SSIEM ACADEMY 2024

Case Discussions presented by delegates

Session 2

A LONG DIAGNOSTIC WANDERING

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University Hospital of Lille

SSIEM Academy 2024, Amsterdam

- No conflict of interest

- Female patient
- 1rst child of 3
- Mother's phenotype :
  - ✓ hypoaccusis
  - ✓ visual impairment
  - ✓ neurological disorders
- Hypoaccusis and visual impairment also in 2 maternal aunts
- Type 2 diabetes in maternal grandmother
- Suspicion of same affection for her younger sister
-

Clinical Evolution

2 years old

Myopia

- More severe on the left than on the right
- With horizontal nystagmus

SSIEM Academy 2024, Amsterdam

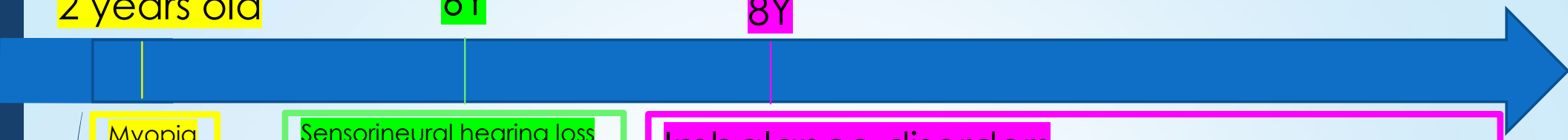
2 years old

6Y

Myopia

Sensorineural hearing loss

- Bilateral
- Severe on the left/ slightly on the right
- Hearing aid
- Evolutive



Myopia

Sensorineural hearing loss

Imbalance disorders

- Upper limb dysmetria
- Action tremor
- Hospitalization in neuropediatry
  - ✓ Family story
  - ✓ Clinical investigation
  - ✓ Neuropsychological assessment
  - ✓ Brain MRI

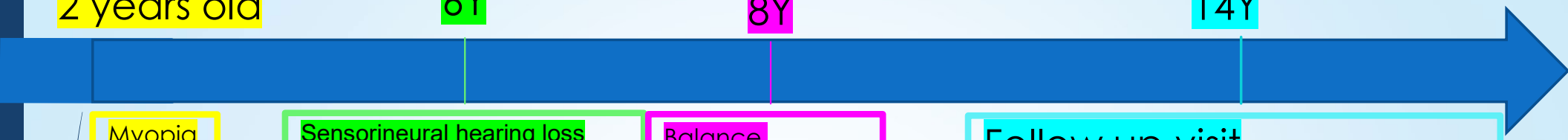
Hospitalization in neuropediatry

- Clinical investigation : suspicion of encephalopathy of antenatal origin
  - ✓ Myopia
  - ✓ Sensorineural hearing loss
  - ✓ Static and kinetic cerebellar syndrom

Hospitalization in neuropediatry (2)

- Neuropsychological assessment
  - ✓ Normal, homogeneous verbal efficiency
  - ✓ Normal visuospatial efficiency
  - ✓ Graphomotor deficit in speed and construction
  - ✓ No attention defect

- Brain MRI
  - ✓ predominantly superior vermian hypoplasia with relative enlargement of the 4th ventricle
  - ✓ Hypoplasia of the corpus callosum



Myopia

Sensorineural hearing loss

Balance disorders and Hospitalization in neuropediatry

Follow up visit

- Metabolic panel
- Genetic studies
- Electromyogram
- Ophtalmological assessment

Follow up visit

- Clinical examination
  - ✓ Moderate axial hypotonia
  - ✓ Moderate peripheral hypotonia
  - ✓ Static and kinetic cerabellar syndrome
  - ✓ Discrete horizontal nystagmus and absence of gag reflex

Follow up visit (2)

- Metabolic panel
  - ✓ Very long chain fatty acids
  - ✓ Urinary organic acids chromatography
  - ✓ Lactate/pyruvate cycle and Ketone bodies in pre and postprandial samples
  - ✓ Muccopolysaccharides profile
  - ✓ Transferrine isoelectrofocalisation
  - ✓ Ammoniemia

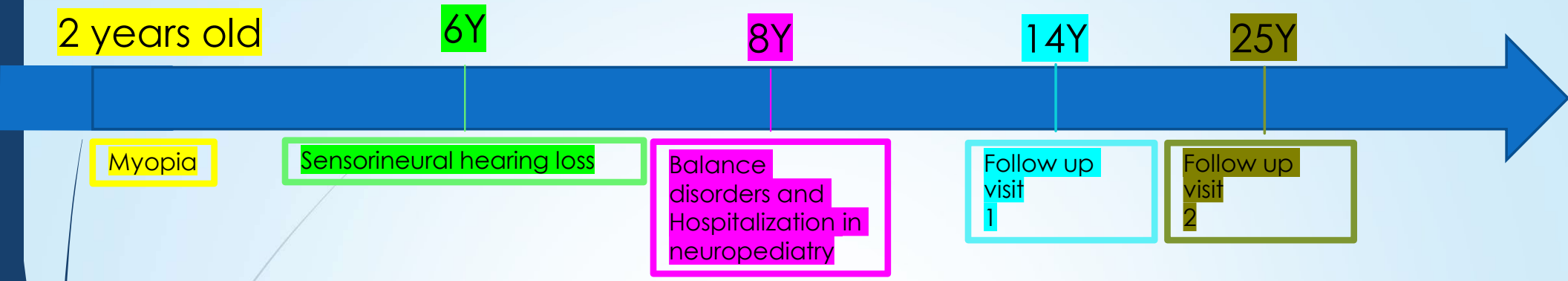
  ➔ Normal

- Genetic studies : spino-cerebellar ataxia research ➔negative

- Electromyogram ➔ sensory neuropathy

Follow up visit (3)

- Ophtalmological assessment
  - ✓ profound amblyopia of the left eye
  - ✓ severe myopia
  - ✓ right papillary pallor
  - ✓ left optic atrophy with small vessel
  - ✓ pigmented retina on fundus
  - ✓ altered scotopic and photopic ERG
  - ✓ bilateral retinal dystrophy

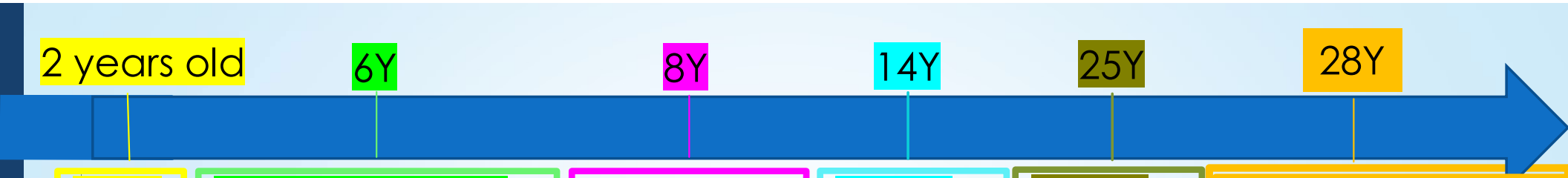

2 years old
6Y
8Y
14Y
25Y
Myopia
Sensorineural hearing loss
Balance disorders and Hospitalization in neuropediatry
Follow up visit 1
Follow up visit 2

Follow up visit

- Walking perimeter 15 minutes (effort linked dyspnea)
- Worsened balance disorders
- Worsened dysarthria
- Neurological examination :
  - ✓ Discrete nystagmus
  - ✓ Slight bilateral dysmetria
  - ✓ Cerebellar tremor
  - ✓ Achilles areflexia with discrete hypopallesthesia
  - ✓ No sign of spasticity or motor deficit
  - ✓ Difficulty with monopodal position
  - ✓ Tandem walking with errors
  - ✓ Oscillations in the Romberg test
  - ✓ Stewart Holmes manoeuvre positive bilaterally.

Diagnostic hypotheses

- Association
  - Deafness,
  - Cerebellar ataxia,
  - Neuropsychological disorders
- Niemann Pick's disease type C : oxysterols measurement ➔ normal
- Friedrich ataxia : molecular biology ➔ negative
- New metabolic screening negative



Myopia

Sensorineural hearing loss

Balance disorders and Hospitalization in neuropediatry

Follow up visit 1

Follow up visit 2

Mitochondrial screening

- Mitochondrial biopsy
- Recurrent mutations research
- Long PCR

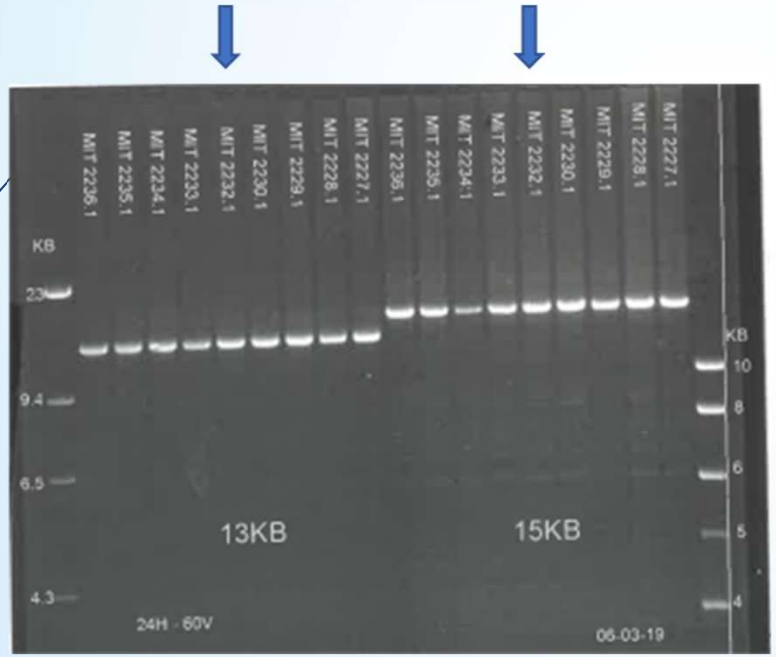
Mitochondrial screening

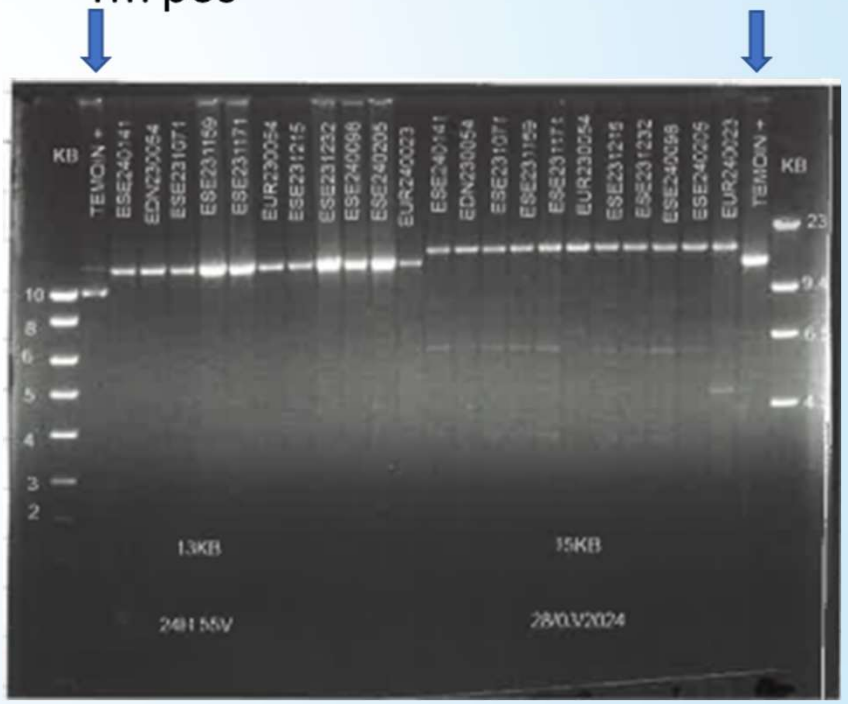
- Muscular biopsy
  - ✓ Presence of clusters of fibers of the same histoenzymological type in favor of neurogenic damage, with no other sign of mitochondrial dysfunction
  - ✓ Mitochondrial respiratory complexes exploration

	Normal Values		Normal values/CS	
CI (NUR)	9-29	10,2	0,06-0,18	0,11
CII (SD)	20-34	24,4	0,10-0,22	0,27
CIII (UCCR)	50-115	81,5	0,40-0,90	0,89
CII+III (SCCR)	30-50	15,4	0,14-0,28	0,17
CIV (COX)	72-144	72,1	0,54-0,98	0,79
CS	105-225	91,5		

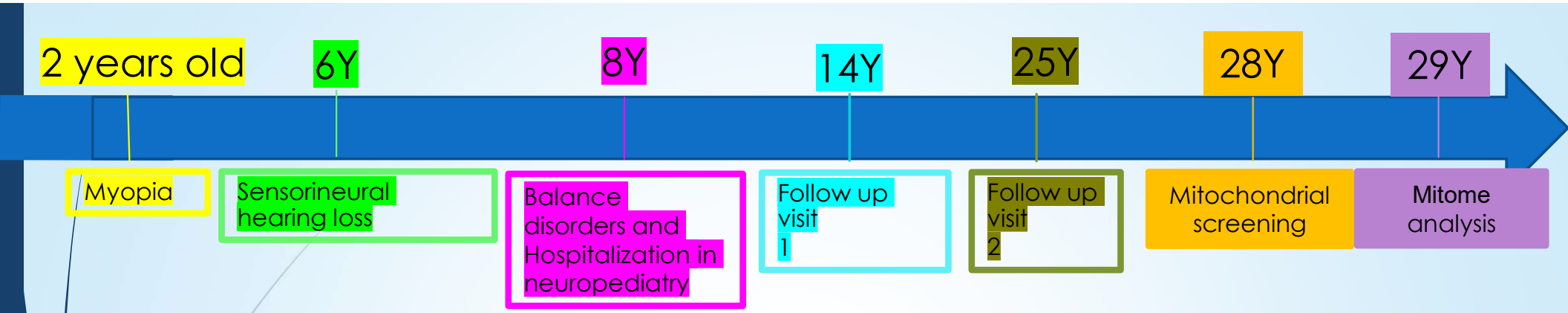
Mitochondrial screening (2)

- Molecular biology
  - ✓ Recurrent mutations research negative
  - ✓ Long PCR normal





+ new whole metabolic and endocrinologic screening
➔ normal


2 years old
6Y
8Y
14Y
25Y
28Y
29Y
Myopia
Sensorineural hearing loss
Balance disorders and Hospitalization in neuropediatry
Follow up visit 1
Follow up visit 2
Mitochondrial screening
Mitome analysis

Mitome analysis

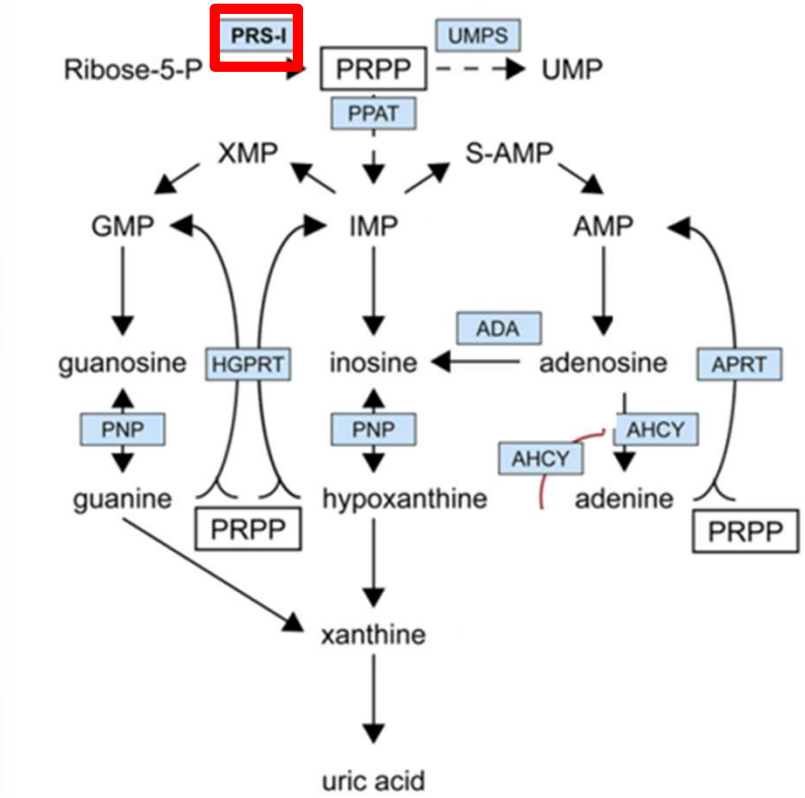
Indication : Recherche d'une cause génétique de maladie mitochondriale

Résultat :

Présence du variant c.640C>T [p.(Arg214Trp)] à l'état hétérozygote dans l'exon 5 du gène *PRPS1* (NM_002764.4)

Interprétation :

Le séquençage de l'exome en simplex a permis l'identification d'un variant faux-sens hétérozygote dans le gène *PRPS1* (phosphoribosyl pyrophosphate synthetase 1 - OMIM*311850) gène reporté dans un large spectre d'atteintes cliniques dont certaines associant une surdité, une atrophie optique et une ataxie (PMID: 20380929). Ce variant est absent de la base de données populationnelle GNOMAD (v.2.1), prédit pathogène par les outils de prédiction *in silico*, classé comme probablement pathogène dans la base de données clinique CLINVAR (v.03/2021) et reporté comme pathogène dans la littérature (PMID: 28967191). D'après l'ensemble de ces paramètres et selon les critères de l'ACMG, il s'agit d'un variant de classe 5.



Simplified overview of the Purine Metabolism Pathway

Derived from KEGG Pathways hsa00230 et hsa240

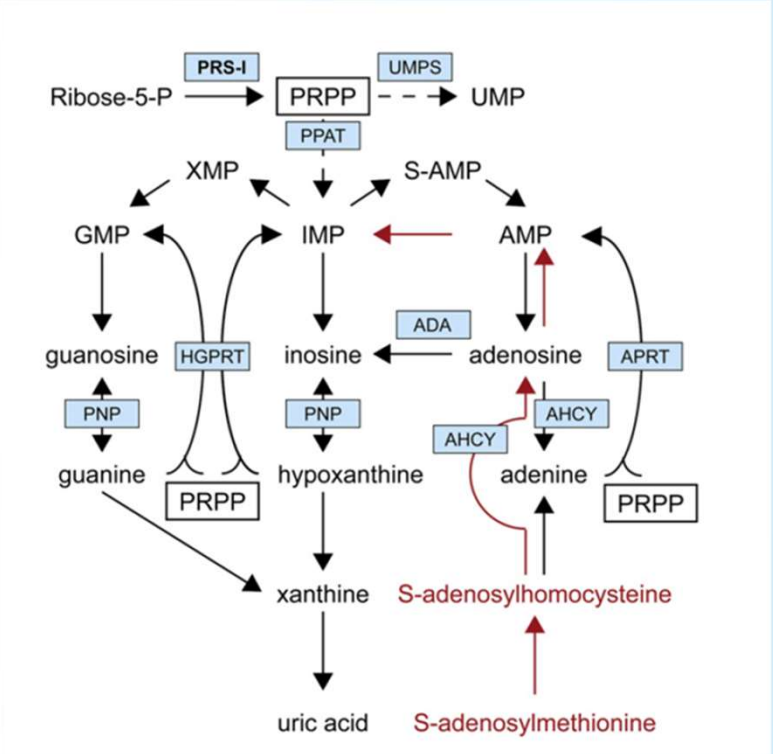
PRPS1 = Key enzyme catalyzing the first step of nucleotide synthesis

Phosphoribosylpyrophosphate synthetase deficiency

- X-linked disorder
- Phenotypic continuum : 3 disorders:
  - Arts syndrom :
    - ✓ congenital sensorineural hearing loss
    - ✓ Hypotonia
    - ✓ delayed acquisition
    - ✓ mild to moderate mental retardation
    - ✓ cerebellar ataxia
    - ✓ sensory neuropathy
    - ✓ optic atrophy
  - Charcot-Marie-Tooth neuropathy X type 5
  - X-linked non syndromic sensorineural hearing loss

Treatment

- Neurological phenotype = result of GTP (and possibly ATP) depletion
- S-Adenosylmethionine (SAM)
  - compensation for this deficiency
  - restoration of purine nucleotide values ➔anaplerotic effect
  - Treatment based on the PRPP-independent pathway for conversion via adenosine to ATP and then to GTP
  - ability to cross both the intestine and the blood-brain barrier
  - Ability to penetrate hair cells ➔ stabilization of hearing loss in patients with Art's syndrome



Today

- Samyr : 200 mg *2 /day started on June 2023

➔Subjective amelioration of neurologic symptoms and pain

- June 2023 : pregnancy
  - 2nd trimester ultrasound performed at 22 SA + 1day
    - ✓ bilateral intracerebral ventricular dilatation
    - ✓ Genetic research for Arts Syndrom positive
  - delivery at 37 weeks and one day of amenorrhea by Caesarean section for severe intrauterine growth retardation (<1st p.) and context of maternal and fetal ARTS syndrome
    - female child
    - weighing 1800 grams
    - initially transferred to the neonatal intensive care unit and put under SAM (20 mg/kg/d)
    - Severe bilateral intracerebral ventricular dilatation (amelioration since ventriculo-peritoneal derivation, mechanic obstruction at the atlato-cervical junction)

Acknowledgements

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European Reference Network | MetabERN
European Reference Network for Hereditary Metabolic Disorders

IPG

Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

Developmental delay, retinal dystrophy, and hearing impairment : is living-donor liver transplantation an option ?

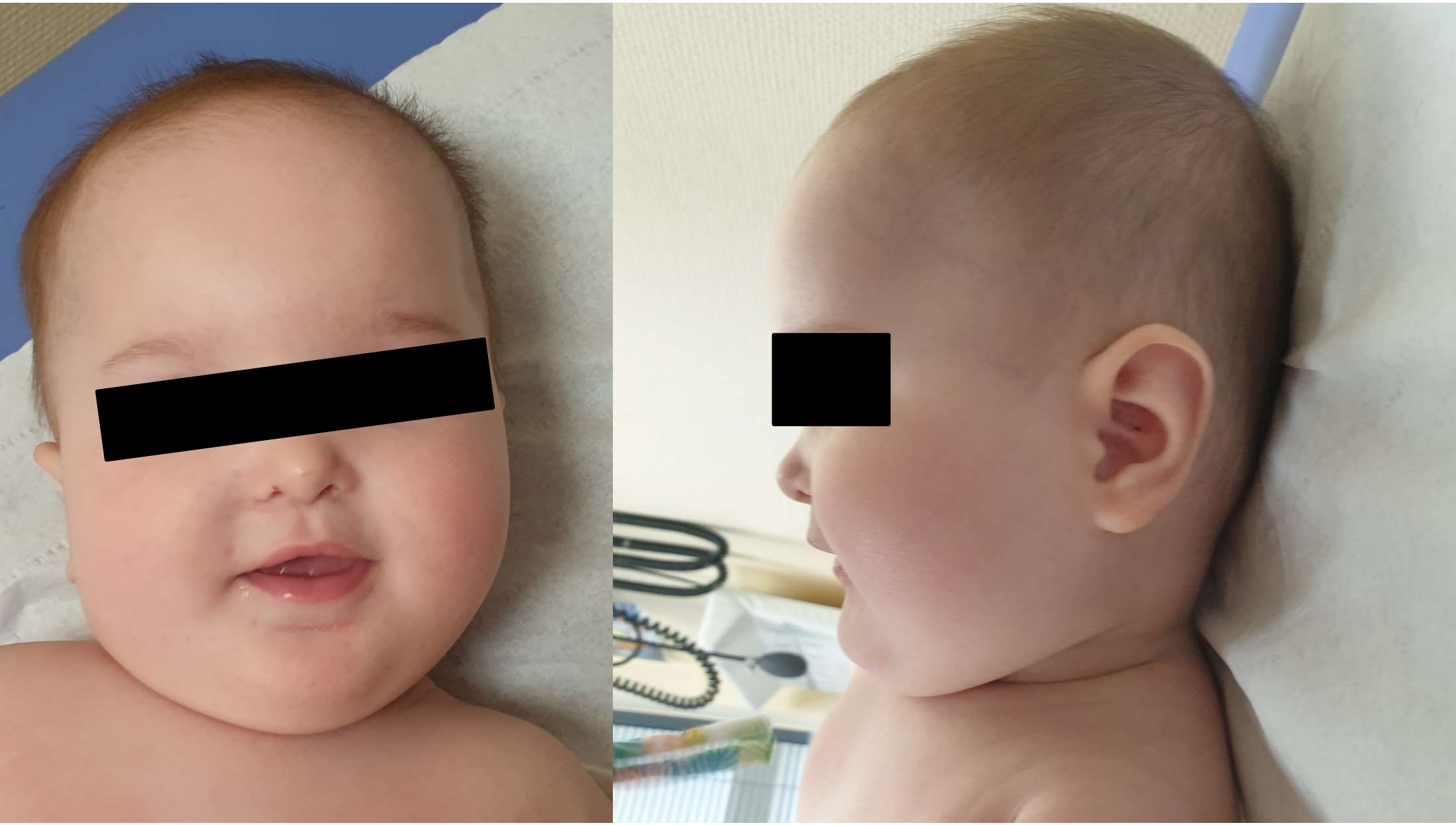
Tanguy Demaret, MD, PhD
Institut de Pathologie et Génétique, Gosselies, Belgium

22-23.04.2024

SSIEM Academy 2024, Amsterdam

Conflict of interest

Apteeus: advisory board member.



F, 7 m, DD, retinal dystrophy, SNHL

Normal pregnancy obtained through IVF (ICSI) < endometriosis

Born at 37+2, **W** P8, **H** P81

D10: jaundice Rx phototherapy (<24h)

Newborn hearing screening: otoacoustic emissions: FAILED x2

- ➔ BERA: treshold: 50 dB x2
- ➔ OCT: retinal dystrophy x2
- ➔ ERG: flat x2

Gross motor delay (not able to sit with support, no rolling over, ..)

Dysmorphic facial features and hypotonia

First child of healthy non-consanguineous parents

Normal growth parameters W P25-50 H P50-75 HC P25-50

Facial dysmorphy Large anterior fontanel with a prominent forehead

Wide nasal bridge with upslanting papebral fissures

Axial hypotonia

No hepatosplenomegaly

Mild elevation of liver enzymes, no cholestasis

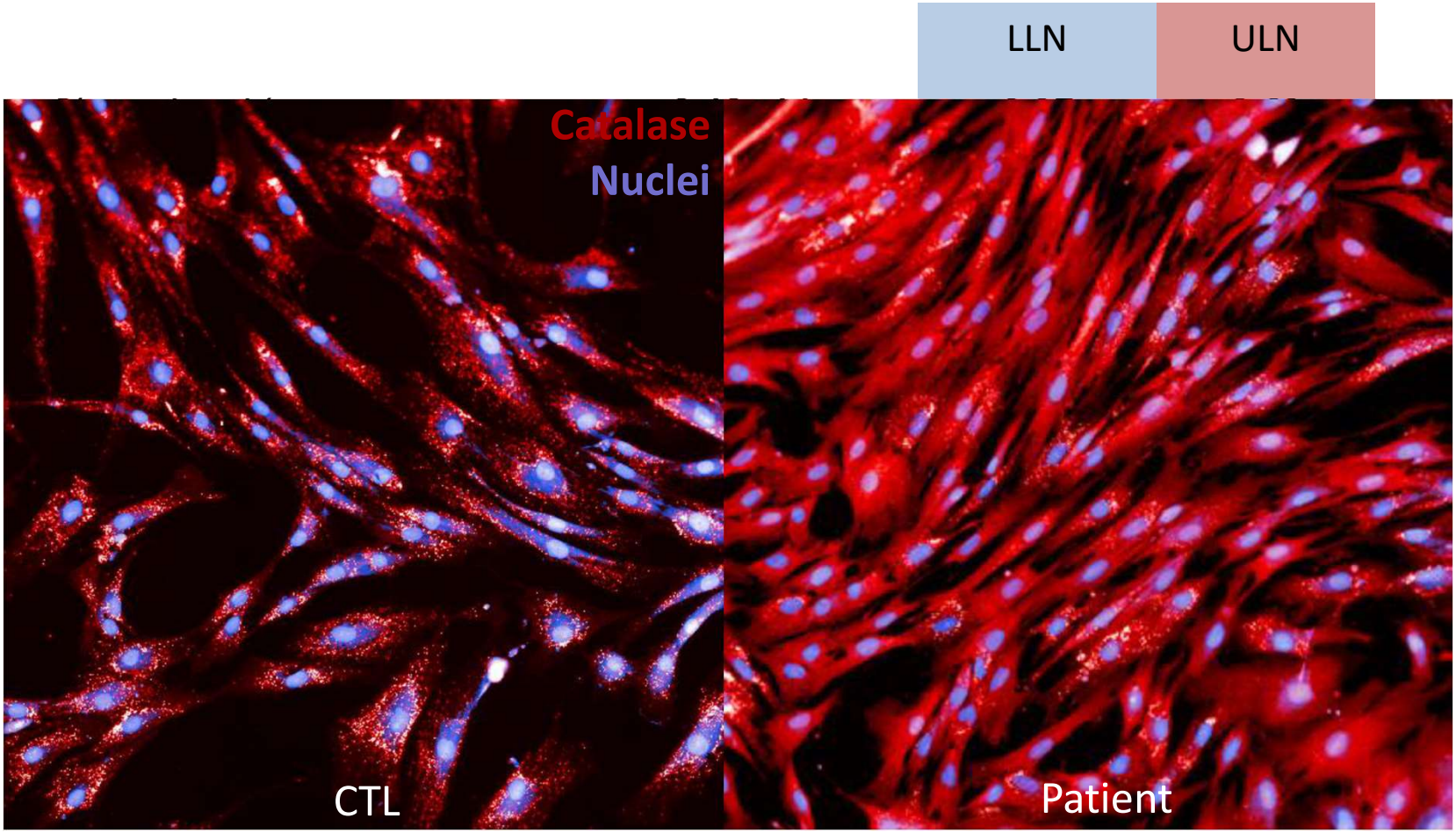
TF US: mild enlargement of the subarachnoid space

Brain MRI: normal

Liver and renal US: normal

GOT/AST: 1,2xULN GPT/ALT: 1,2xULN gGT & TSB: normal

Which test do you ask ?



WES: bi-allelic *PEX6* variants c.2482C>T p.(Gln828Ter) < mother (class 4)
c.929C>T p.(Ser310Leu) < father (class 3 -> 4)

Zellweger spectrum disorder

LDLT was discussed with the parents n = 4 → n = 7

Hypothesis: delivering a high number of functional peroxisomes

normalizing the levels of toxic circulating metabolites

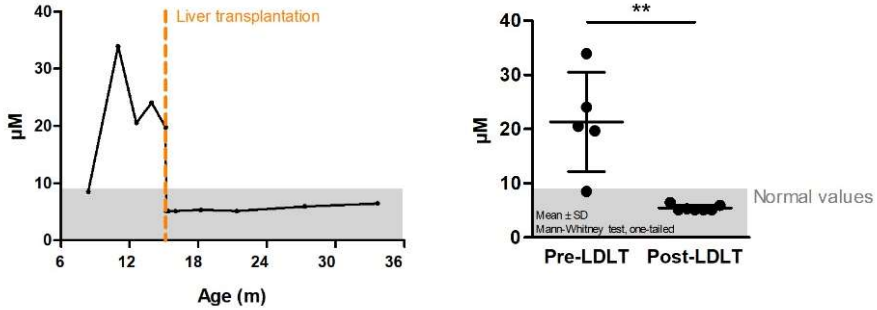
preventing further clinical deterioration

Pre-transplant work-up: Synacthen® test: normal

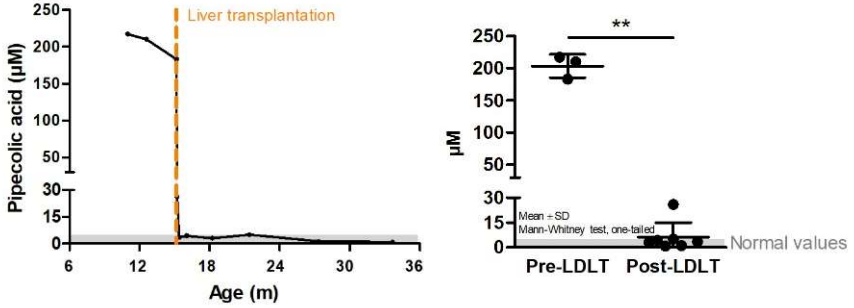
LDLT took place at 14 months

Discharge home POD20

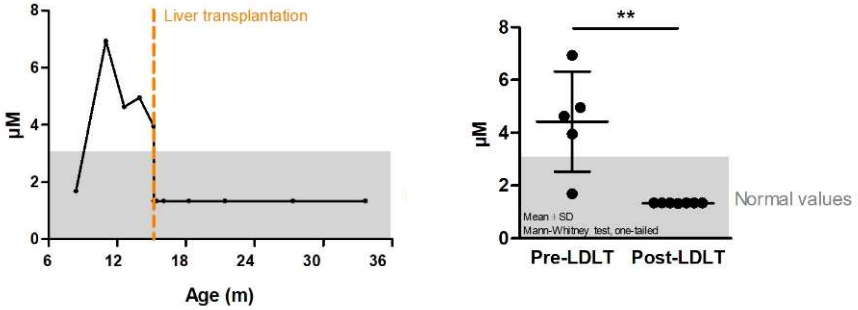
Phytanic acid



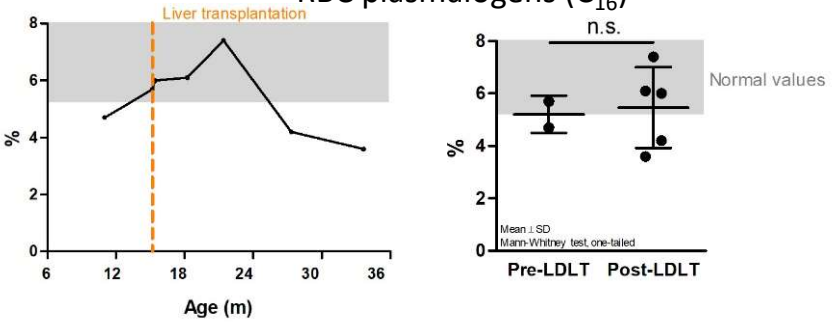
Pipecolic acid



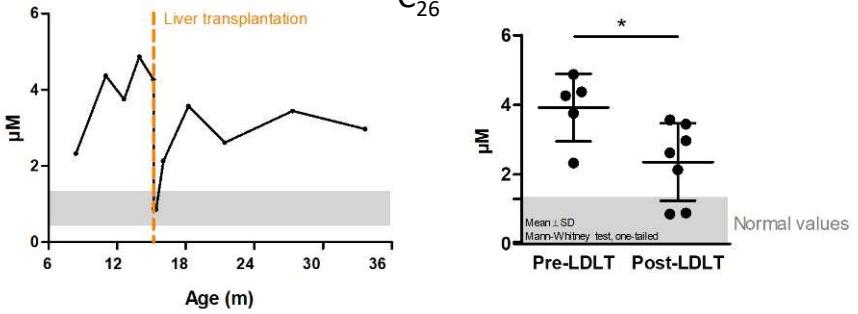
Pristanic acid



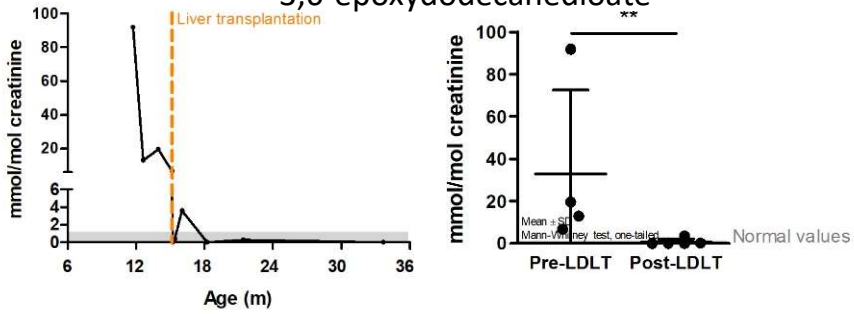
RBC plasmalogens (C_{16})



C_{26}



3,6-epoxydodecanedioate



She is a very interactive girl, 22 m post-LDLT (3 y)

Post-LDLT evolution:

10 d (14m): chilous ascites → fasting 3d + BASIC-F

9 m (1y11m): severe bronchiolitis (3d in PICU)

10 m post-LT (2y) : small bowel obstruction (flanges) → surgery

Neurodvp: crawling, sitting without help, standing with support, very interactive

Vision: stable

Hearing: 3 m post-LDLT: 10 dB loss → cochlear implant 14 m post-LDLT (2y4m)

Liver function test: N

Growth: **W** P10, **H** P25, **BMI** P10, **OFC** P25-50

ZSD is an unmet medical need

LDLT outcome in ZSD is similar to other indications — Synacthen test®

LDLT is associated with clear biochemical improvement — B+U

SNHL degredation is possible post-LDLT — Cochlear implant

Retinal GT & small molecules (chaperone, …) trials are on the horizon

Acknowledgements

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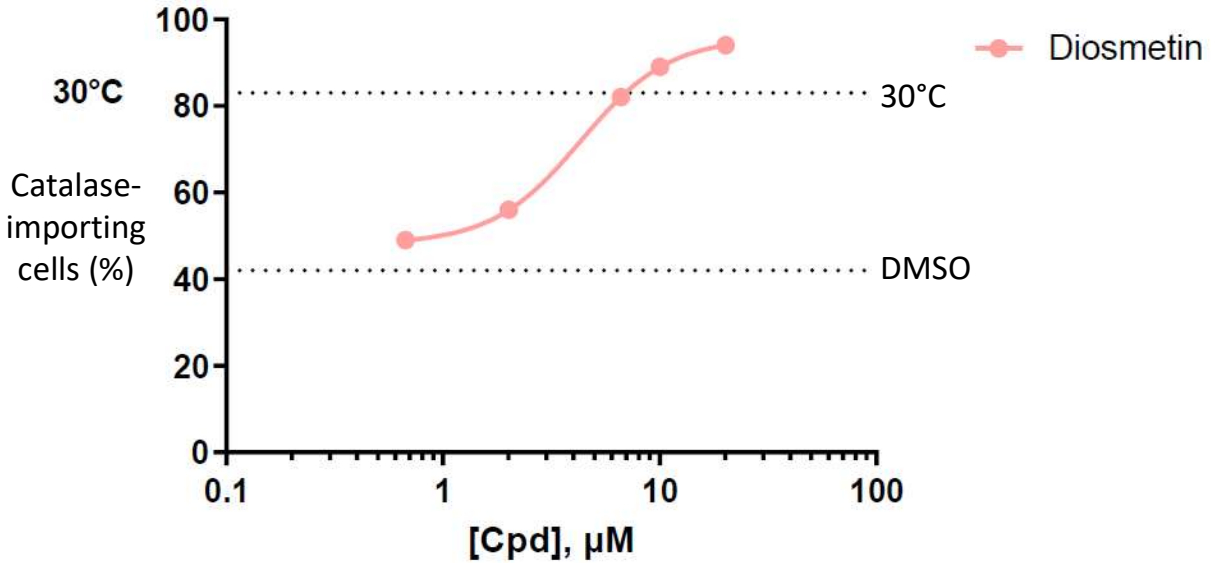
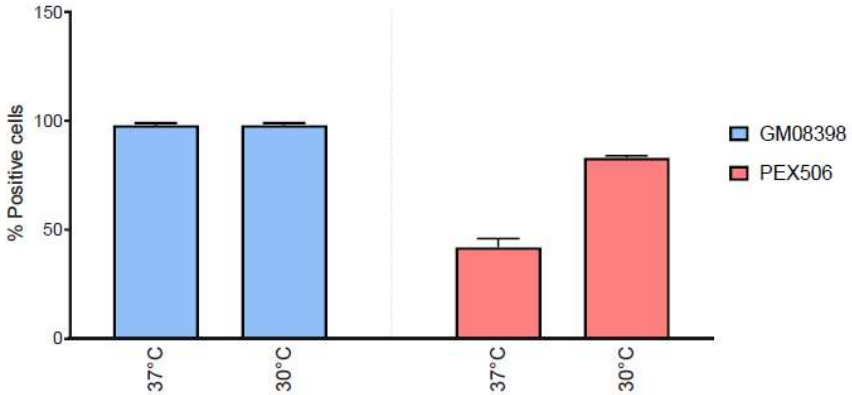
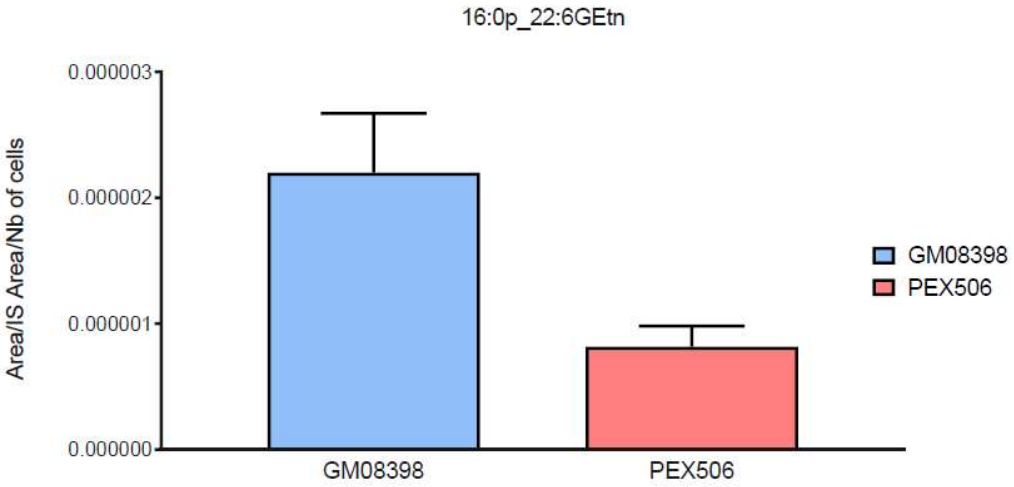
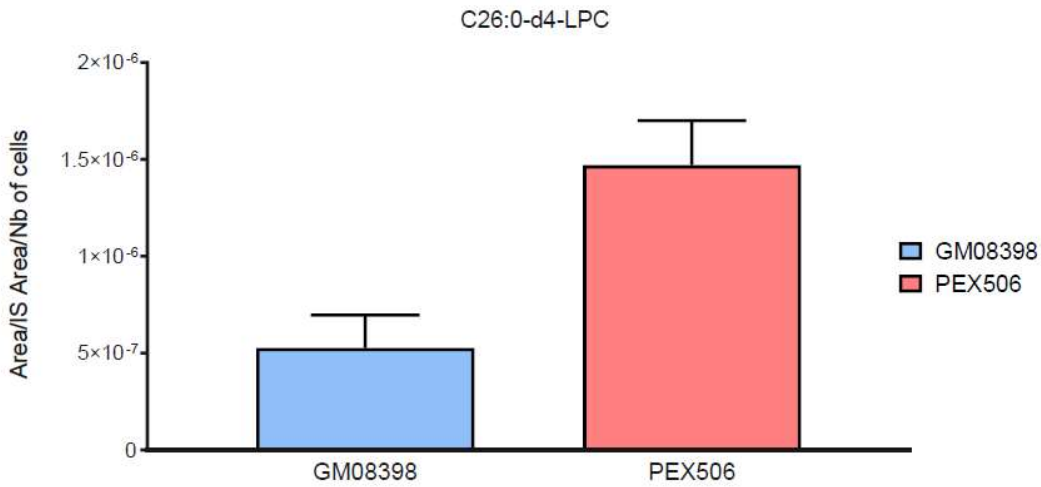

Diosmetin
30°C
30°C
DMSO
Catalase-importing cells (%)
100
80
60
40
20
0
0.1
1
10
100
[Cpd], µM

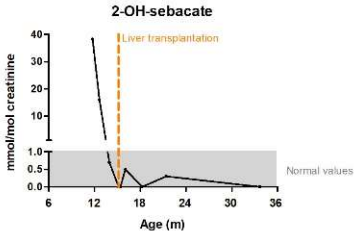

% Positive cells
150
100
50
0
37°C
30°C
37°C
30°C
GM08398
PEX506

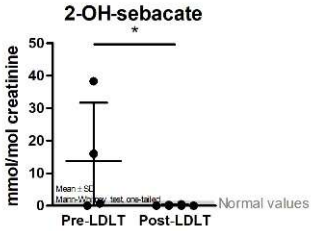
Plasmalogènes

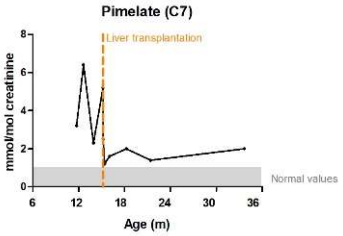


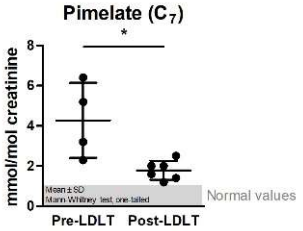
AGTLC

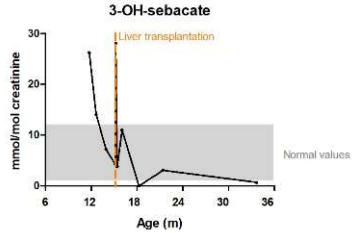


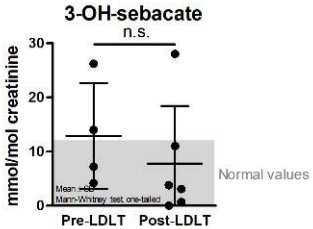

2-OH-sebacate
Liver transplantation
mmol/mol creatinine
Normal values
Age (m)

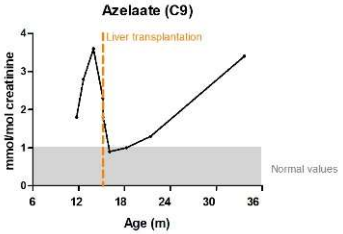

2-OH-sebacate
*
mmol/mol creatinine
Normal values
Pre-LDLT
Post-LDLT

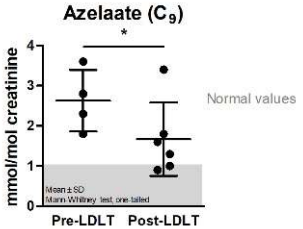

Pimelate (C7)
Liver transplantation
mmol/mol creatinine
Normal values
Age (m)

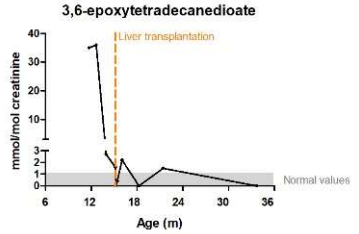

Pimelate (C7)
*
mmol/mol creatinine
Normal values
Pre-LDLT
Post-LDLT

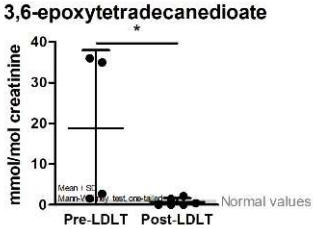

3-OH-sebacate
Liver transplantation
mmol/mol creatinine
Normal values
Age (m)

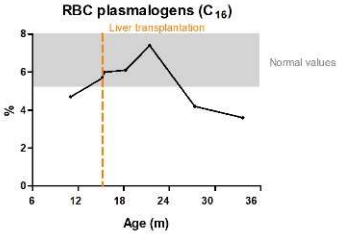

3-OH-sebacate
n.s.
mmol/mol creatinine
Normal values
Pre-LDLT
Post-LDLT

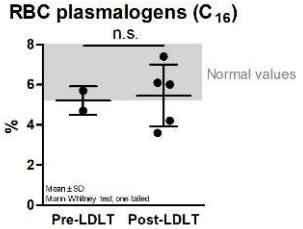

Azelaate (C9)
Liver transplantation
mmol/mol creatinine
Normal values
Age (m)

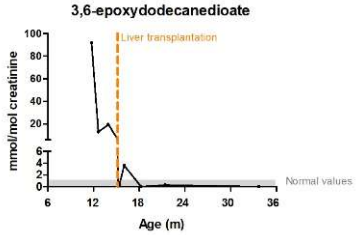

Azelaate (C9)
*
mmol/mol creatinine
Normal values
Pre-LDLT
Post-LDLT

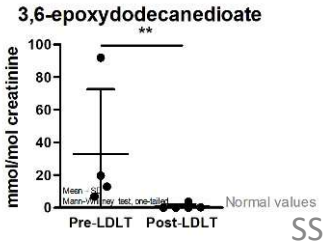

3,6-epoxytetradecanedioate
Liver transplantation
mmol/mol creatinine
Normal values
Age (m)

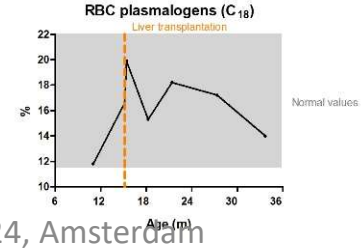

3,6-epoxytetradecanedioate
*
mmol/mol creatinine
Normal values
Pre-LDLT
Post-LDLT

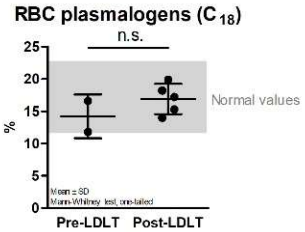

RBC plasmalogens (C16)
Liver transplantation
%
Normal values
Age (m)


RBC plasmalogens (C16)
n.s.
%
Normal values
Pre-LDLT
Post-LDLT

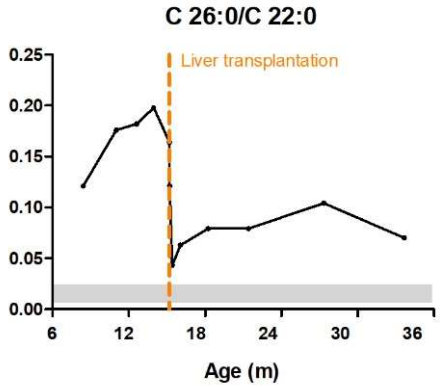

3,6-epoxydodecanedioate
Liver transplantation
mmol/mol creatinine
Normal values
Age (m)

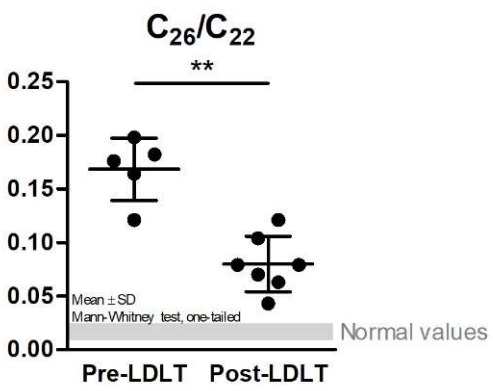

3,6-epoxydodecanedioate
**
mmol/mol creatinine
Normal values
Pre-LDLT
Post-LDLT

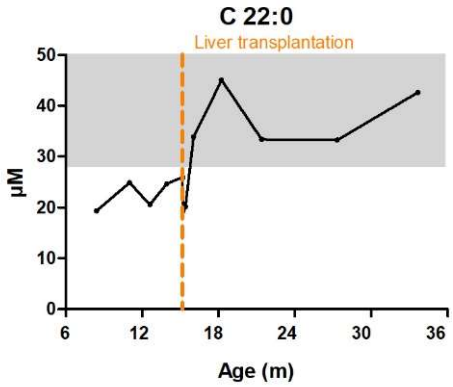

RBC plasmalogens (C18)
Liver transplantation
%
Normal values
Age (m)

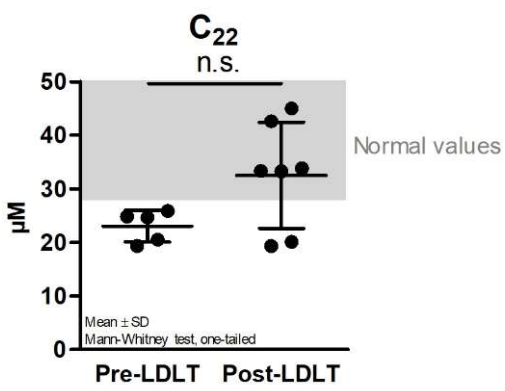

RBC plasmalogens (C18)
n.s.
%
Normal values
Pre-LDLT
Post-LDLT

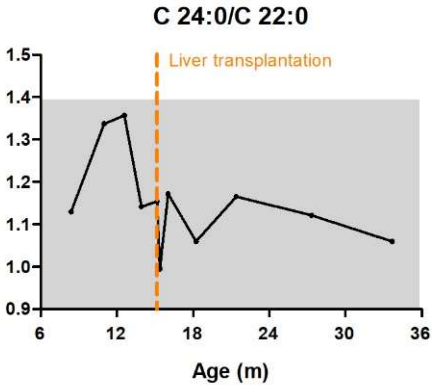
DD & LDLT

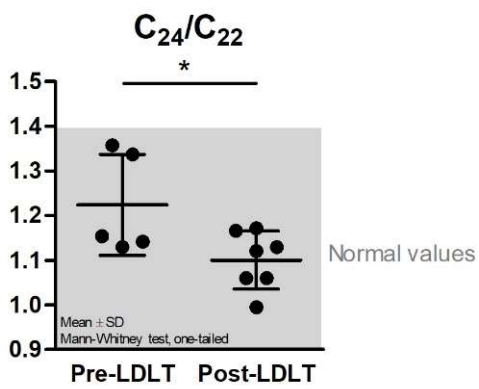

C 26:0/C 22:0
Liver transplantation
0.25
0.20
0.15
0.10
0.05
0.00
6
12
18
24
30
36
Age (m)

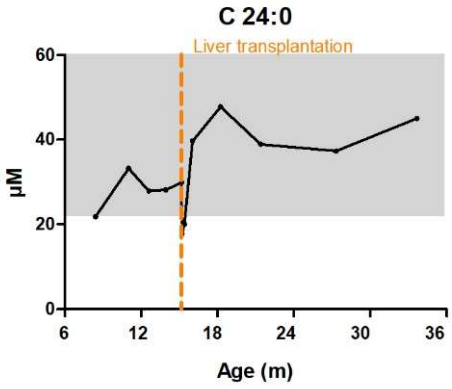

C26/C22
**
0.25
0.20
0.15
0.10
0.05
0.00
Mean ± SD
Mann-Whitney test, one-tailed
Normal values
Pre-LDLT
Post-LDLT

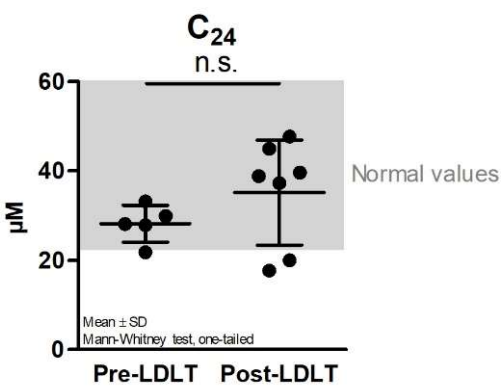

C 22:0
Liver transplantation
µM
50
40
30
20
10
0
6
12
18
24
30
36
Age (m)


C22
n.s.
µM
50
40
30
20
10
0
Mean ± SD
Mann-Whitney test, one-tailed
Normal values
Pre-LDLT
Post-LDLT


C 24:0/C 22:0
Liver transplantation
1.5
1.4
1.3
1.2
1.1
1.0
0.9
6
12
18
24
30
36
Age (m)


C24/C22
*
1.5
1.4
1.3
1.2
1.1
1.0
0.9
Mean ± SD
Mann-Whitney test, one-tailed
Normal values
Pre-LDLT
Post-LDLT


C 24:0
Liver transplantation
µM
60
40
20
0
6
12
18
24
30
36
Age (m)

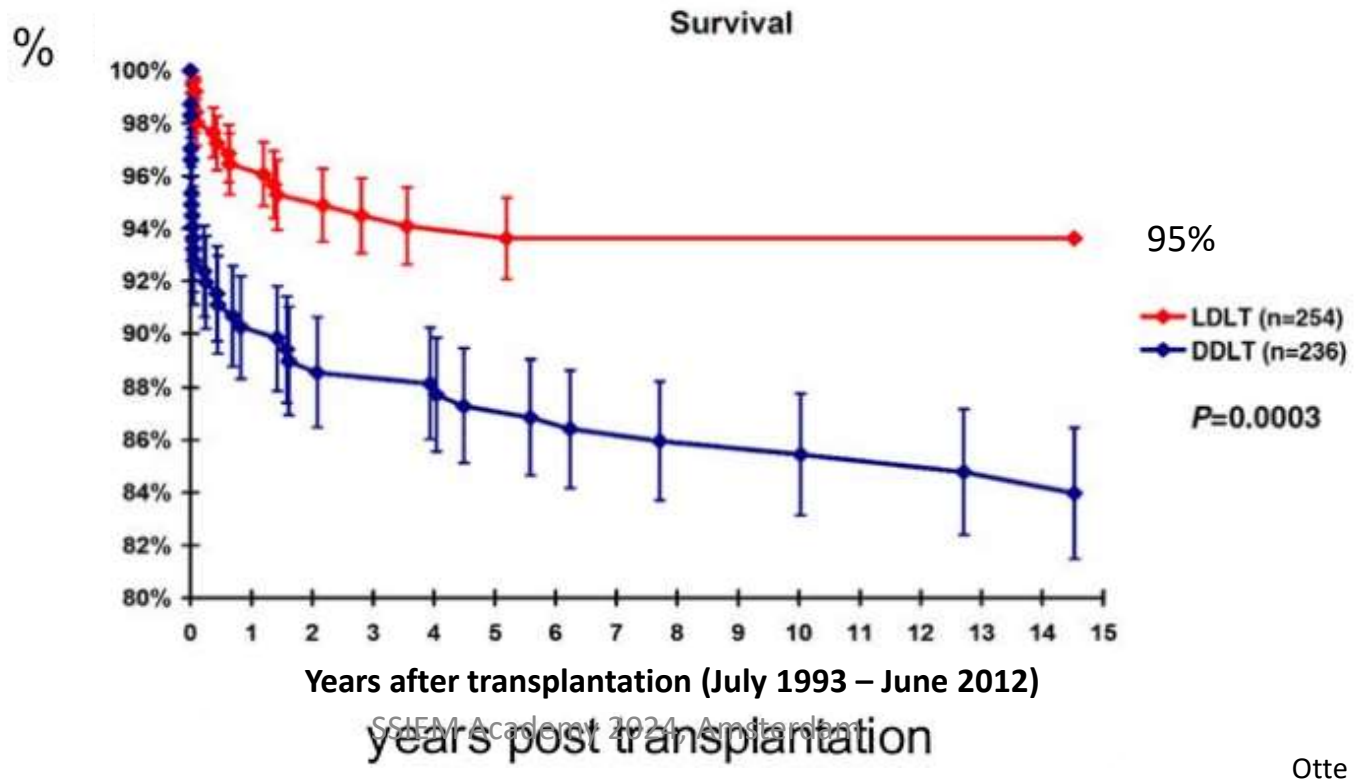

C24
n.s.
µM
60
40
20
0
Mean ± SD
Mann-Whitney test, one-tailed
Normal values
Pre-LDLT
Post-LDLT

Patient survival post-LT is high in IEM patients

Pr. E. Sokal

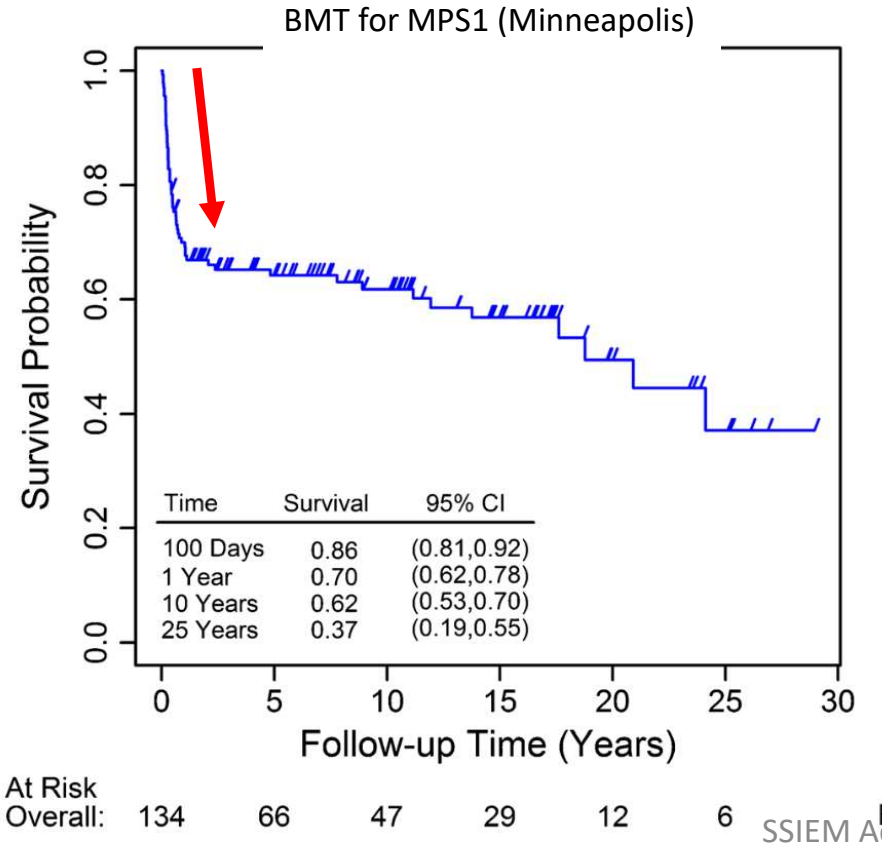
Pr. em. JB Otte

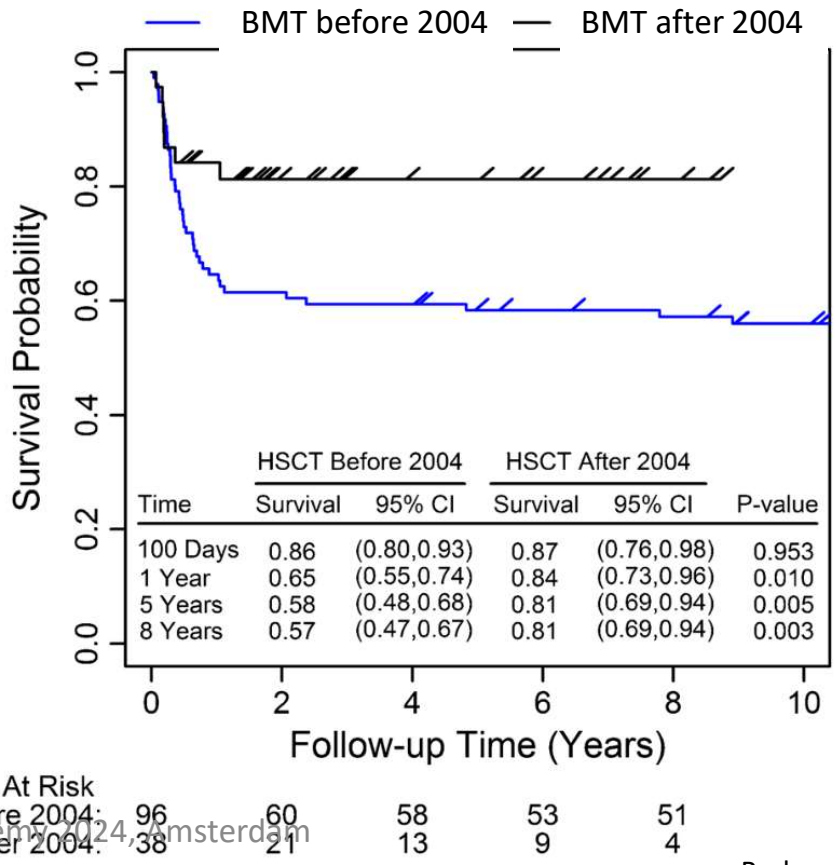
Pr. R. Reding



Otte *et al.*, Liver Transpl, 2016

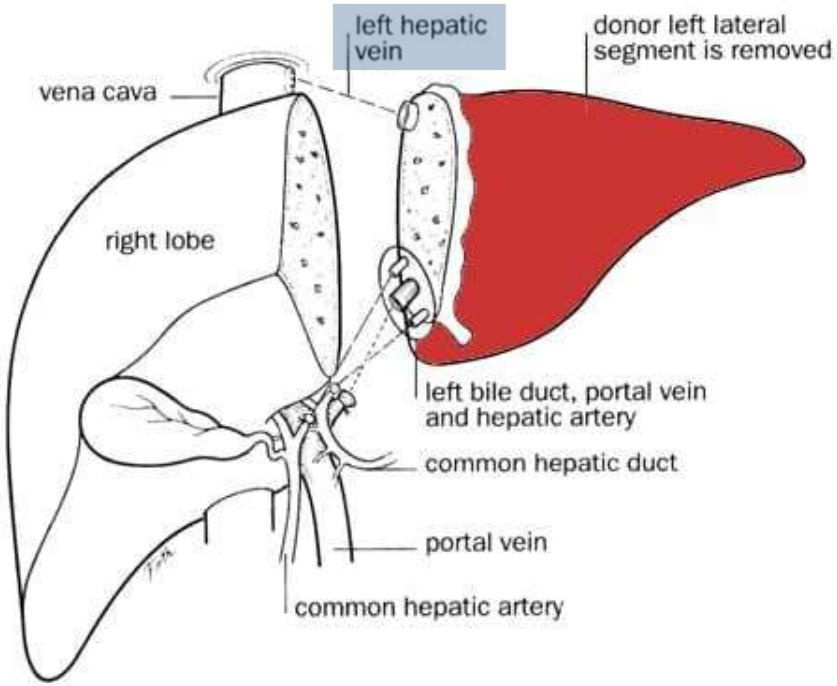
BMT procedure is less invasive than LT, but patient survival is lower post-BMT than post-LT



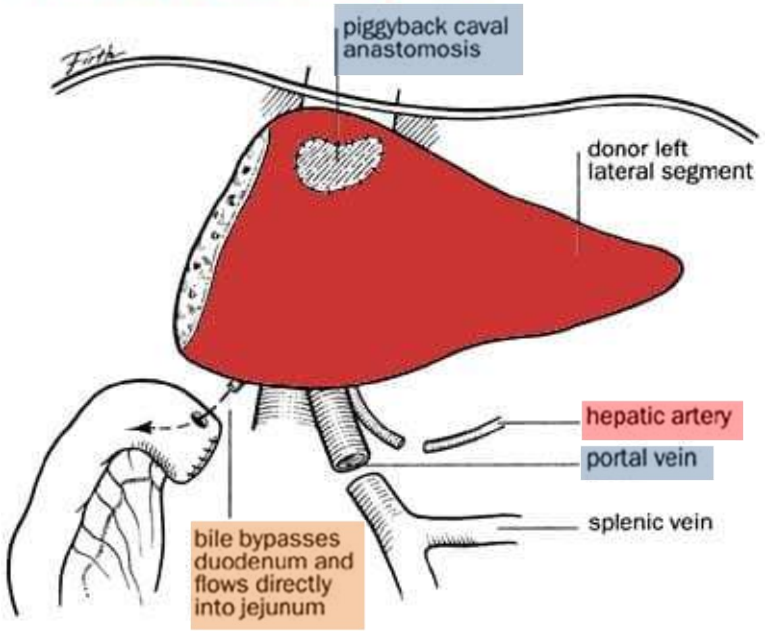


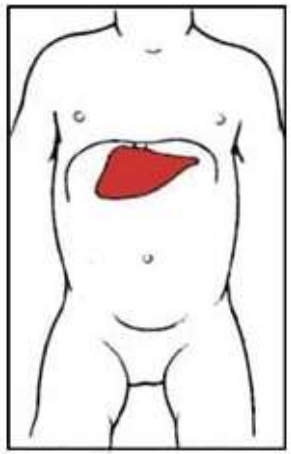
Rodgers *et al.*, JIMD, 2016

Adult Liver Donor



Pediatric Liver Recipient





Children's Hospital Los Angeles

Most of the severe LT complications are treatable

- Biliary complications 23% (98/429) — Darius et al., *Liver Transp*, 2014
  - 2/3 = anastomotic complications 14% (60/429)
- Vascular complications: 10% (25*/250) — Gurevich et al., *Ann Surg*, 2015
  - Portal vein thrombosis 9% (22*/250)
  - Arterial thrombosis 0,8% (2*/250)
  - Hepatic vein stenosis/thrombosis: 0,8% (2/250)
- Post-tx lymphoproliferative disease (PTLD) 16% (7/45) — Smets et al., *Transplantation*, 2002
- 1-year acute rejection free survival 48% (120/250) — Gurevich et al., *Ann Surg*, 2015


SSIEM
ACADEMY 2024

USE OF LCMSMS, ENZYMOLOGY AND NEXT-GENERATION SEQUENCING FOR THE DIAGNOSIS OF METABOLIC NEPHROLITHIASIS

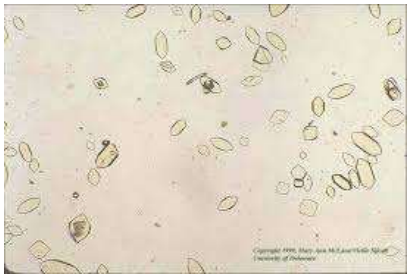
NICOLA GREEN

SSIEM ACADEMY 2024

PATHWEST LABORATORY MEDICINE, WESTERN AUSTRALIA

NO CONFLICTS OF INTEREST TO DECLARE

CASE KB - PRESENTATION



- Two year old male
- Abnormal urethral discharge
- Cytoscopy revealed urinary crystals
- Urine uric acid concentration 2.90 mol/mol Cr [NR 0.25 – 1.20]
- Review of family history revealed the maternal grandfather had a history of renal stones and was treated with allopurinol.
- Suspicion was raised of an X-linked inherited disorder

CASE KB – PURINE AND PYRIMIDINE SCREEN (VCGS)

- Urine metabolic screen (~ 40 metabolites on LCMSMS): normal profile, xanthine not increased
- Urine sent to Victorian Clinical Genetic Services for purine and pyrimidine analysis by HPLC.
- Panel includes purine metabolites guanine, adenine, xanthine and hypoxanthine

Specimen Source: Urine - Random

PURINE AND PYRIMIDINE SCREEN		Result Value	Reference Range	Units
Creatinine		2.4	-	mmol/L
Urate		2201	200 - 2500	µmol/mmol creatinine
Hypoxanthine	**H**	91	0 - 60	µmol/mmol creatinine
Xanthine		36	0 - 60	µmol/mmol creatinine

CASE KB – HPRT ENZYMOLOGY

- Whole blood washed with saline to produce erythrocyte pellet.
- Sent on dry ice to South Australia Pathology Biochemical Genetics laboratory.
- Testing showed a reduced HPRT enzyme activity

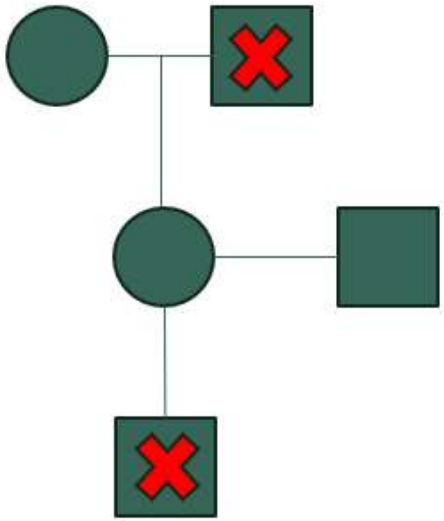
  HPRT Activity = 0.2 nmol/min/mg Hb [2.9 – 10.0]

CASE KB - DIAGNOSIS

- Hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency
  - Increased urine urate
  - Increased urine hypoxanthine
  - Reduced erythrocyte HPRT enzyme activity

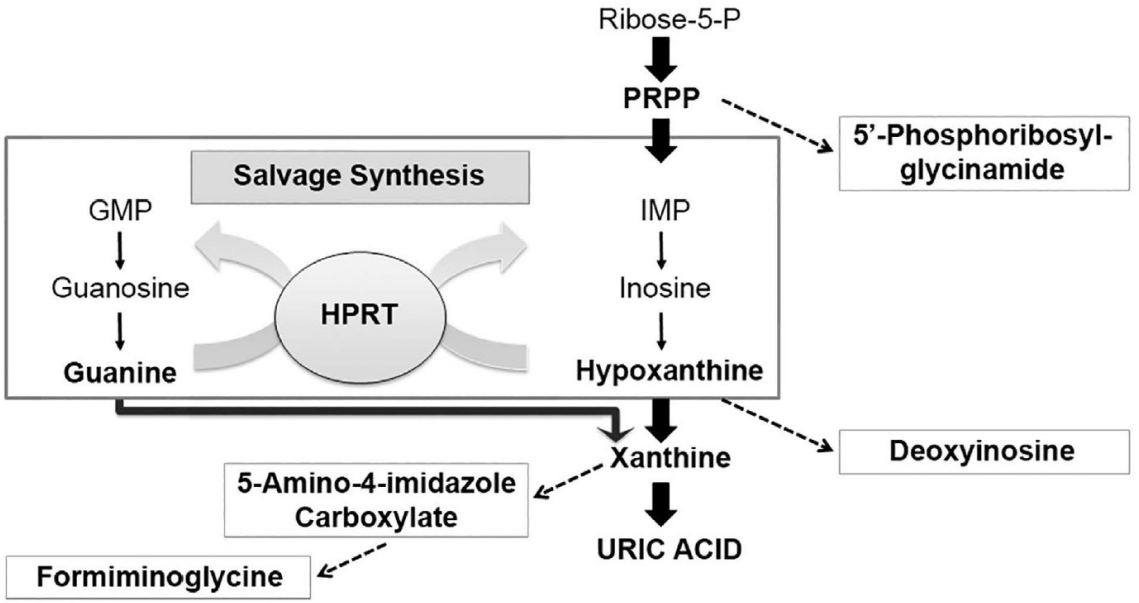
CASE-KB GENOTYPING

- Next generation sequencing by whole exome capture
- Hemizygous HPRT1 variant c.27+174G>T
- Deep intronic variant
- Not previously reported in gnomAD
- Classified as likely pathogenic based on gene modelling and ACMG criteria



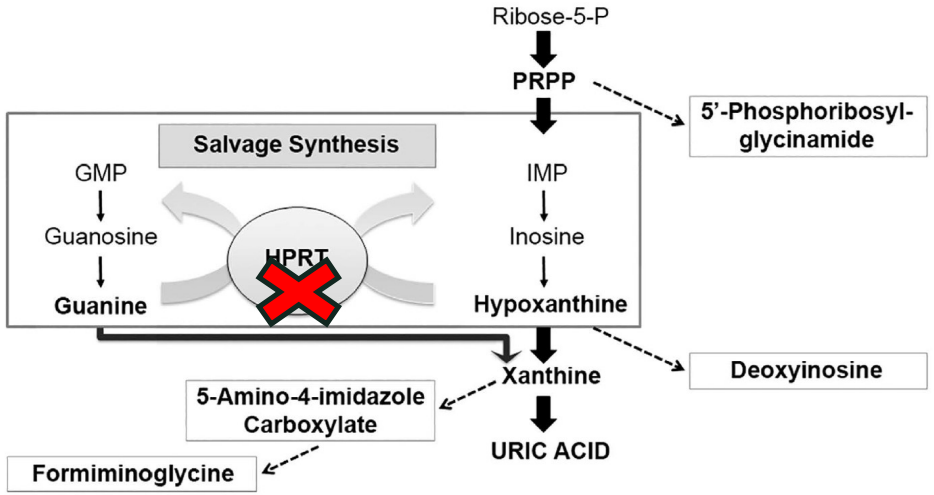
PURINE PATHWAY

- The HPRT is an enzyme in the purine salvage pathway that converts hypoxanthine and guanine to inosine monophosphate (IMP) and guanosine monophosphate (GMP)



HPRT DEFICIENCY

- HPRT deficiency leads to an excess of hypoxanthine that is then converted to xanthine and uric acid.
- Results in excess uric acid production.

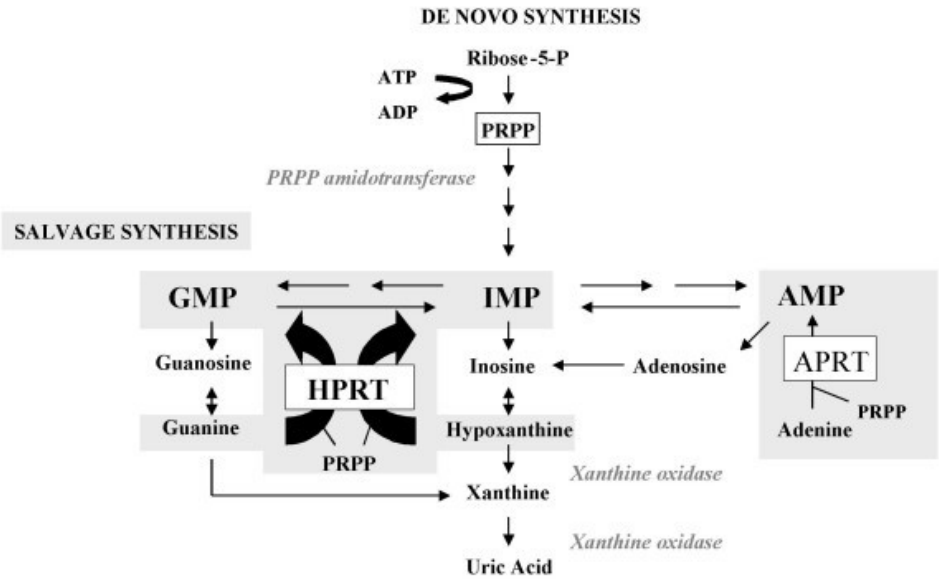


HPRT DEFICIENCY

- Partial HPRT deficiency usually limited to renal stones and gout due to excess uric acid.
- Severe form (Lesch-Nyhan Syndrome) is characterised by additional neurological symptoms such as self injury.
- Disease severity is dependent on level of residual HPRT enzyme activity.
- Due to the lack of neurological symptoms and level of residual HPRT activity, this case KB was classified as HPRT deficiency.

CASE KB- TREATMENT

- Allopurinol therapy (50 mg doses, 5-10 mg/kg/day) was commenced to reduce the uric acid levels.
- Allopurinol inhibits the xanthine oxidase enzyme that converts hypoxanthine to xanthine and xanthine to uric acid.
- Treatment regarded as successful. Only one episode of urethral discharge and abdominal pain since treatment commenced.



CASE KB- MONITORING

- Regular urine purine metabolite testing performed to monitor hypoxanthine and xanthine concentrations.
- High xanthine concentrations may also result in urine crystal formation
- 6 months post diagnosis
  - Urine urate creatinine ratio= 1.33 mol/mol Cr [0.25 – 1.20]
  - Xanthine = 230 umol/mmol Cr [0 – 60]
  - Hypoxanthine = 435 umol/mmol Cr [0 – 60]

CONCLUSION

- A combination of testing including LCMSMS, HPLC, enzymology and next-generation sequencing were required to inform this diagnosis.
- These results in combination with the clinical phenotype informed the final diagnosis of HPRT deficiency.
- Expansion of our urine LCMSMS method in development to include more purine and pyrimidine metabolites.

ACKNOWLEDGEMENTS

- Lawrence Greed Clinical Scientist PathWest
- Dr Nicholas Larkins Perth Children's Hospital
- Dr James Pitt, Kai Mun Hong VCGS
- Dr Carol Siu, Prof Maria Fuller SA Pathology


SSIEM
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A Triad of Intellectual Disability, Focal Seizures, and Chorioretinal Atrophy

Julien Park

University Hospital Münster – Department of General Paediatrics

Münster, Germany

SSIEM Academy 2024, Amsterdam

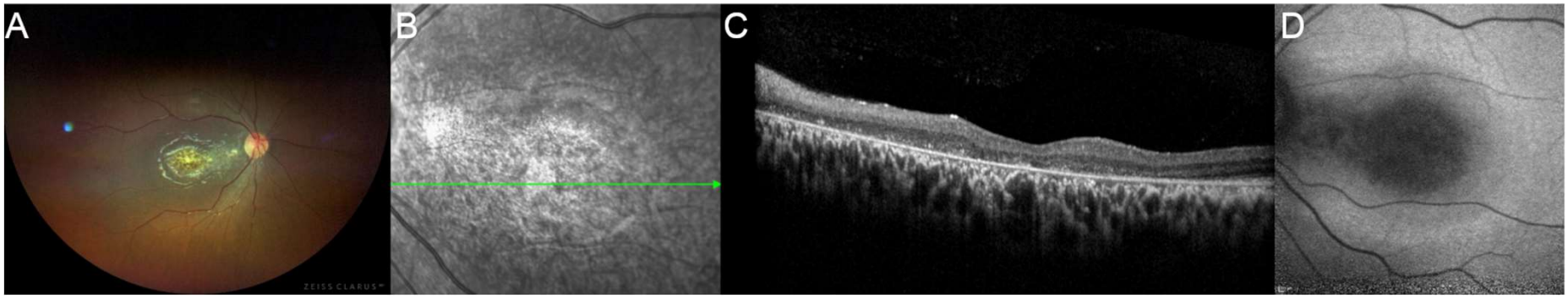
Conflicts of interest

No conflicts of interest related to this case presentation.

Travel funds by Amicus, Recordati Rare Diseases, Biomarin.

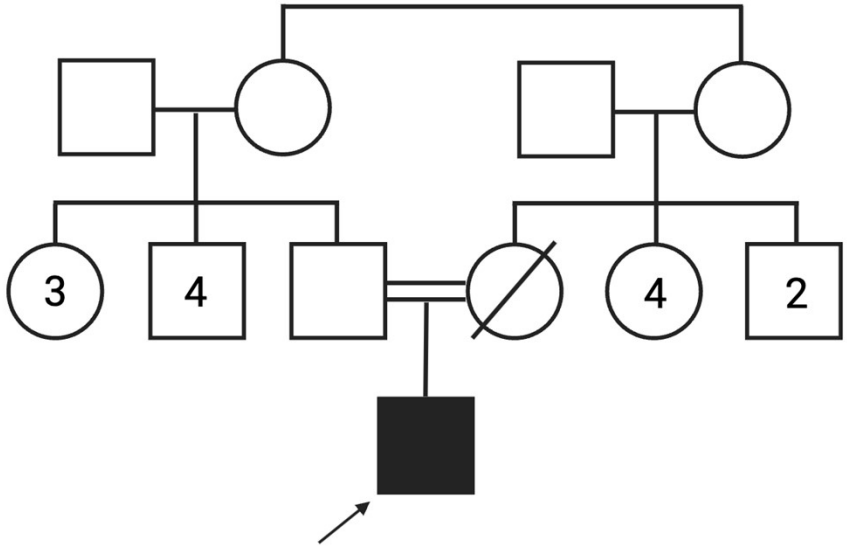
Patient history

- *17 year-old male*
- *Parents consanguineous (1st degree cousins)*
- *Focal seizures with rhythmic, parieto-occipital spike-waves*
- *WISC V: overall IQ 44 (90% CI: 42-51, < 0.1 percentile)*
- *Low visual acuity*



Family history

- *No comparable cases in the extended family*
- *Family of Syrian origin with additional consanguineous unions over several generations*
- *Mother died aged 42 from unknown liver disease*



ID, Seizures, and Chorioretinal Atrophy

Laboratory findings

Basic clinical chemistry	*low Ca^{2+}, otherwise n*
Amino acids (P)	*n*
Organic acids	*n*
Transferrin glycosylation	*n*
Lysosphingolipids	*n*

ID, Seizures, and Chorioretinal Atrophy

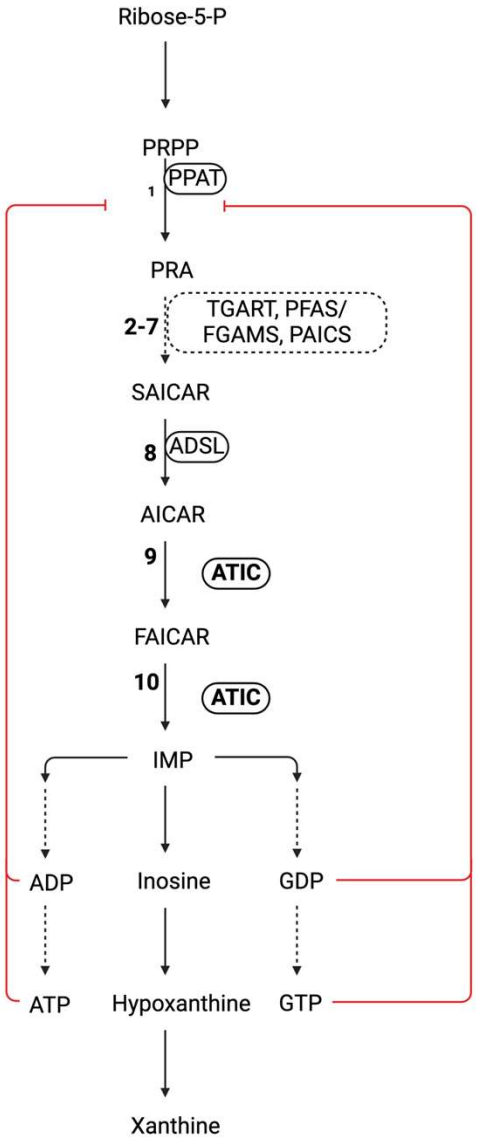
Purine / pyrimidine analysis

Succinyladenosine (SAdo): 12 mmol/mol Crea (< 10)
AICA-riboside: 78 mmol/mol Crea (< 5) ,

otherwise normal

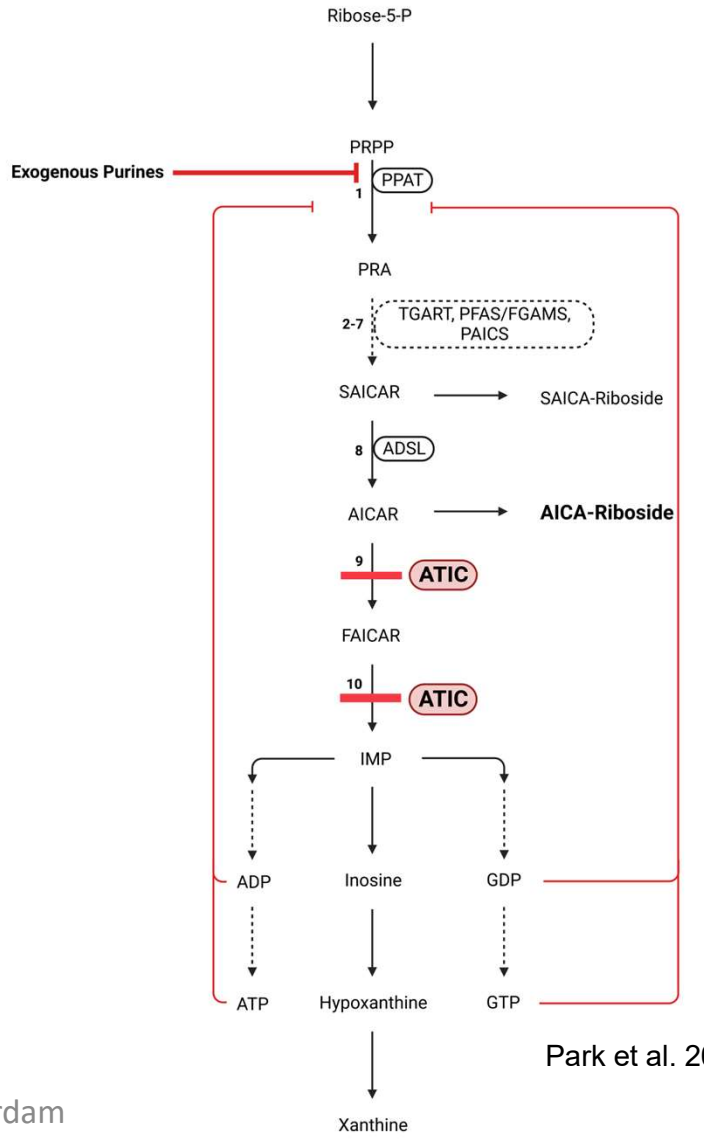
ID, Seizures, and Chorioretinal Atrophy

Purine metabolism



ID, Seizures, and Chorioretinal Atrophy

Purine metabolism



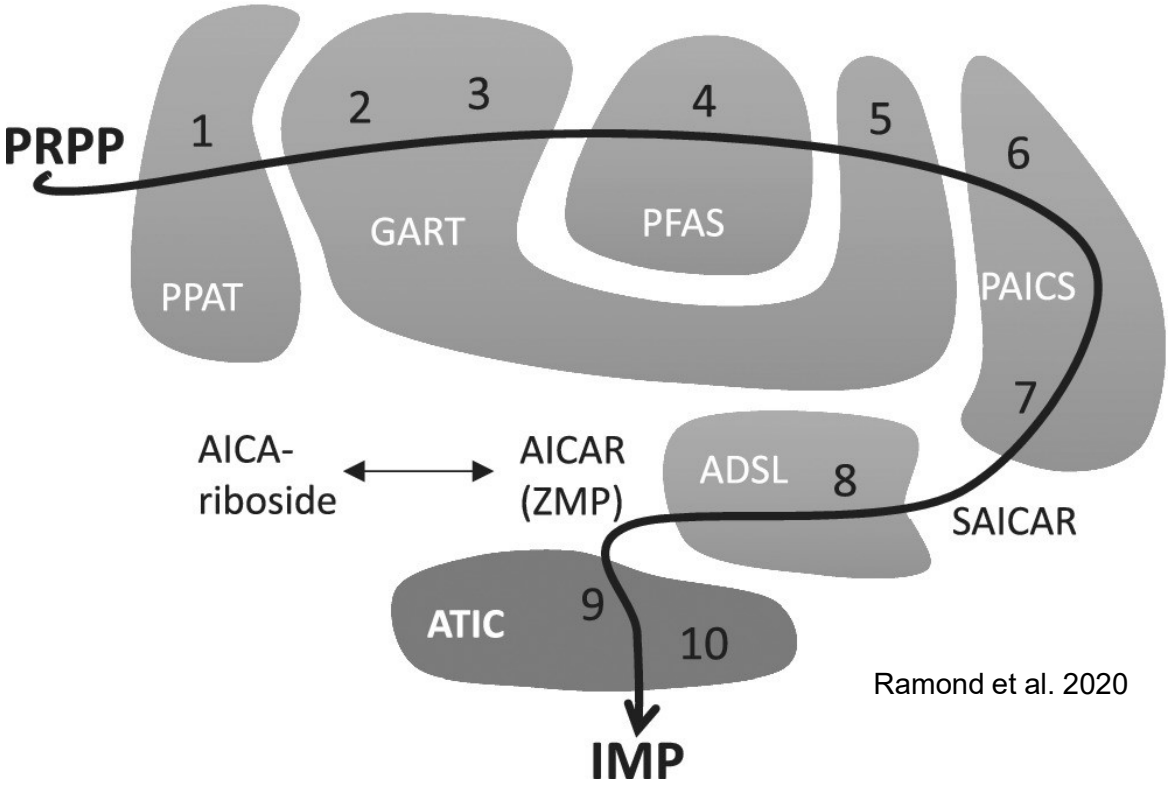
Park et al. 2024

Genetic analysis

Duo-exome sequencing

Patient:
ATIC c.1277A>G (p.K426R);
c.642G>C (p.Q214H)

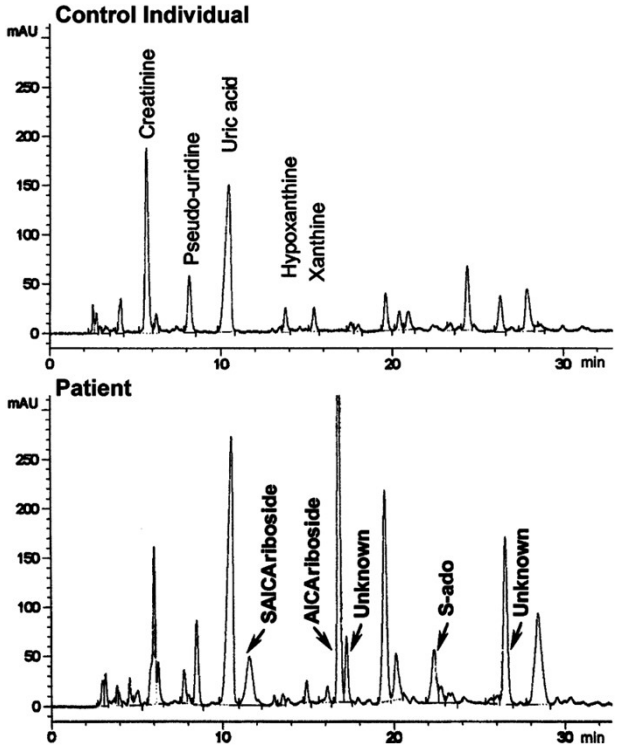
Father: *ATIC* c.1277A>G (p.K426R)



Ramond et al. 2020

AICA ribosiduria

- *Biallelic pathogenic variants in ATIC*
- *Elevated AICA-riboside (pathognomonic), SAdo (+ SAICA-riboside) in urine and CSF*
- *neurodevelopmental phenotype with developmental delay, seizures, and chorioretinal atrophy*



Marie et al. 2004

Acknowledgements

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