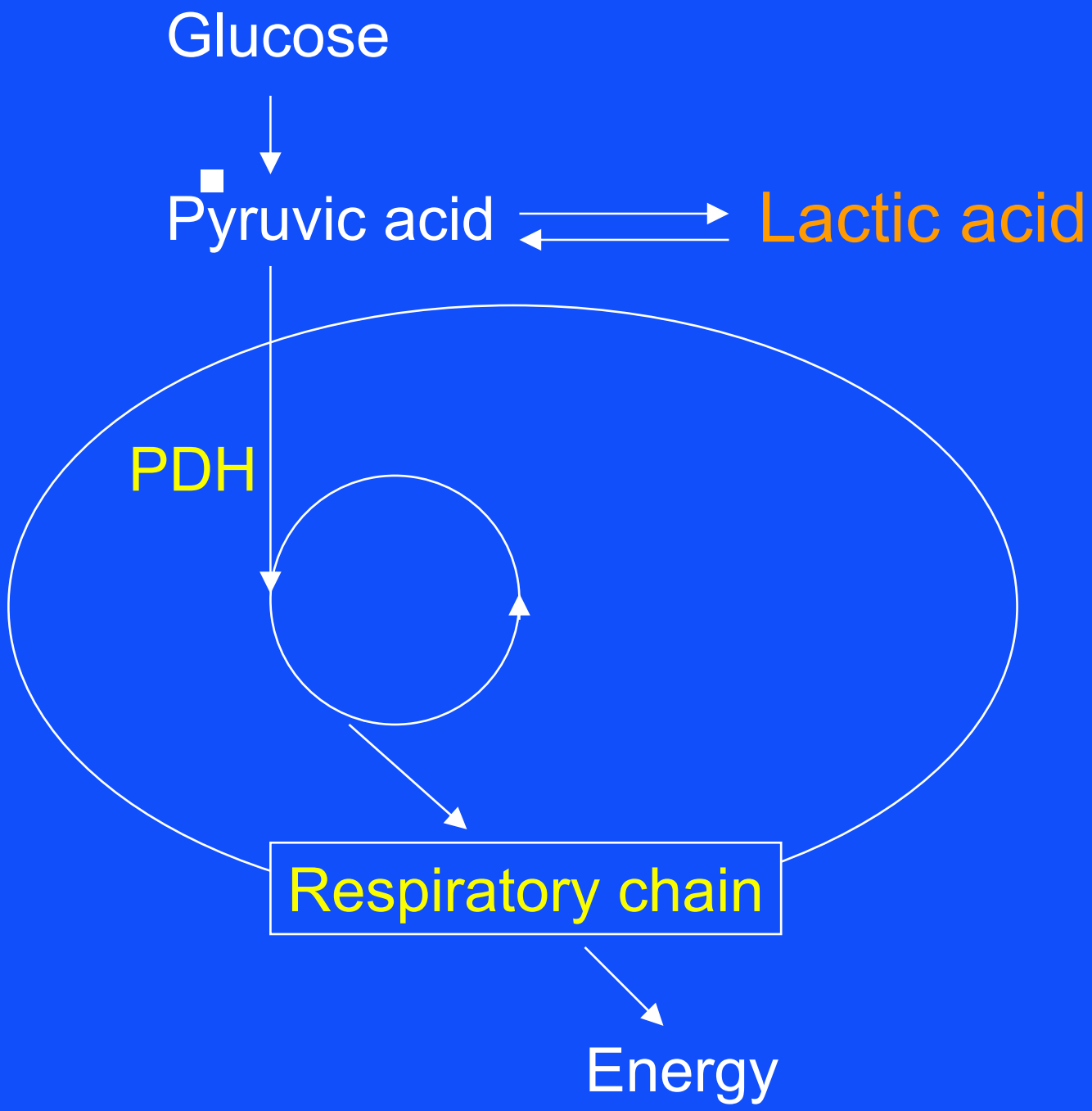
  without anatomical, biochemical or embryological link

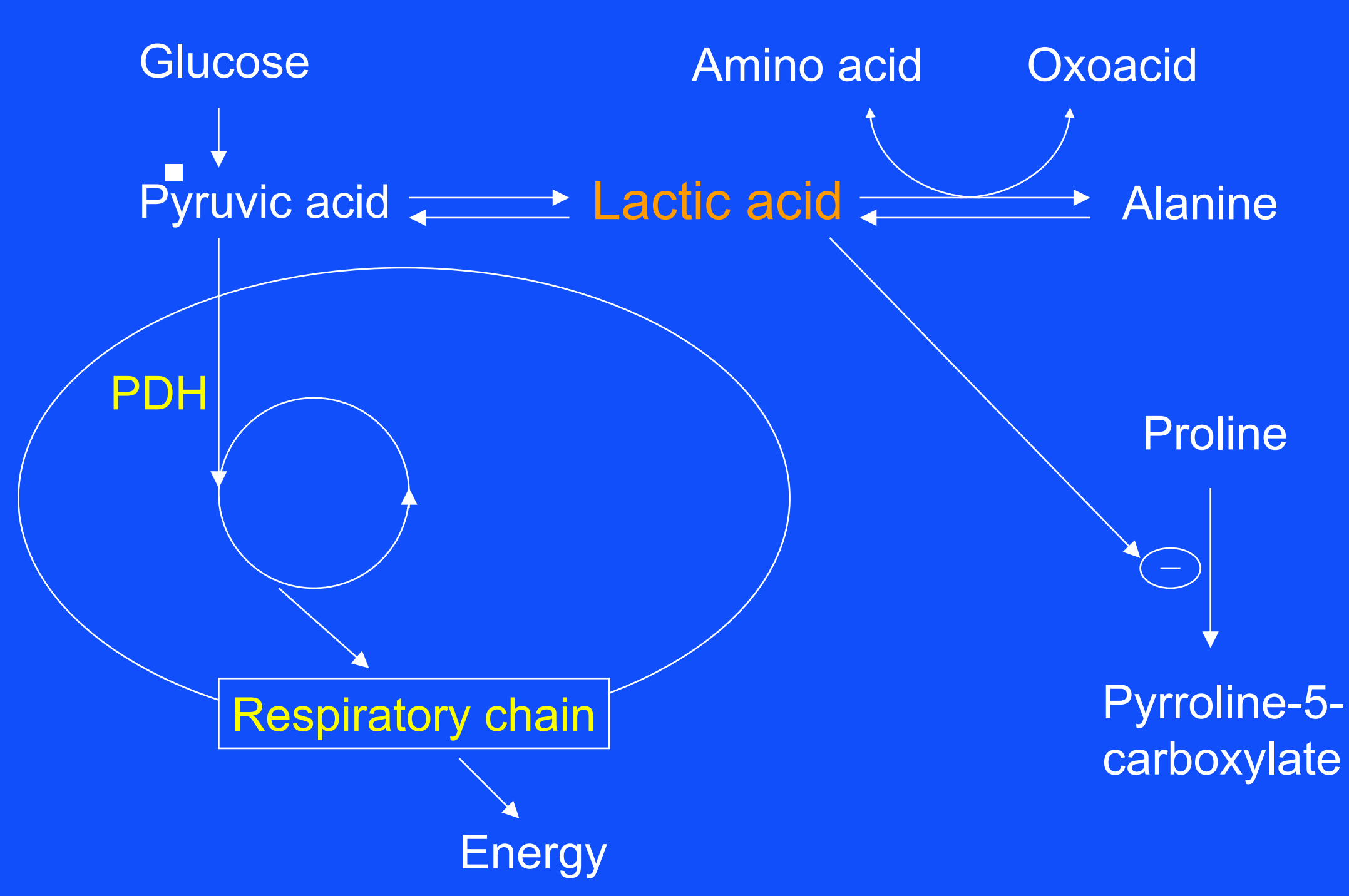
- Type of disease in an organ

  e.g. tubulopathy not glomerular disease

Chemical clues to mitochondrial disease

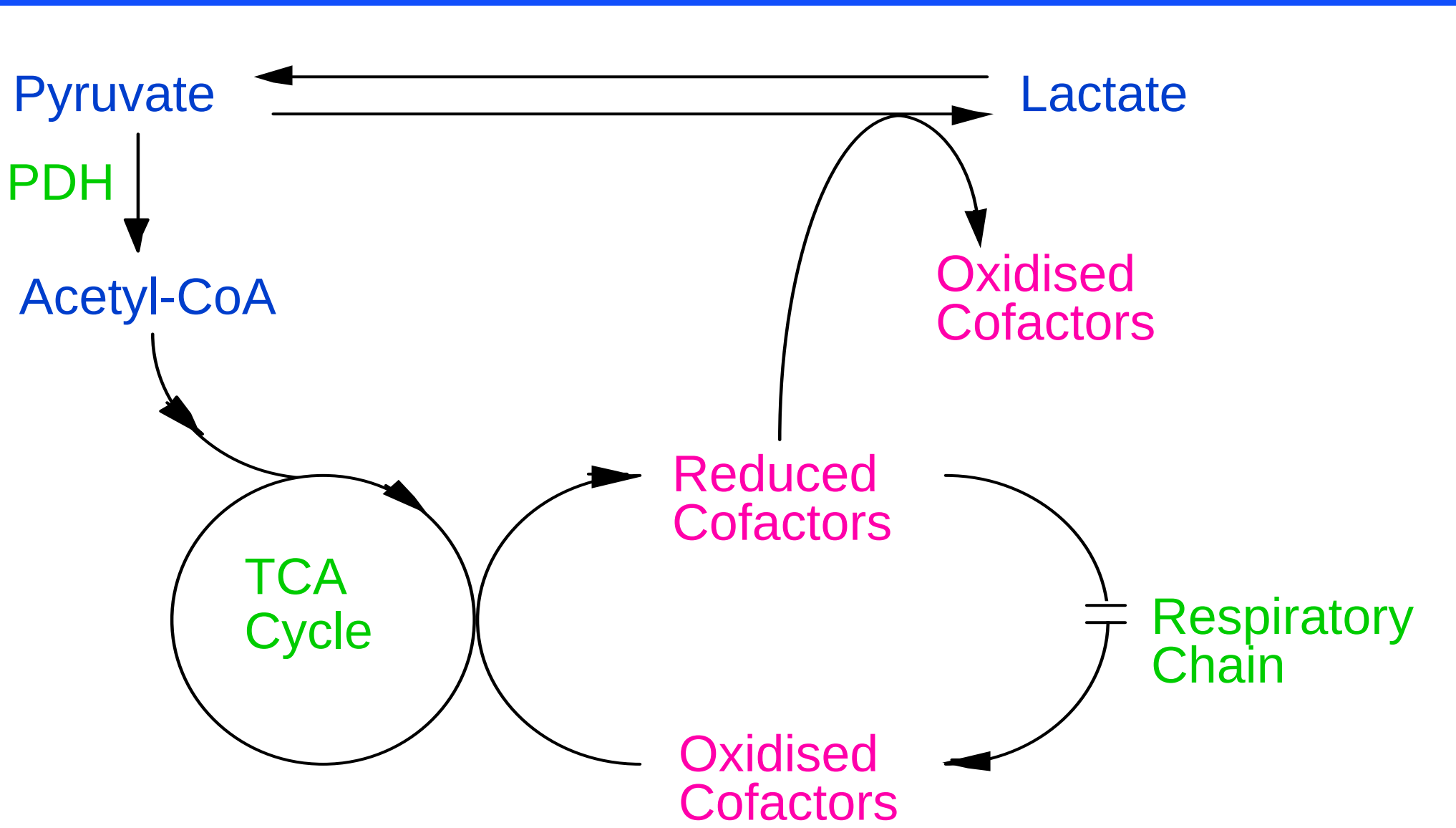
- Raised lactic acid concentrations
- Raised plasma alanine & proline
- 3-methylglutaconic aciduria
- Raised lactate: pyruvate ratios


Glucose
Pyruvic acid
Lactic acid
PDH
Respiratory chain
Energy

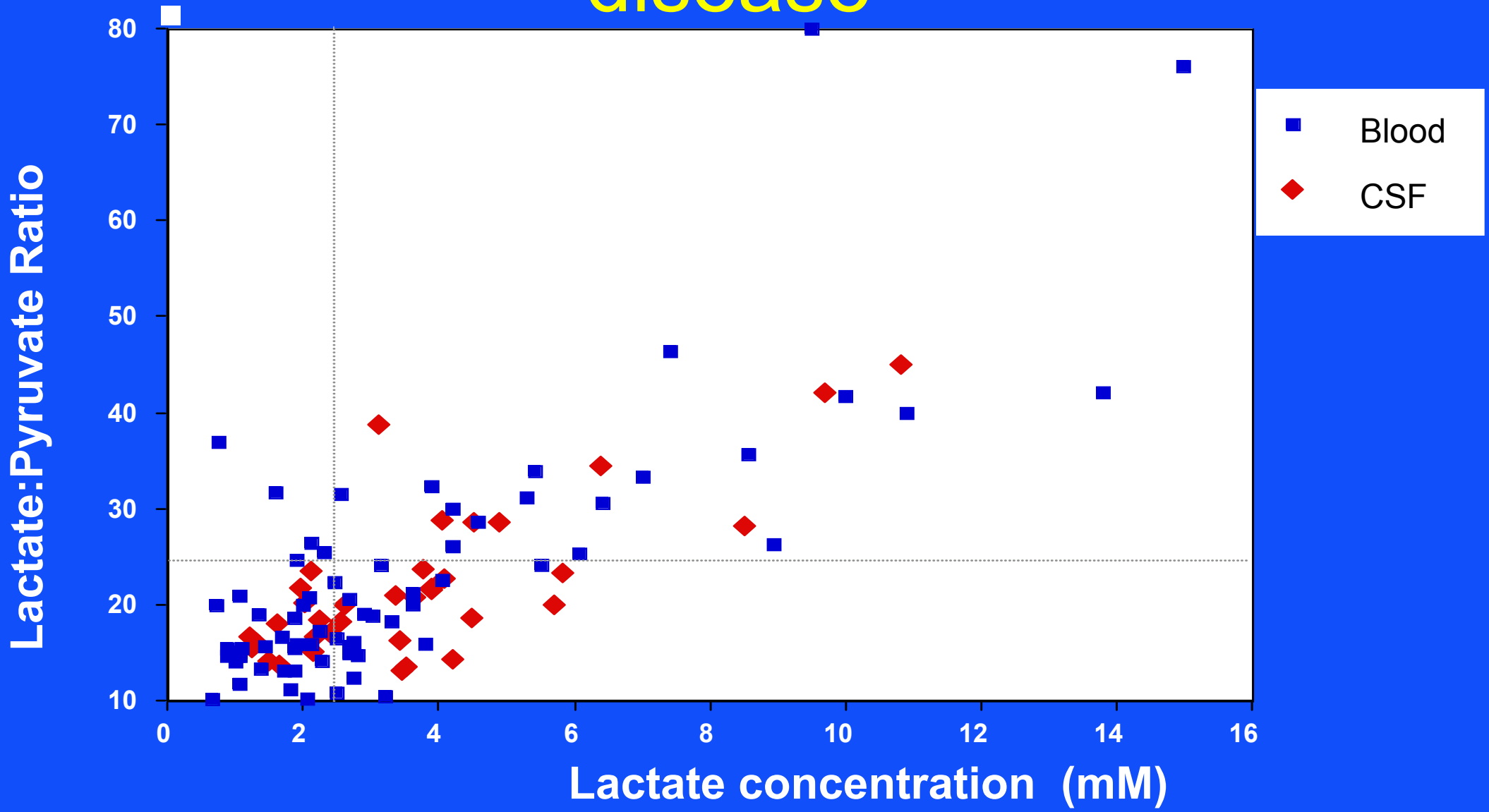

Glucose
Amino acid
Oxoacid
Pyruvic acid
Lactic acid
Alanine
PDH
Proline
Respiratory chain
Pyrroline-5-carboxylate
Energy

Chemical clues to mitochondrial disease

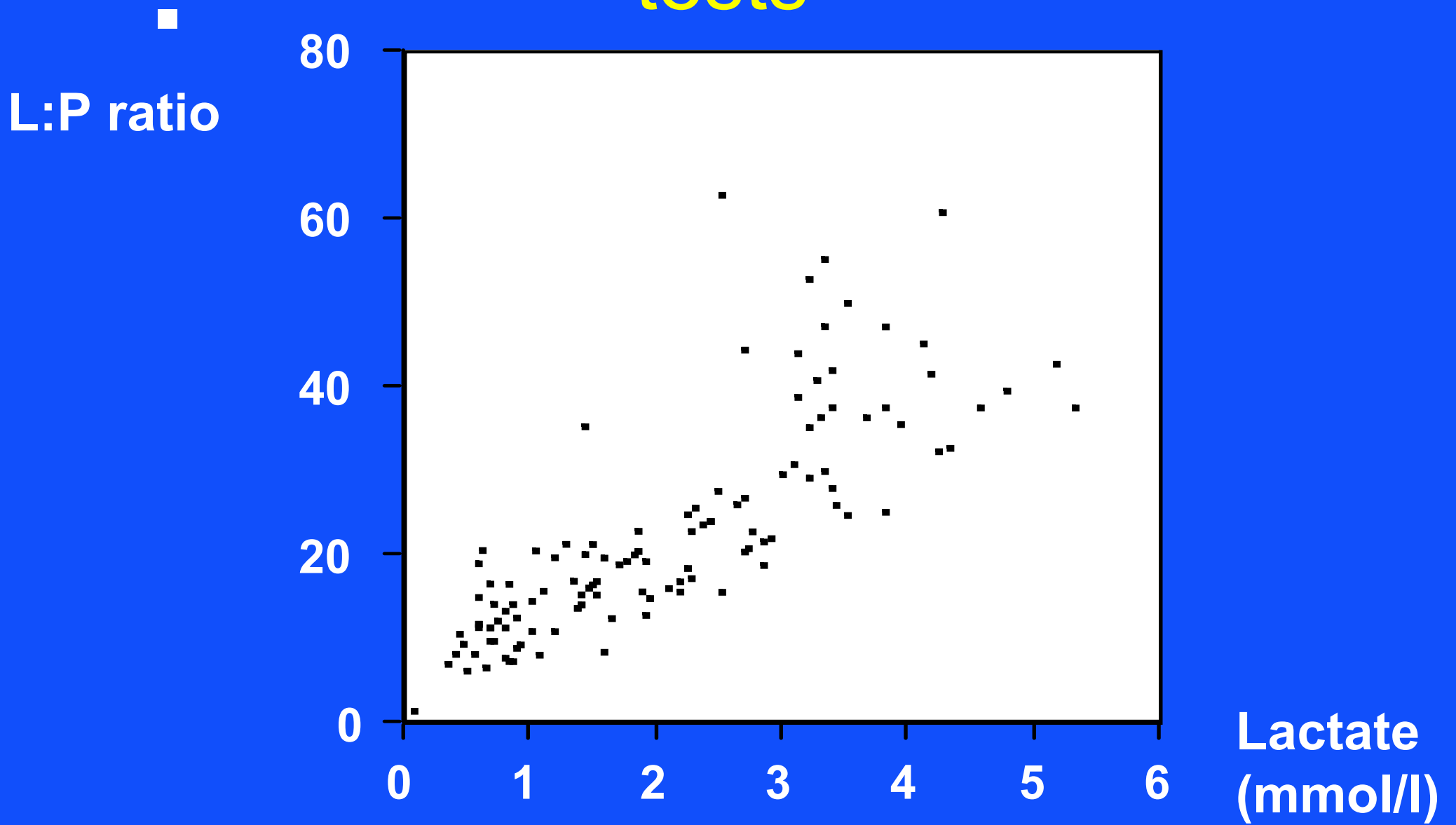
- Raised lactic acid concentrations
- Raised plasma alanine & proline
- 3-methylglutaconic aciduria
- Raised lactate: pyruvate ratios


Pyruvate
Lactate
PDH
Acetyl-CoA
Oxidised
Cofactors
Reduced
Cofactors
TCA
Cycle
Respiratory
Chain
Oxidised
Cofactors

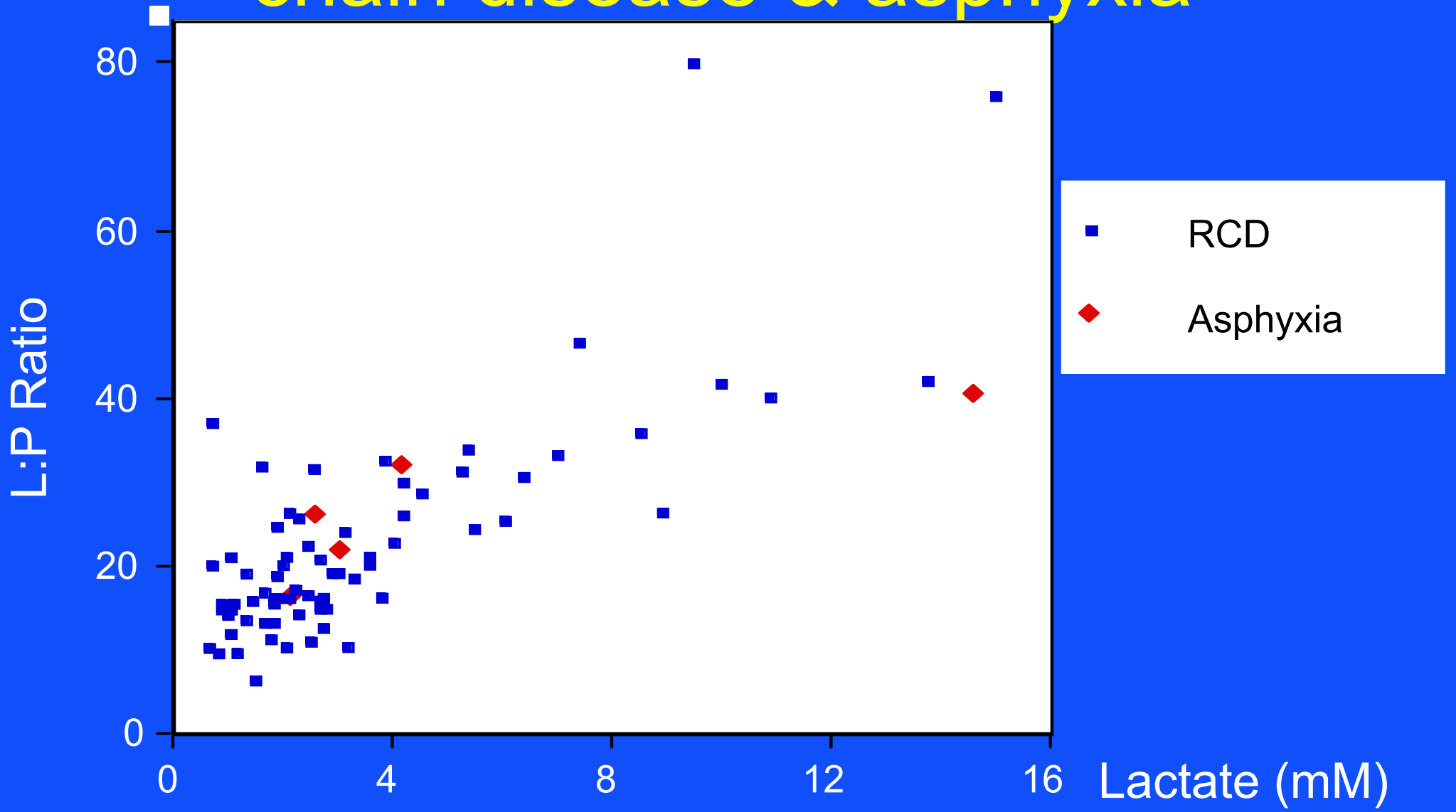
Lactate vs L:P ratio in respiratory chain disease



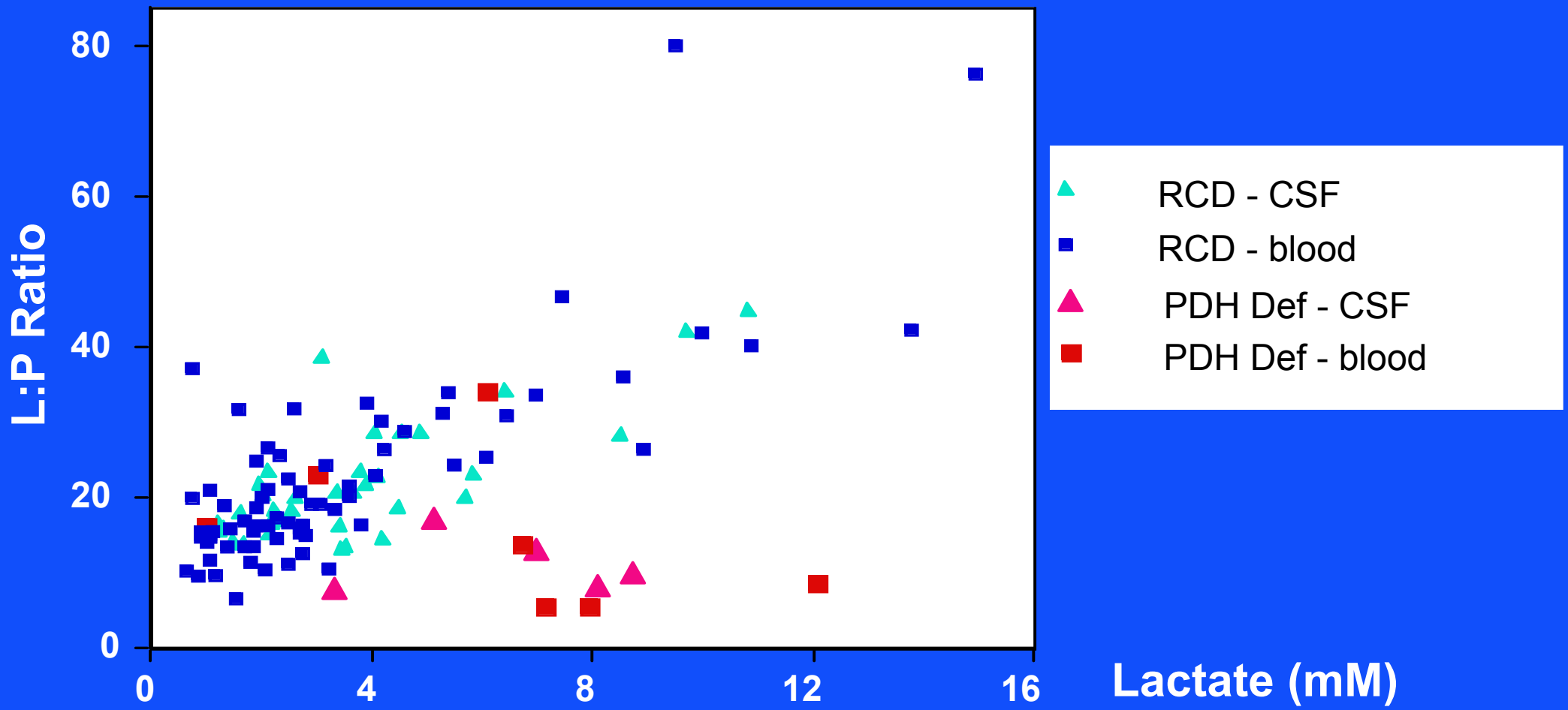
Lactate vs L:P ratio in ischaemic lactate tests



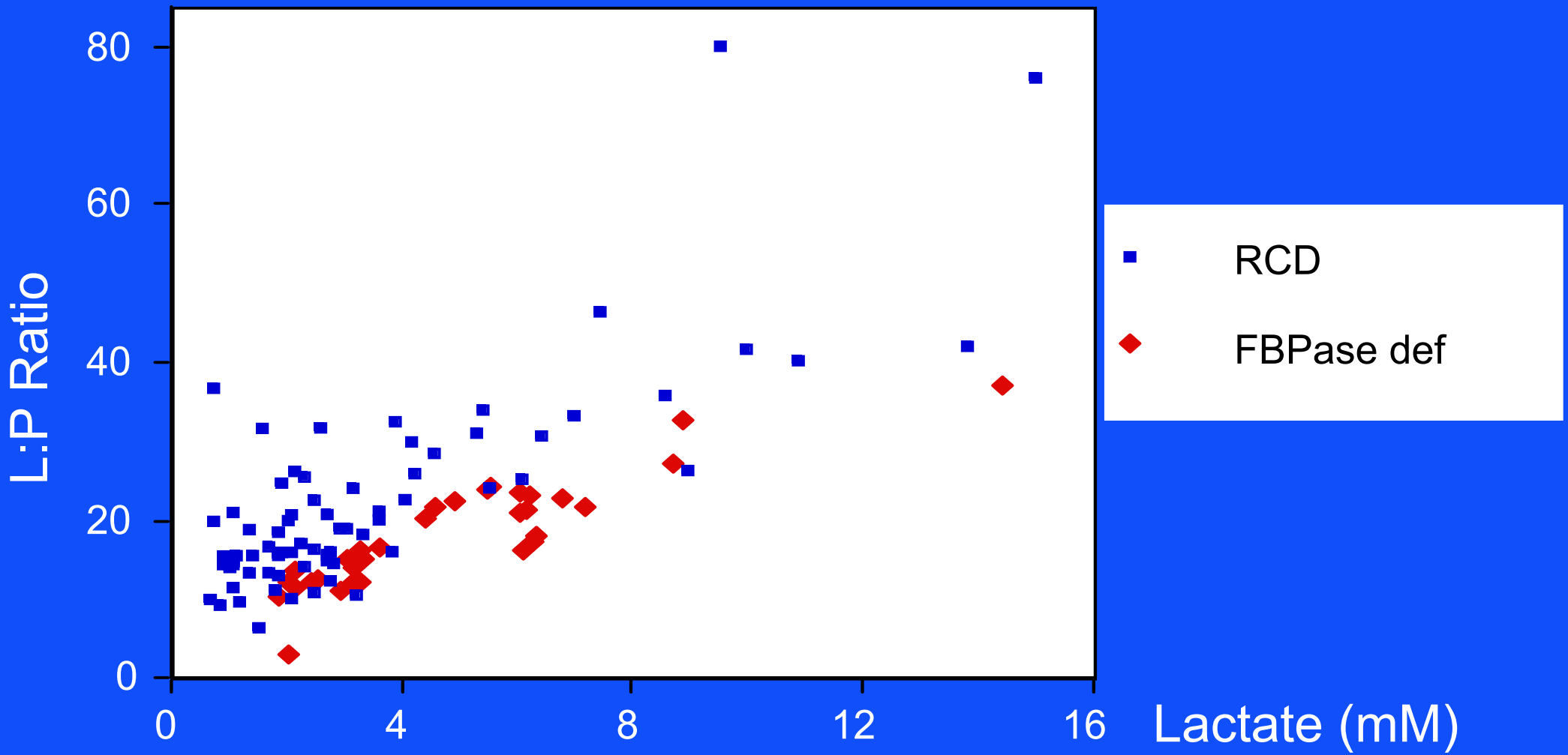
Blood lactate & L:P ratios in respiratory chain disease & asphyxia



Lactate & L:P ratios in respiratory chain disease & PDH deficiency



Blood lactate & L:P ratios in RCD & fructose bisphosphatase deficiency



Investigation of suspected mitochondrial disease

- Definition of clinical phenotype
  - cerebral imaging, echocardiography, glucose tolerance etc
- Differential diagnosis
  - acylcarnitines, organic acids, biotinidase etc
- Definitive tests
  - genetic or biochemical?
  - which tissue?

Investigation of suspected mitochondrial disease

- DNA studies if syndrome with specific mutations
  e.g. Barth, MELAS & Pearson syndromes & LHON
- Muscle & skin biopsies (& CSF lactate)
  - Respiratory chain assays
  - Histochemistry
  - MtDNA studies
  - PDH assay (if relevant)

Proceed to DNA studies as appropriate

- Respiratory chain assays on affected tissue

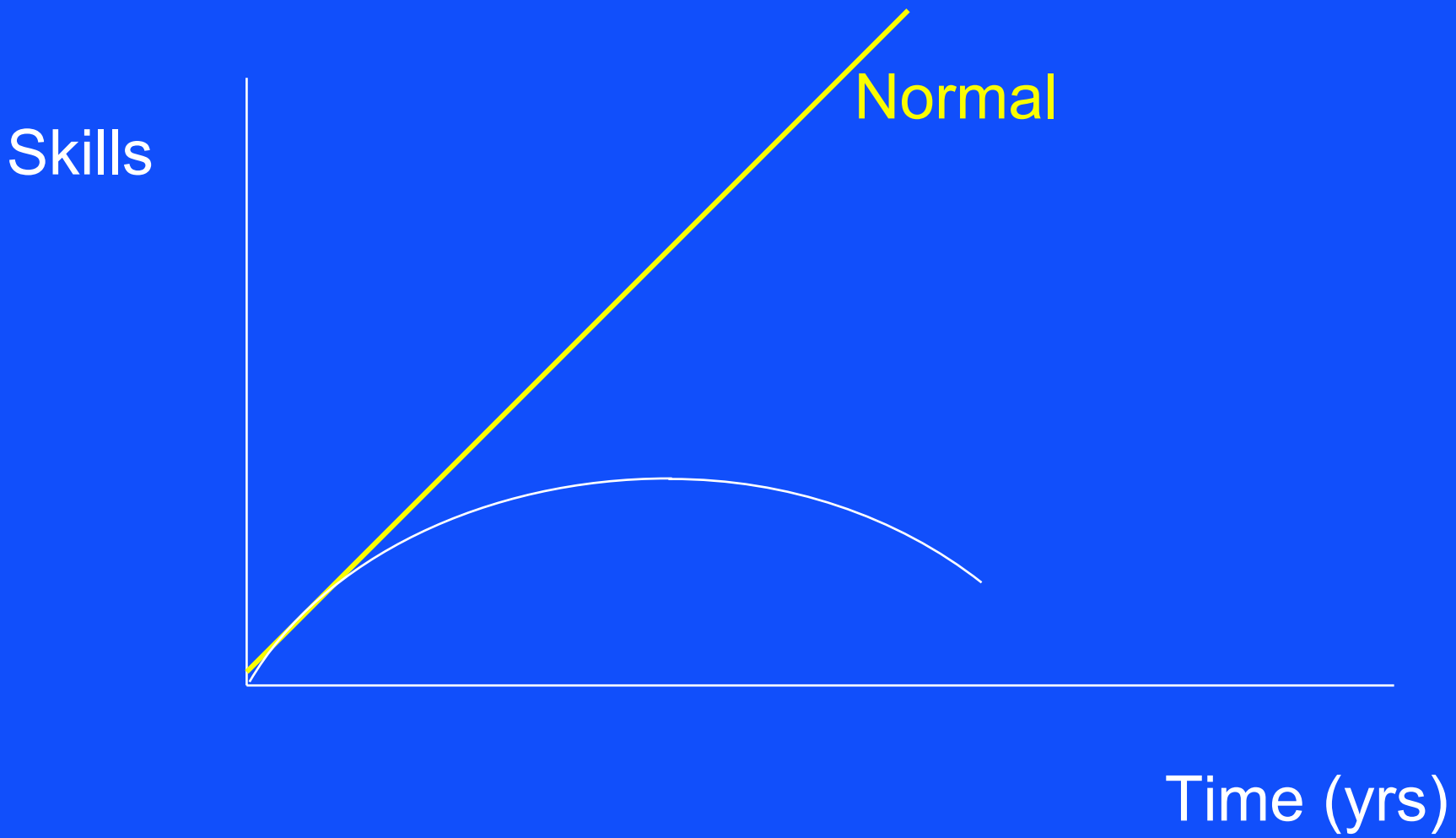
Paediatric presentations

- Leigh syndrome
- Other neurological presentations
- Multisystem disease in infancy
- Cardiomyopathy
- (Leber hereditary optic neuropathy)

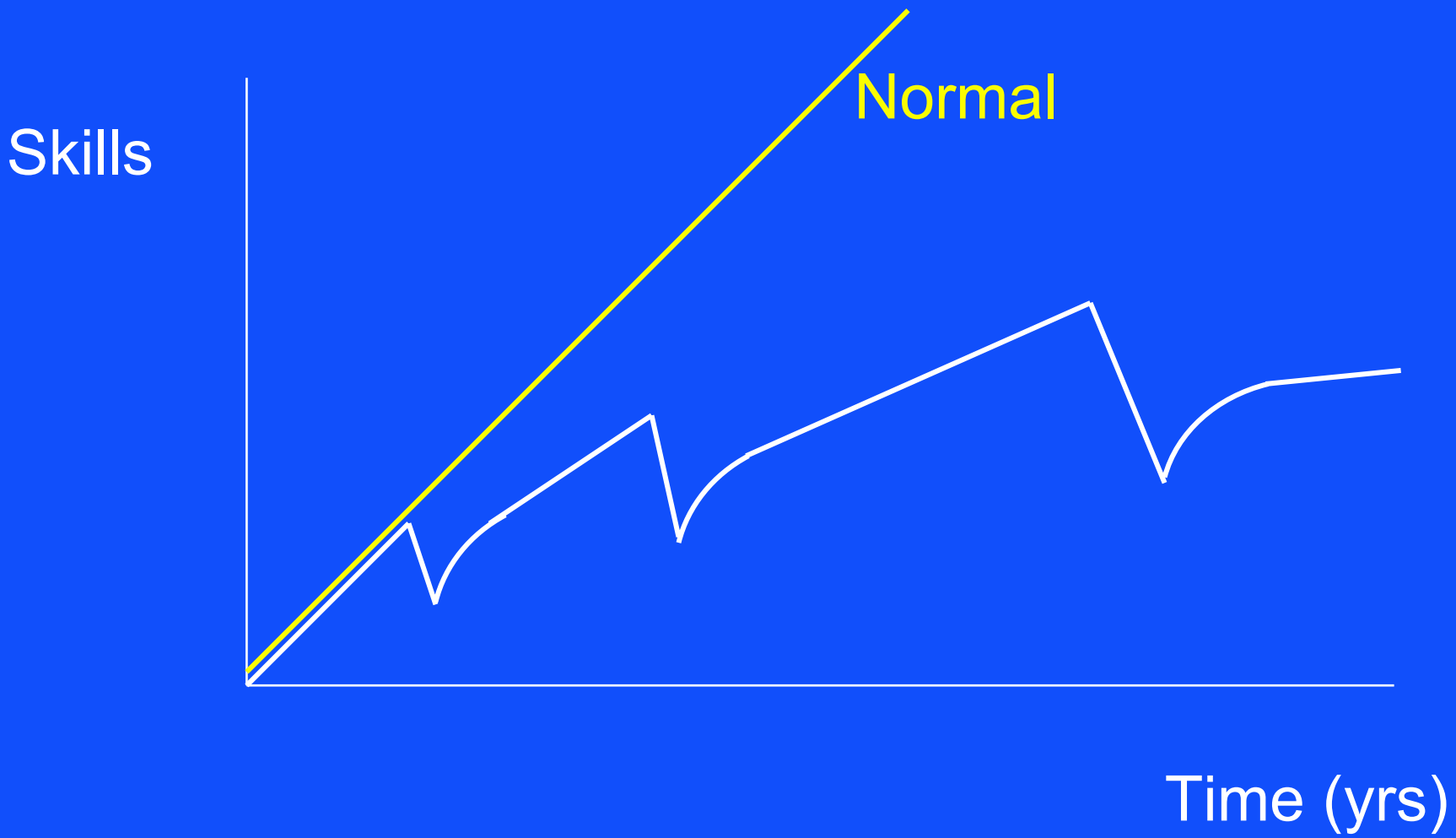
Leigh syndrome: clinical features

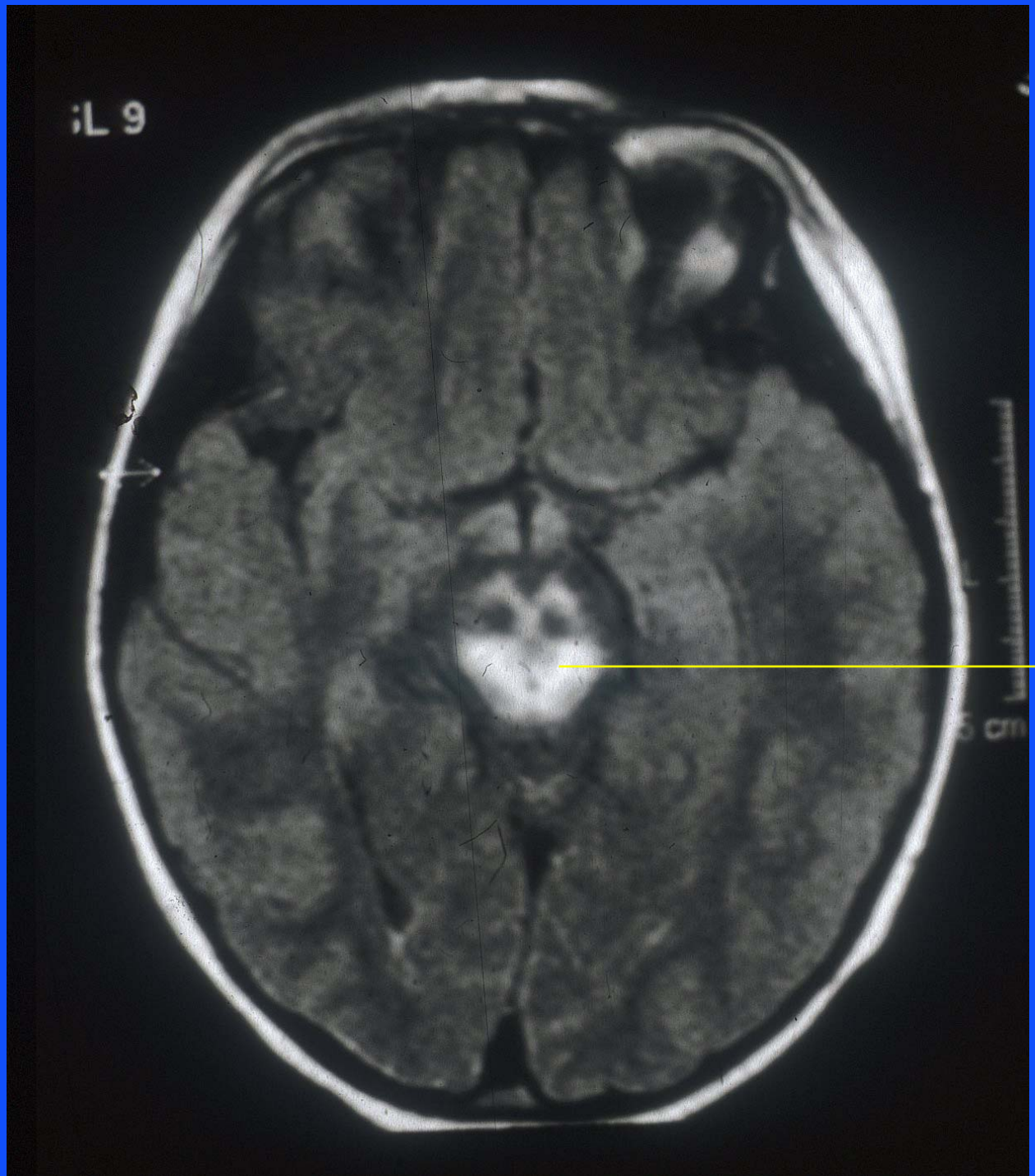
- Onset often by 2 years
- Presentation non-specific: failure to thrive
  hypotonia
  motor retardation
- Brainstem or extrapyramidal signs later
  ventilatory disturbances
  difficulty swallowing
  eye movement disorders
  dystonia
- Course: highly variable

Time-course in Leigh syndrome

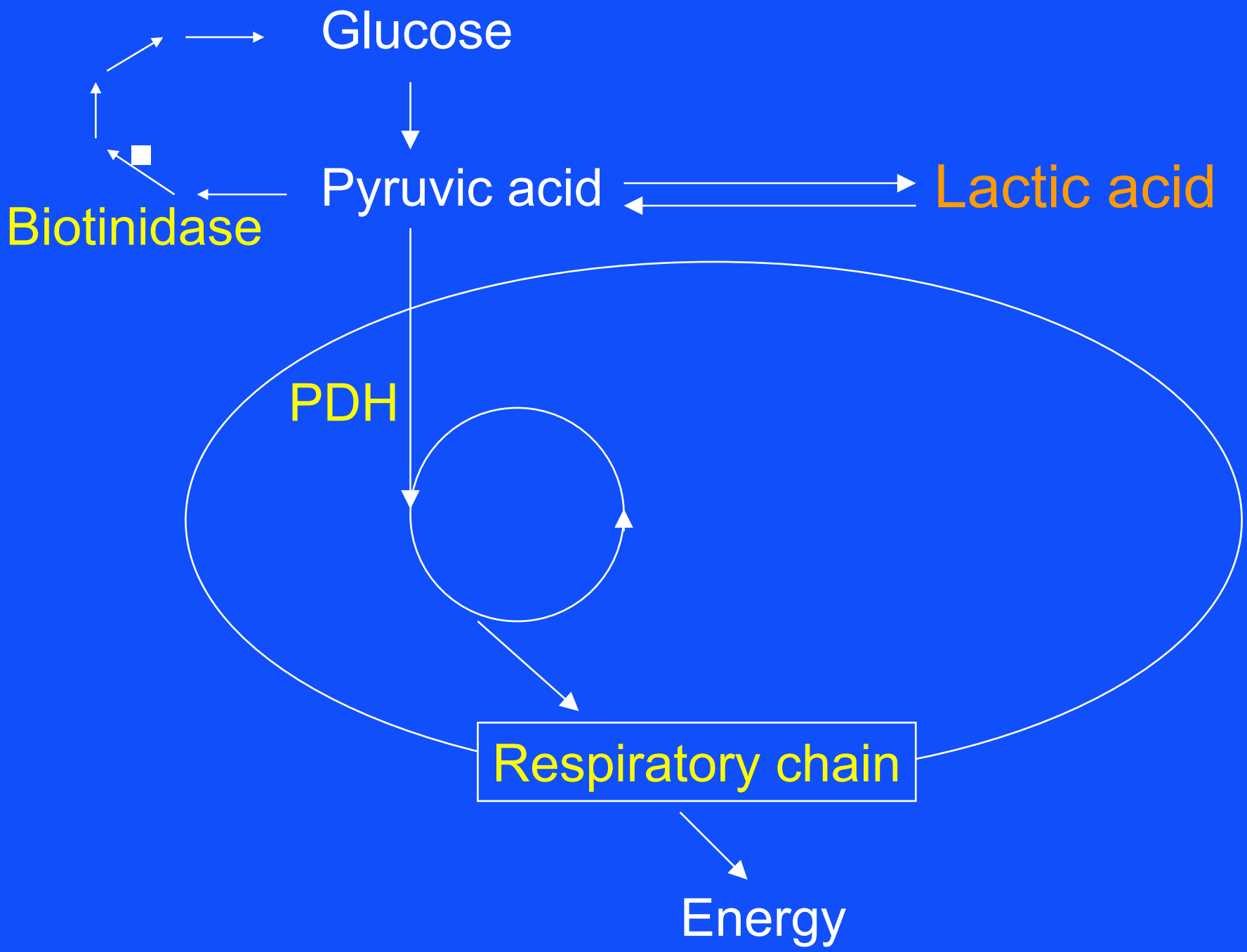


Time-course in Leigh syndrome

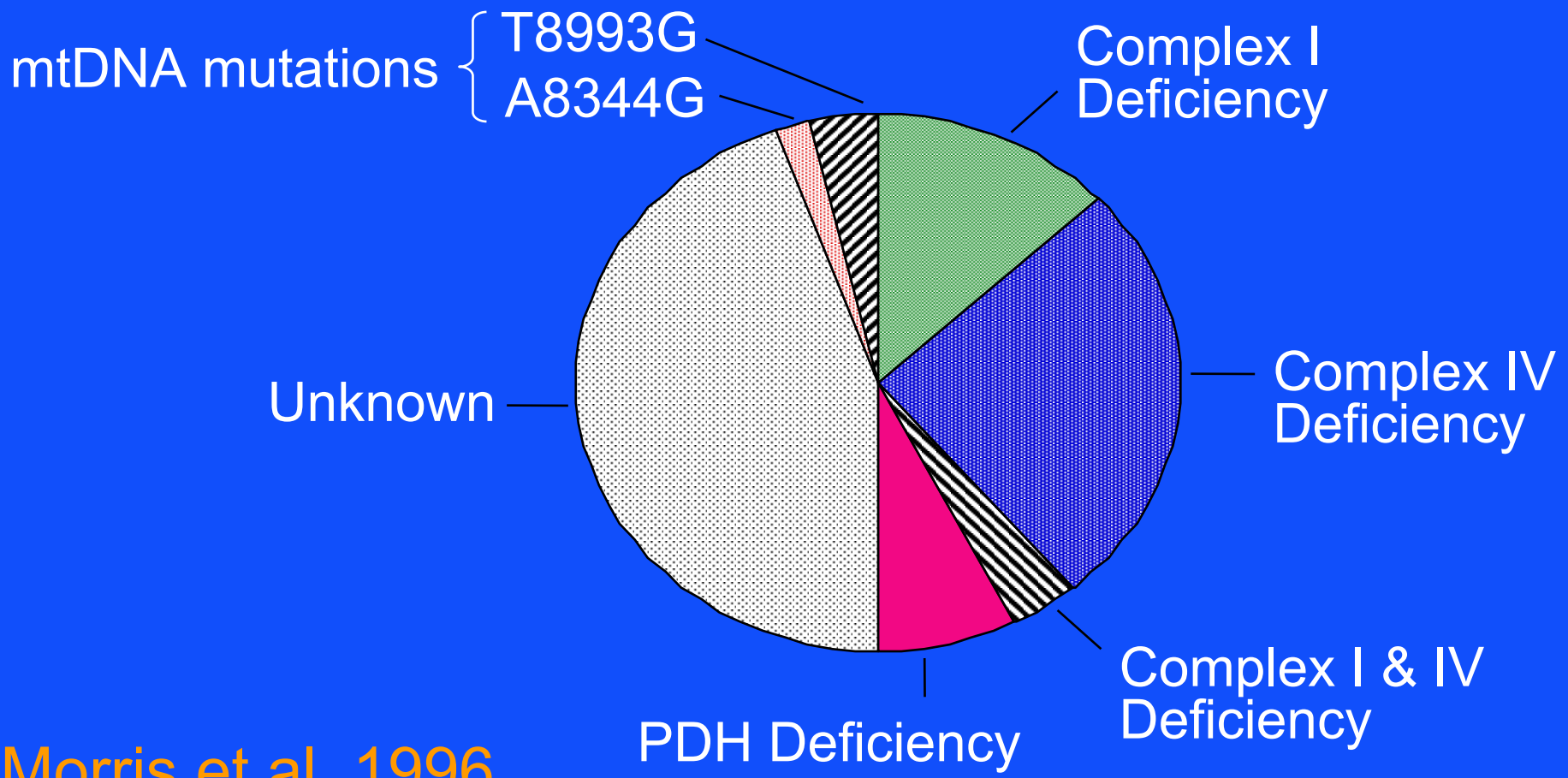




High signal in
dorsal brainstem


Glucose
Pyruvic acid
Lactic acid
Biotinidase
PDH
Respiratory chain
Energy

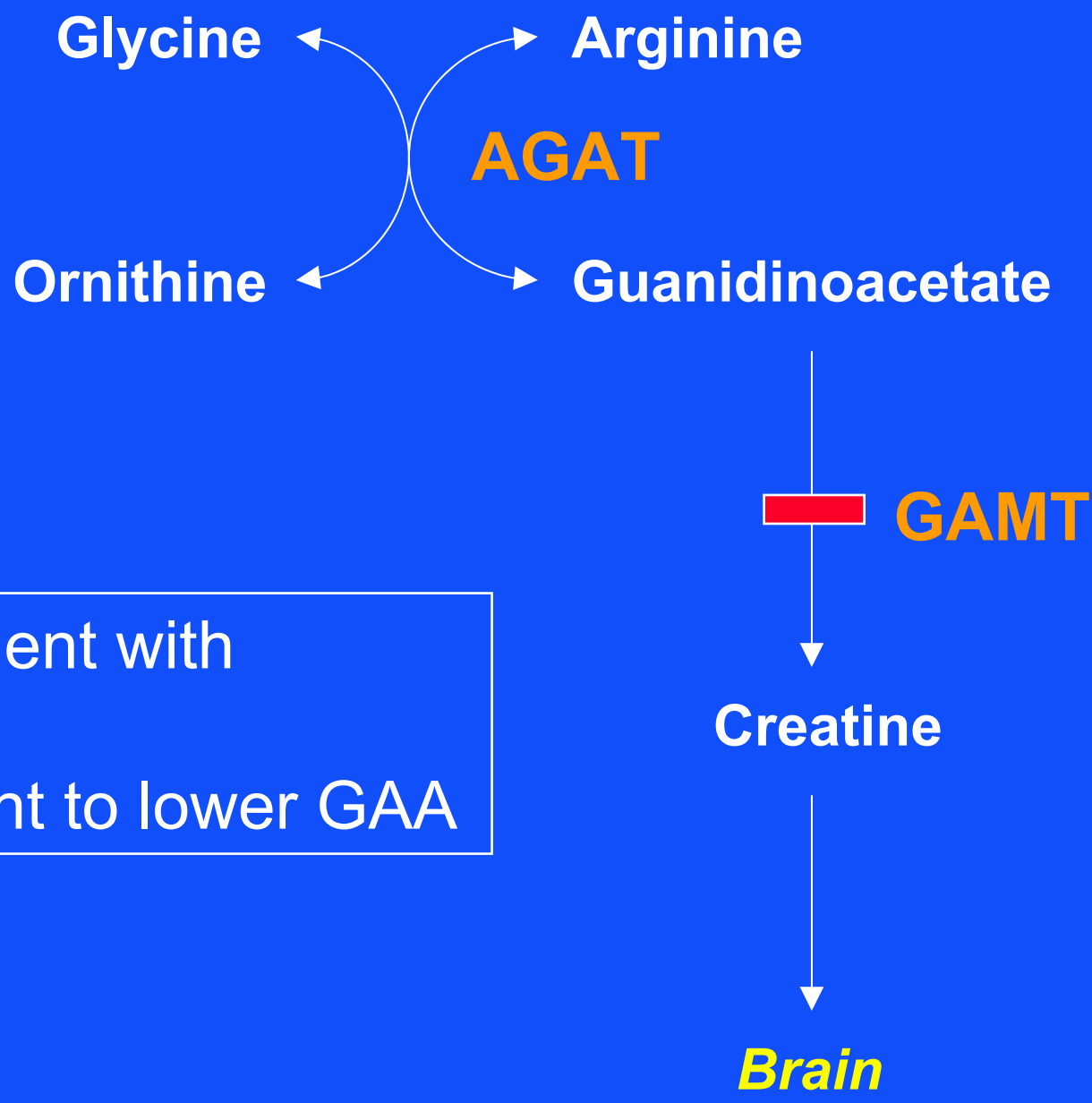
Leigh syndrome survey: Aetiologies in 54 pedigrees



Morris et al, 1996

Leigh syndrome ?

- Developmental delay & FTT at 11 months
- MRI – symmetrical lesions in globus pallidus
- CSF lactate 1.5 mmol/l
- Cx I deficiency in muscle & fibroblasts
- 2nd year: seizures
- Low urine creatinine
- Low GAMT activity in lymphoblasts



Clinical improvement with
- Creatine
- Dietary treatment to lower GAA

Paediatric presentations

- Leigh syndrome
- Other neurological presentations
  - Alpers syndrome
  - Kearns-Sayre syndrome
  - MELAS syndrome
  - Malformations
- Multisystem disease in infancy
- Cardiomyopathy

Alpers syndrome

- Mild developmental delay
- Explosive onset of intractable seizures
  - EEG: high amplitude slow waves + polyspikes
- Regression & loss of vision

  ± stroke-like episodes affecting occipital cortex
- Terminal liver failure (± valproate)

Kearns-Sayre syndrome

Onset before 20 yrs

- PEO
- Pigmentary retinopathy

At least one of

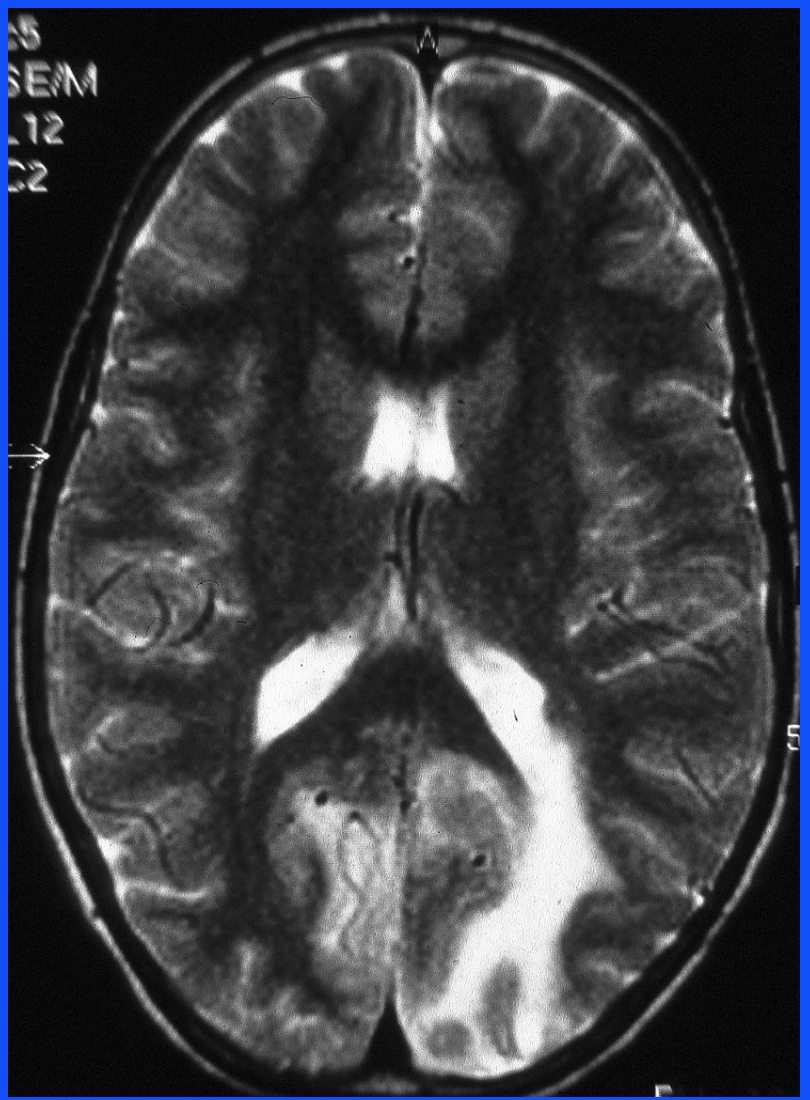
- Ataxia
- Heart block
- CSF protein > 1 g/l

± endocrinopathy etc

MELAS syndrome

- Myopathy
- Encephalopathy
- Lactic acidosis
- Stroke-like episodes

- Diabetes
- Deafness
- Cardiomyopathy



KSS & MELAS syndromes

Investigation

Kearns-Sayre syndrome: mtDNA rearrangements

- Muscle biopsy: Southern blot / long-range PCR

MELAS syndrome: 80% A3243G

- Look for A3243G in blood
- Otherwise muscle biopsy: A3243G
  other mutations
  biochem & histochem

CNS malformations

PDH deficiency

- Agenesis of corpus callosum
- Aplasia of corticospinal tracts
- Neuronal migration defects

Respiratory chain disease

- Rare
- Lissencephaly (1 recent case)

Paediatric presentations

- Leigh syndrome
- Other neurological presentations
- Multisystem disease in infancy
- Cardiomyopathy

Multisystem disease, especially in infancy

- Lactic acidosis
- Tubulopathy, including RTA
- Liver failure
- GI disease (enteropathy, abnormal motility, pancreatic insufficiency)
- Blood disorders e.g. sideroblastic anaemia
- CNS disease / Myopathy

Multisystem disease, especially in infancy

Investigation

- Define problem – tubulopathy tests, clotting, feacal elastase, bone marrow etc
- Exclude treatable diagnoses – galactosaemia, tyrosinaemia etc
- Pearson syndrome: mtDNA deletion in blood
- Otherwise muscle (± liver) biopsy

Paediatric presentations

- Leigh syndrome
- Other neurological presentations
- Multisystem disease in infancy
- Cardiomyopathy

Cardiomyopathy

- Barth syndrome – X-linked, with myopathy, neutropenia & 3-methylglutaconic aciduria
- Sengers syndrome – with cataracts
- mtDNA mutations
- Nuclear defects e.g. SCO2

Cardiomyopathy

Investigation

- Define problem – CK, serial FBC, OAs
- Exclude treatable diagnoses – acylcarnitines
- Barth syndrome: G4.5 mutation studies
- Otherwise muscle biopsy
- ? Endocardial biopsy

Mitochondrial disease in children

Conclusions

- Clinical presentation is variable
- Neurological & infantile presentations commonest
- Raised lactate is a useful marker (esp in CSF)
- In a few syndromes, start with mutation studies
- Muscle biopsies needed in most cases