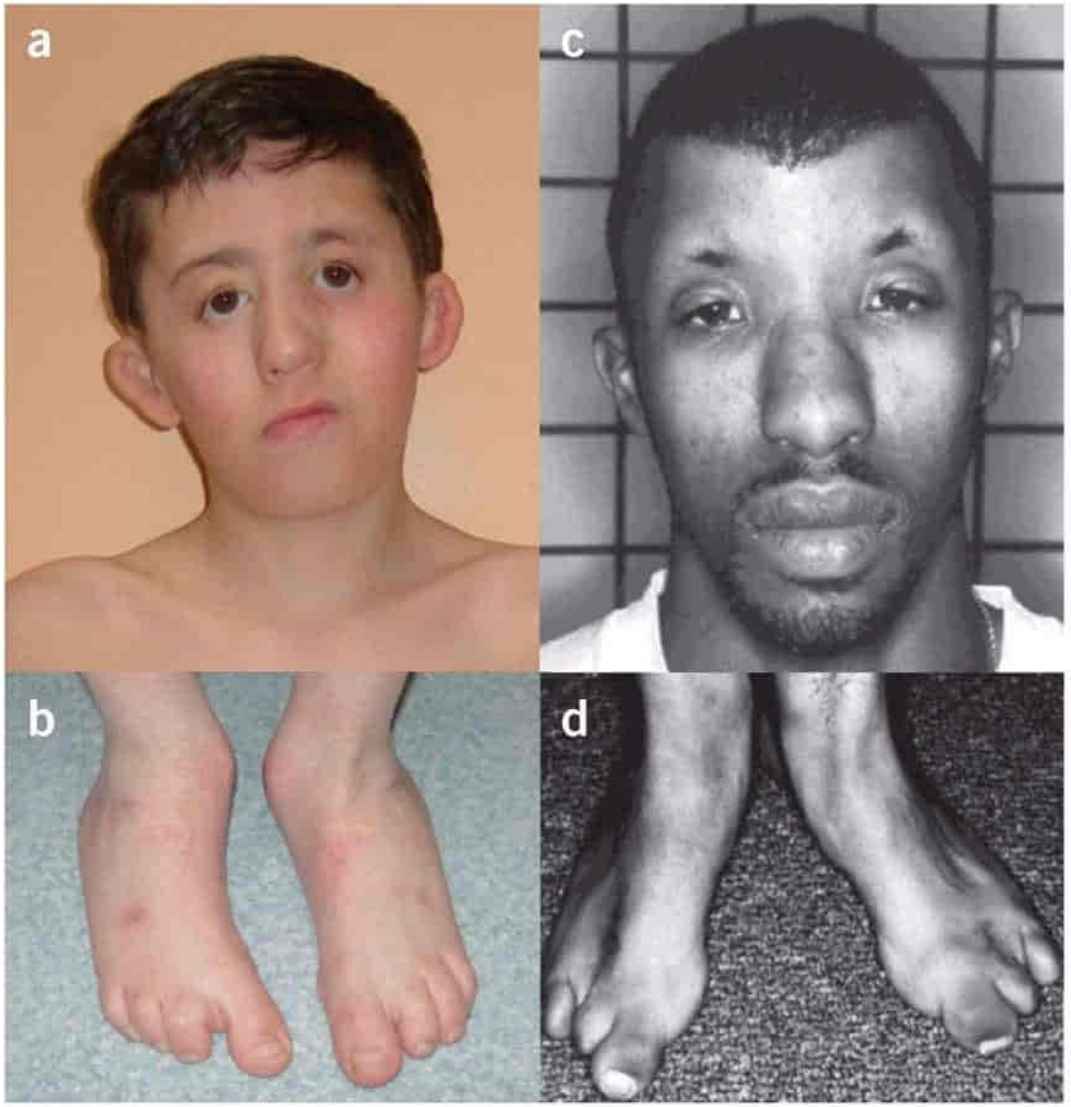
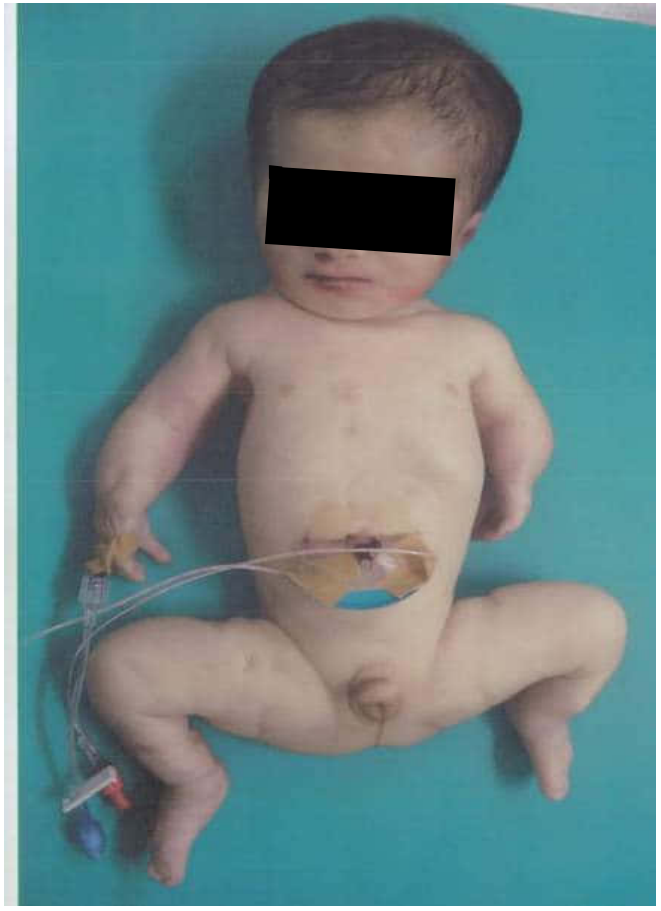
Dihydro-orotate dehydrogenase (DHODH) deficiency

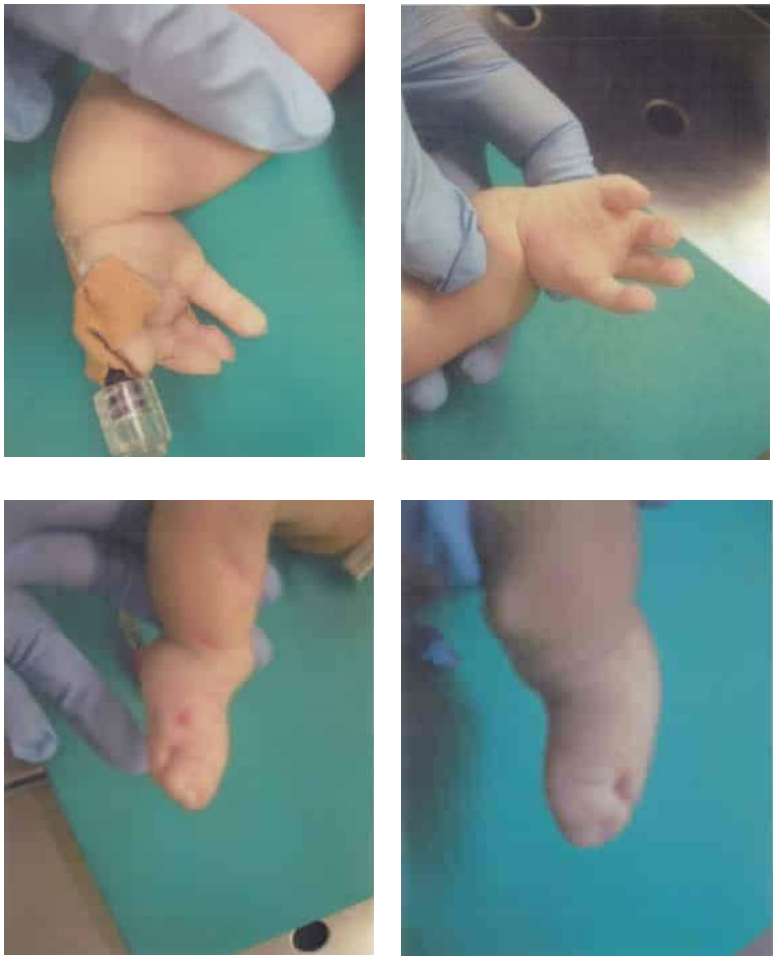


Reused with permission from Ng et al Nature Genetics 42, 30-35 (2010)

ERNDIM
QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

Dihydro-orotate dehydrogenase deficiency- Maastricht patient





- Bilateral mesomelic dysplasia
- Shortened radius and tibia
- Shortening and bowing of ulna and fibula

- Both hands 4 digits (incl. thumb.)
- Both feet 3 digits
- Cutaneous syndactyly digit I & II right foot
- Abnormal stance of ankles and feet

263750

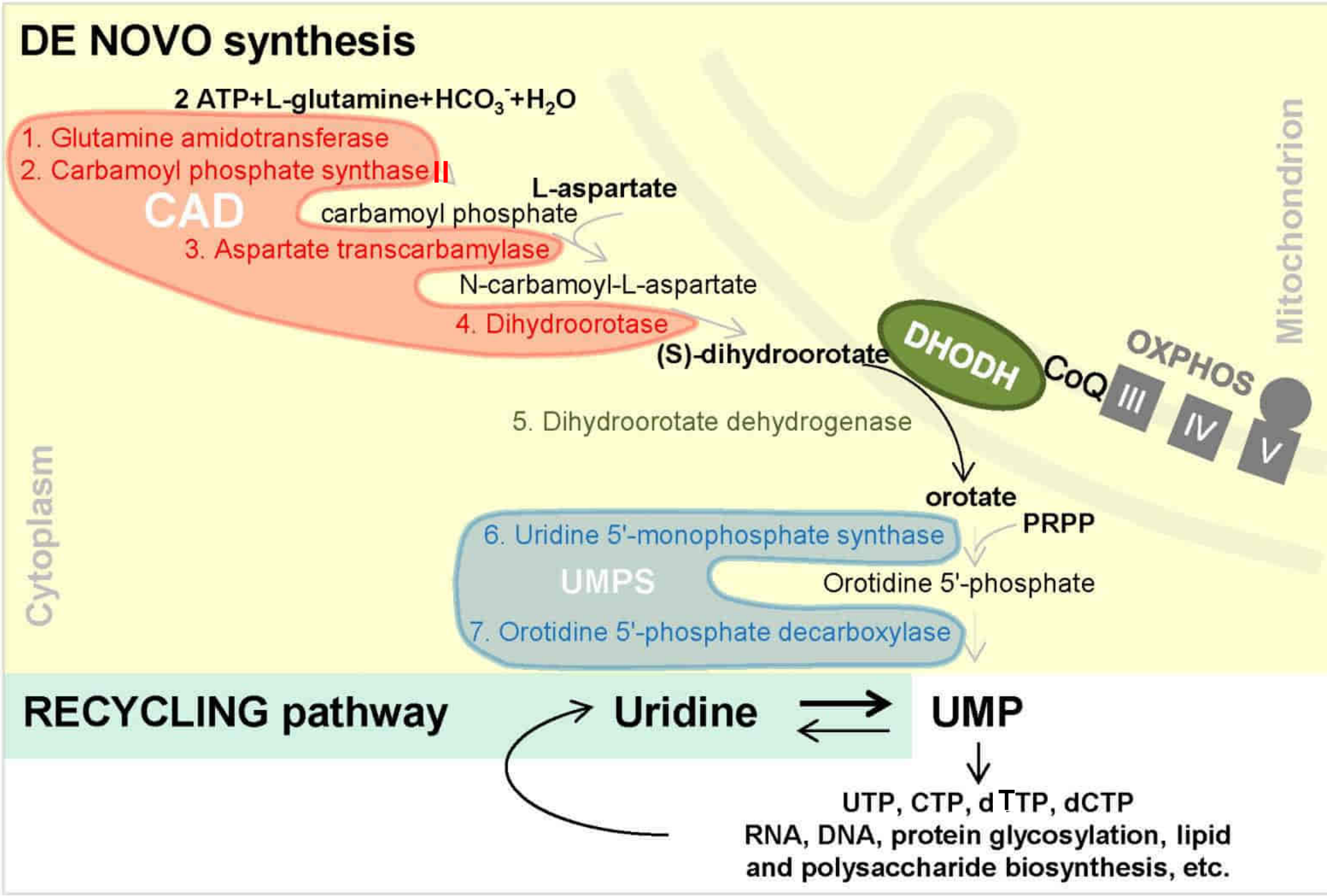
POSTAXIAL ACROFACIAL DYSOSTOSIS; POADS

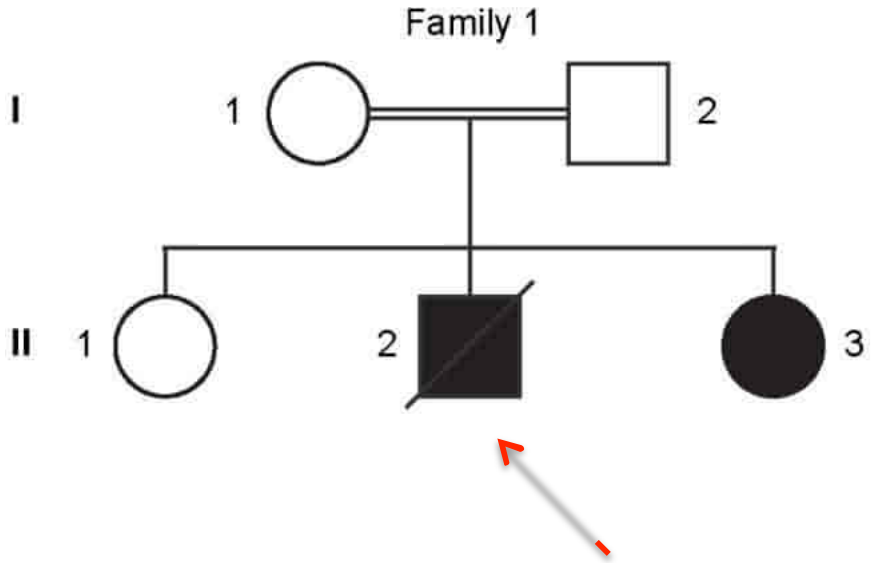
Alternative titles; symbols

MILLER SYNDROME

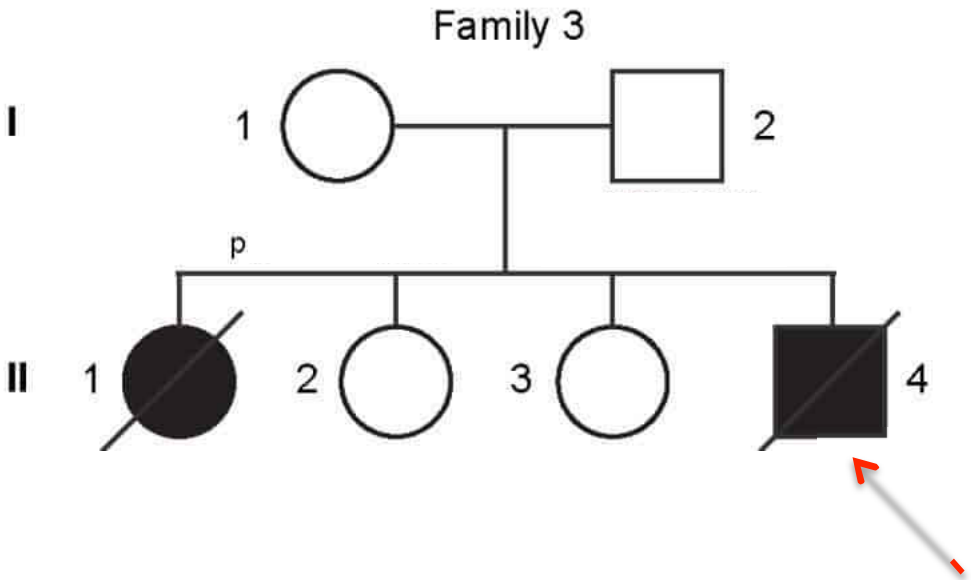
GENEE-WIEDEMANN SYNDROME

- severe micrognathia
- cleft lip and/or palate
- hypoplasia or aplasia of the postaxial elements of the limbs
- coloboma of the eyelids
- supernumerary nipples
- ?liver dysfunction?
- *DHODH* – Dihydroorotate Dehydrogenase deficiency
- Ng, S. B. et al. Exome sequencing identifies the cause of a mendelian disorder. Nature Genet. 42: 30-35, 2010.
- 3 months tereatment with uridine at age 4 years for behavioural problems unsuccesful (Duley et al, MGM, 2016)
- >>>> “Potential uridine treatment in early pregnancy to prevent morphological anomalies presents an exciting but untested possibility.”

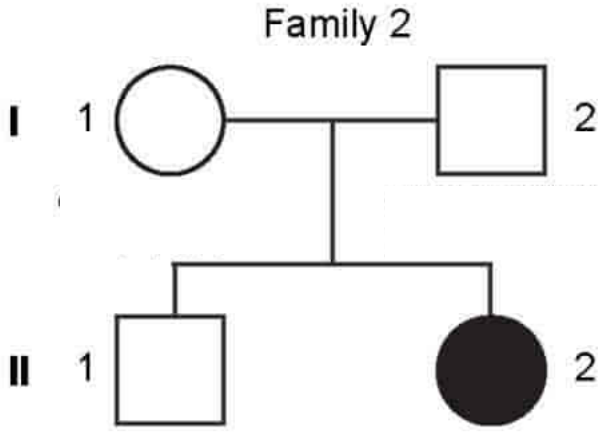

DE NOVO synthesis
2 ATP+L-glutamine+HCO3-+H2O
1. Glutamine amidotransferase
2. Carbamoyl phosphate synthase II
CAD
L-aspartate
carbamoyl phosphate
3. Aspartate transcarbamylase
N-carbamoyl-L-aspartate
4. Dihydroorotase
(S)-dihydroorotate
DHODH
CoQ
OXPHOS
III
IV
V
Mitochondrion
5. Dihydroorotate dehydrogenase
orotate
PRPP
6. Uridine 5'-monophosphate synthase
UMPS
Orotidine 5'-phosphate
7. Orotidine 5'-phosphate decarboxylase
Cytoplasm
RECYCLING pathway
Uridine
UMP
UTP, CTP, dTTP, dCTP
RNA, DNA, protein glycosylation, lipid
and polysaccharide biosynthesis, etc.



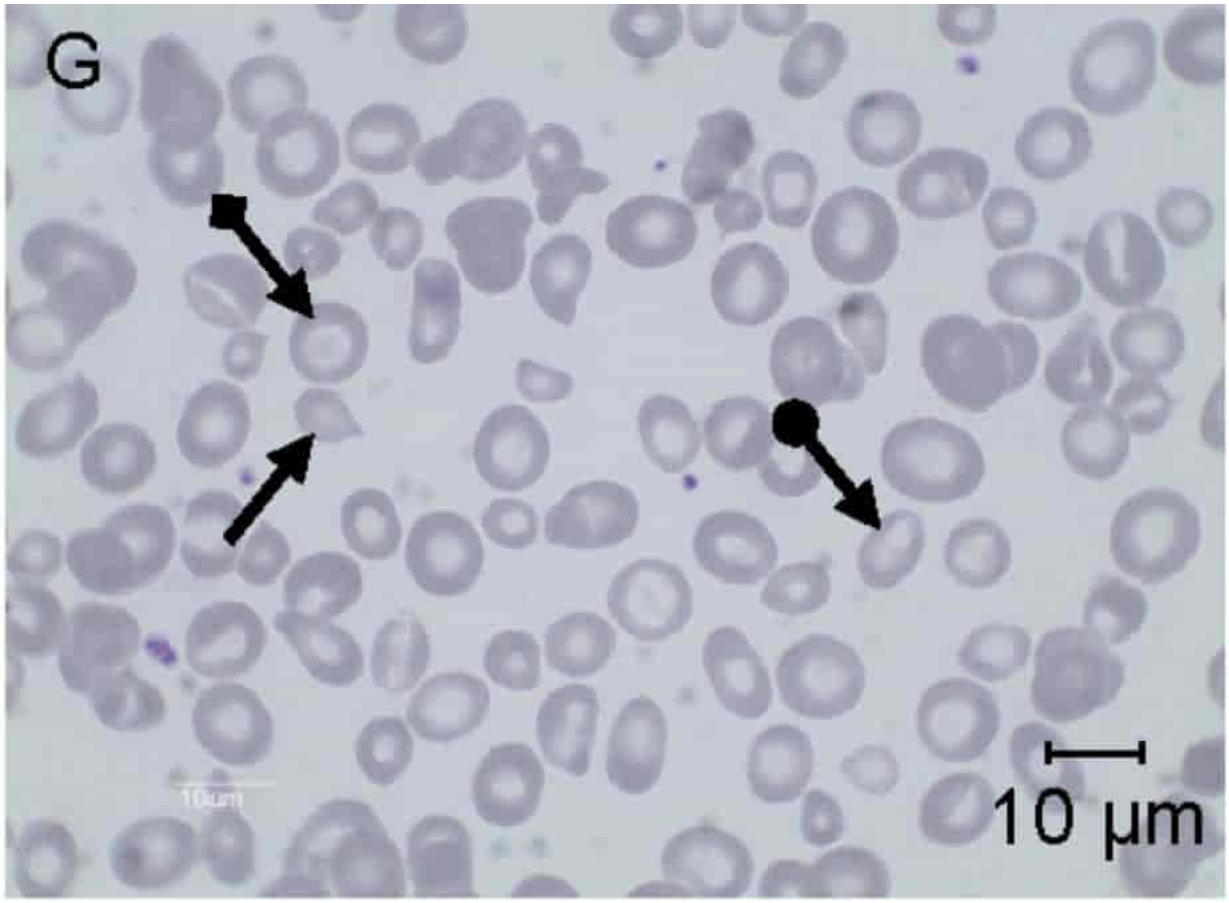
- Serbian Roma, bottle fed
- Developmental delay < 1y
- First seizure 20 m
  >>> several super-refractory status epilepticus
- Loss of skills 3y
  > swallowing problems, inable to move, minimal concious state > deceased at age 4 y
- Parents: sister “healthy”



- Serbian Roma, bottle fed
- First child had died of epilepsy (no details)
- Developmental delay 18m (cave refugees)
- 1st seizure 24 m
- >>> several super-refractory status epilepticus
- Loss of skills 4 y > swallowing problems, inable to move, minimal concious state > deceased at age 5 y



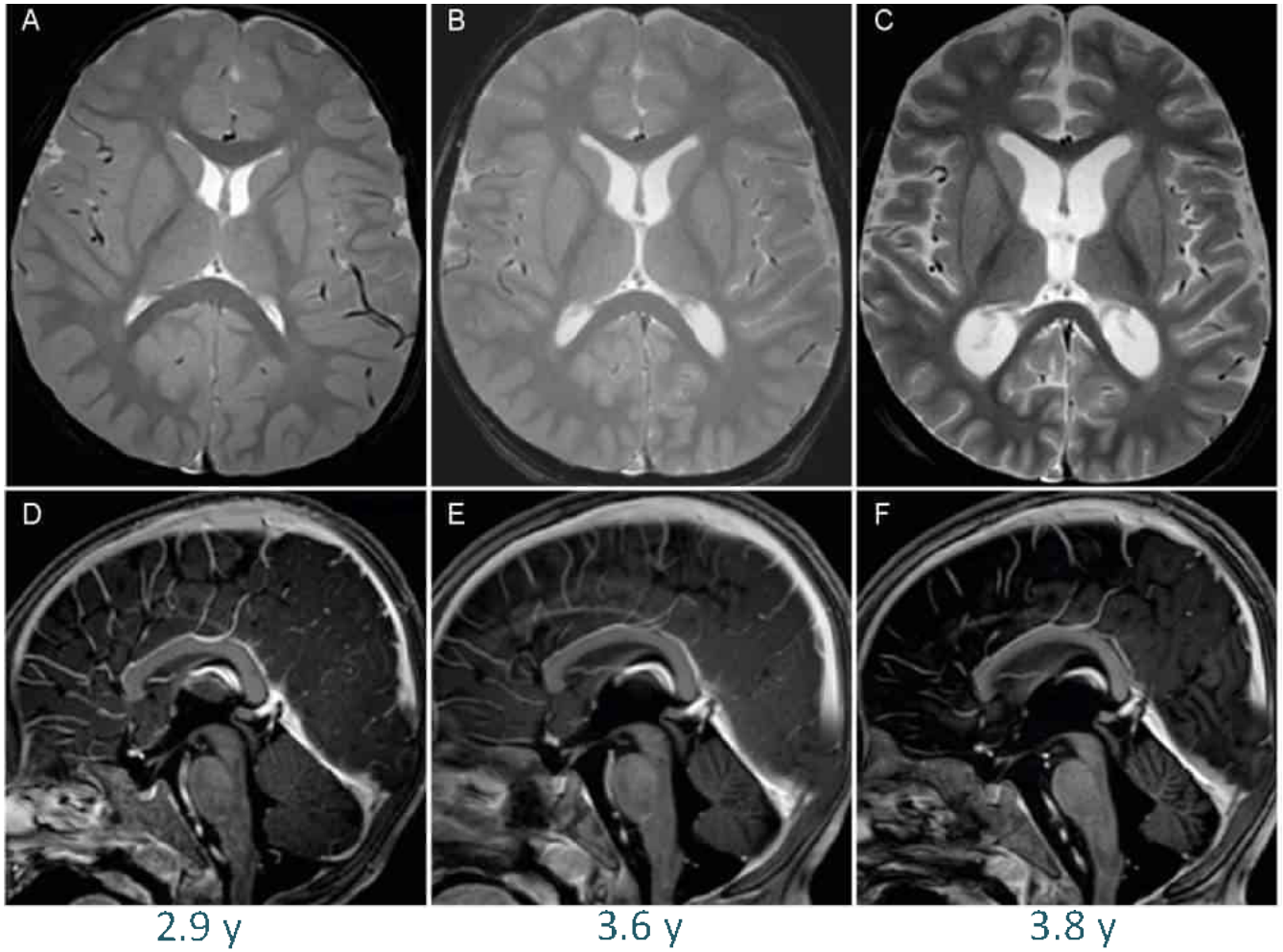
- German, breast fed
- Developmental delay 4 m
- 1st seizure 6 m >>> several super-refractory status epilepticus
- Loss of skills 4 y > swallowing problems, inable to move, minimal conscious state

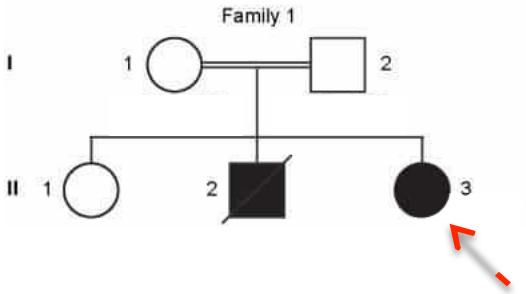


teardrop cell

target cell

- Mild anemia (HB 10% below ref. range)
- Normal MCV
- Anisopoikilocytosis in peripheral blood smear

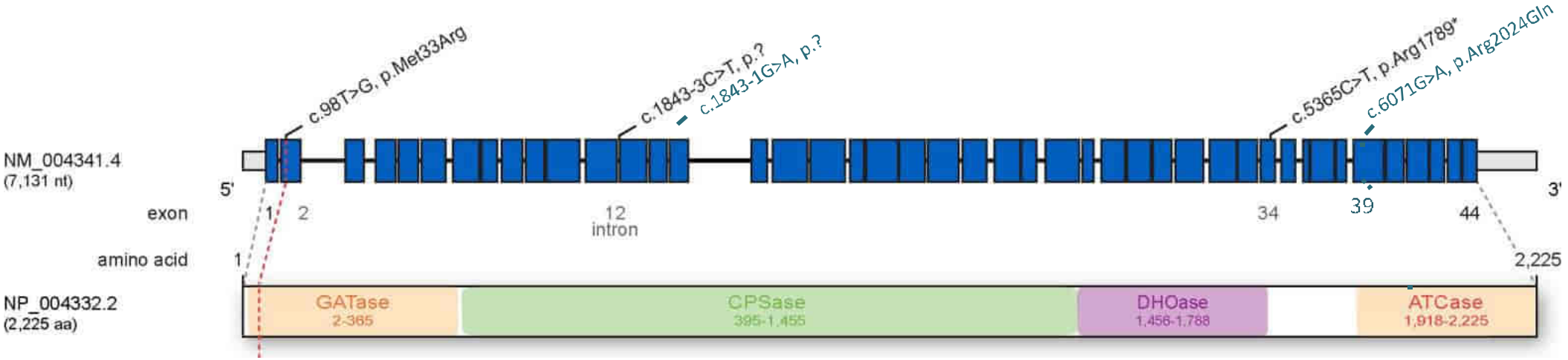




MRI: progressive global atrophy

- Extensive clinical chemical and metabolic screening unremarkable
- Transferrine isoelectric focussing (TIEF) unremarkable
- Purines/Pyrimidines (urine, serum) unremarkable

NGS: rare variants in *CAD*



OXFORD

Human Molecular Genetics, 2015, Vol. 24, No. 11 3050–3057

doi: 10.1093/hmg/ddv057
Advance Access Publication Date: 12 February 2015
Original Article

ORIGINAL ARTICLE

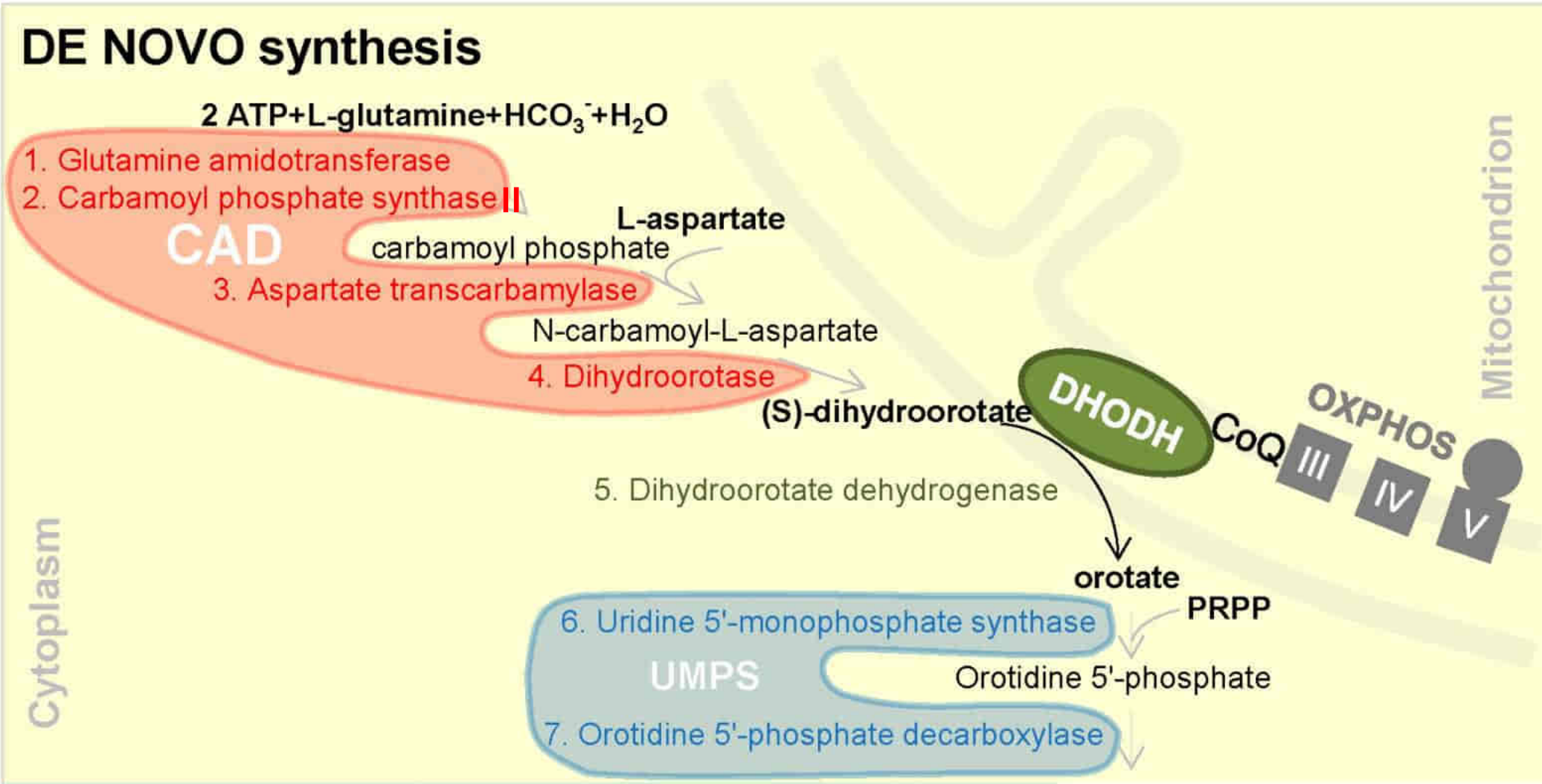
Biallelic mutations in CAD, impair *de novo* pyrimidine biosynthesis and decrease glycosylation precursors

Bobby G. Ng[1,†], Lynne A. Wolfe[2,†], Mie Ichikawa[1], Thomas Markello[2], Miao He[4], Cynthia J. Tifft[2,3], William A. Gahl[2,3] and Hudson H. Freeze[1,*]

[1]Human Genetics Program, Sanford - Burnham Medical Research Institute, 10901 N. Torrey Pines Rd, La Jolla, CA 92037, USA, [2]NIH Undiagnosed Diseases Program, Common Fund, Office of the Director and [3]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA and [4]Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA 19103, USA

- ?North American female
- (FTT, diarrhea 1m)
- Developmental Delay < 1y
- One seizure 17 m
- Mild anemia, anisopoikilocytosis
- TIEF unremarkable, urinary orotic acid 1x decreased, 1x normal
- No follow up

DE NOVO synthesis



RECYCLING pathway

Uridine ⇌ UMP

UMP → UTP, CTP, dTTP, dCTP

RNA, DNA, protein glycosylation, lipid and polysaccharide biosynthesis, etc.

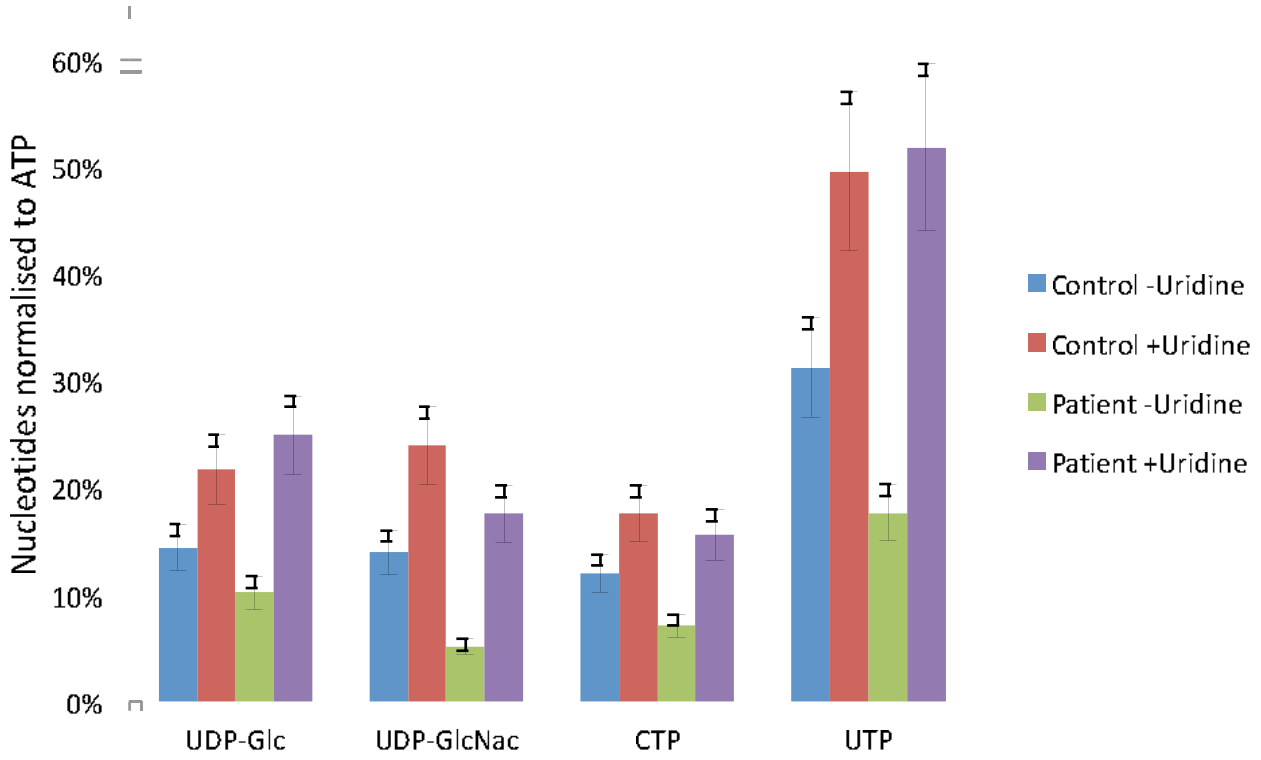
BRAIN
A JOURNAL OF NEUROLOGY

REPORT

CAD mutations and uridine-responsive epileptic encephalopathy

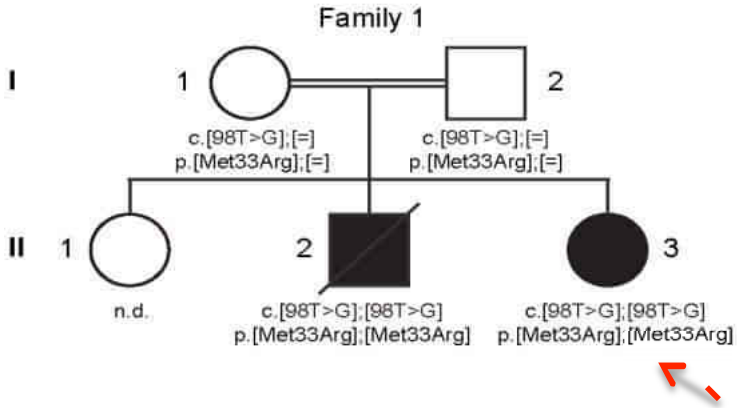
Johannes Koch,[1,*] Johannes A. Mayr,[1,*] Bader Alhaddad,[2] Christian Rauscher,[1] Jürgen Bierau,[3] Reka Kovacs-Nagy,[3] Karlien L. M. Coene,[4,5,6] Ingrid Bader,[1] Monika Holzhacker,[1] Holger Prokisch,[2,7] Hanka Venselaar,[5] Ron A. Wevers,[4] Felix Distelmaier,[8] Tilman Polster,[9] Steffen Leiz,[10] Cornelia Betzler,[11] Tim M. Strom,[2,7] Wolfgang Sperl,[1] Thomas Meitinger,[2,7,12] Saskia B. Wortmann[1,2,7,*] and Tobias B. Haack[2,7,*]

Uridine restores nucleotide sugar levels in patient fibroblasts

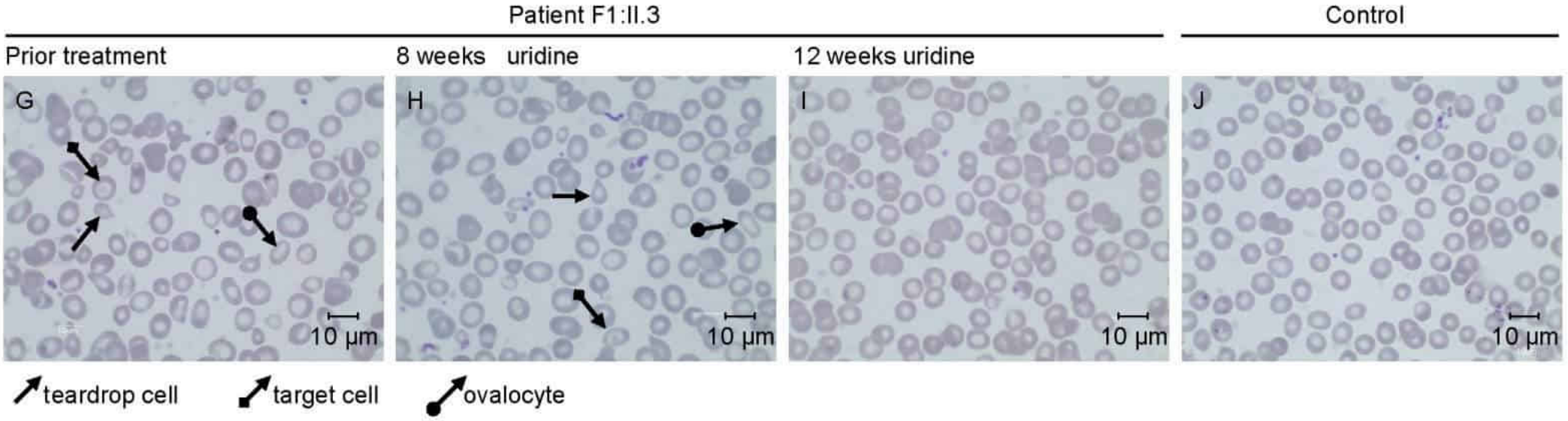


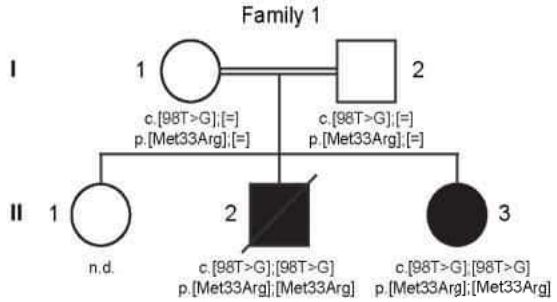
Uridine treatment 4 x 25 mg/kg (100 mg/kg/day)

- Younger sister:
  - Serbian Roma, bottle fed
  - Developmental Delay < 1y
  - First seizure 24 m
    >>> several seizures per week, UNTREATED
  - Developmental arrest
  - Anemia, anisopoikilocytosis



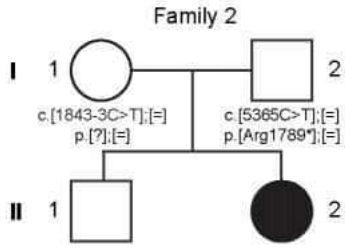
Uridine resolves anemia





Uridine leads to immediate cessation of seizures

Seizure free since 11 months



Uridine: lost developmental skills regained

Prior treatment

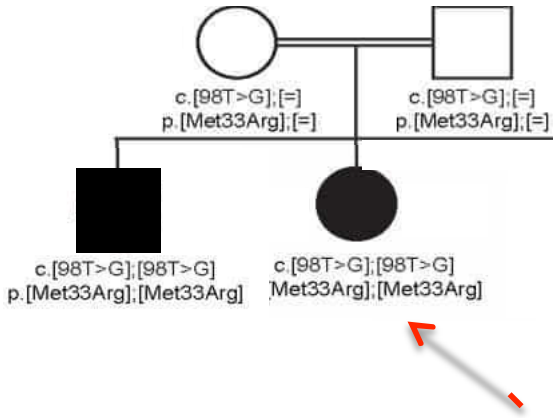
2018: ?????

9 weeks treatment

Additional patients – milder phenotype!

- *Brazilian family, lost to follow up*
- *Several US-based patients (C. Ficioglu, H. Freeze) treatment succesful for epilepsy, no details for other s/s*
- *Russo et al AJ of Hematology: anemia, epilepsy*

- Germany (Dr. Benkel) august 2018
  - Girl 2 y, 4 x AED, loss of skills (walking, crawling)
  - Regained crawling, (instable) walking within 3 w of uridine
  - Older brother 10 y:
    - learning difficulties, attention deficit
    - Focal seizures “Rolando epilepsy”
    - blood smear pending, uridine started



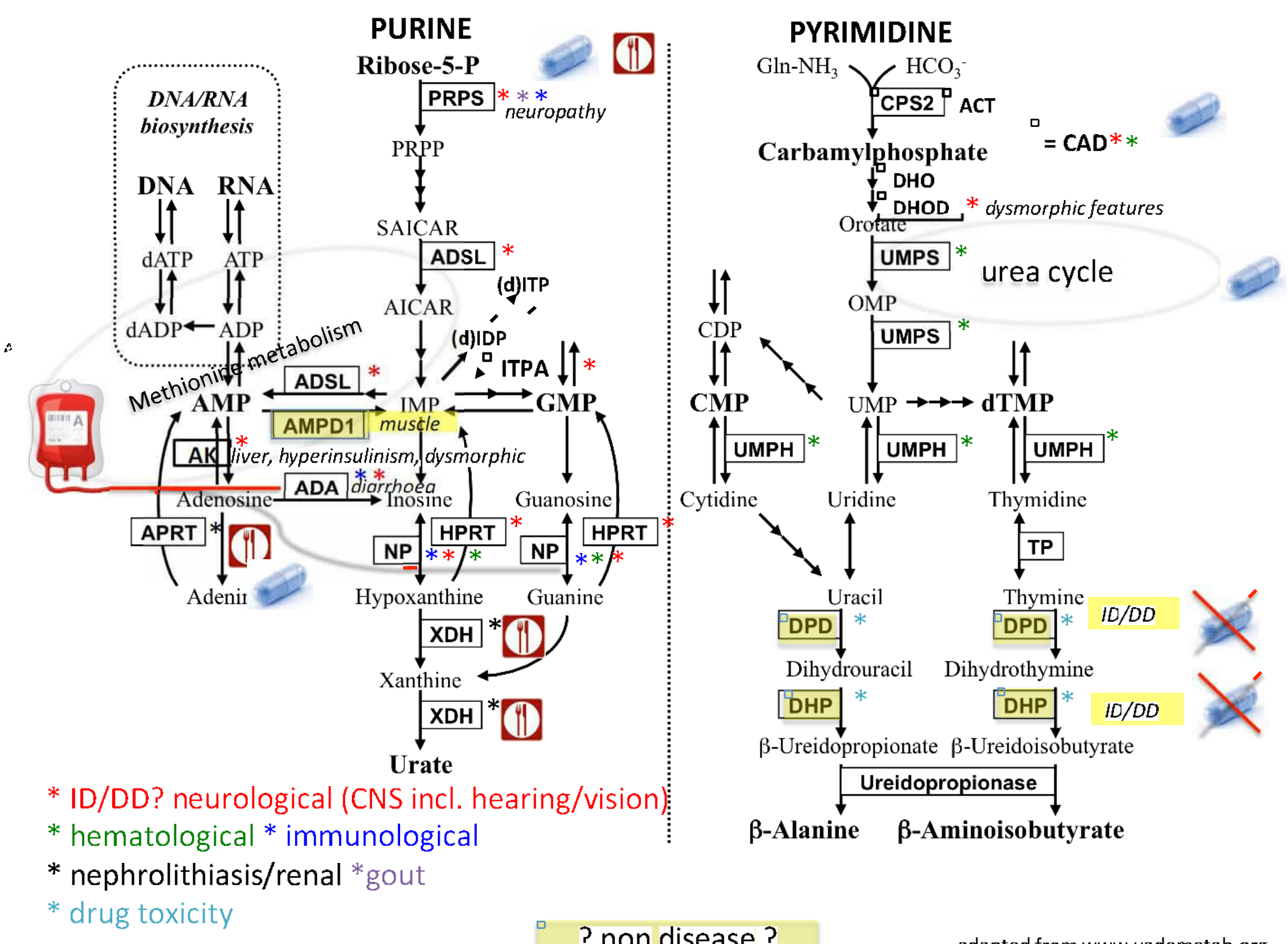
CAD-deficiency:
De novo pyrimidine synthesis disorder

- Recognizable phenotype:
  - Developmental delay/intellectual disability
  - Seizures/epileptic encephalopathy
  - +/- Progressive neurodegeneration
  - Anisopoikilocytosis in peripheral blood smear, +/- anemia
  - +/-Early death

- Treatable IEM: Uridine 4 x 25 mg/kg (100 mg/kg/day)
  - **Immediate cessation of seizures**
  - Blood smear normalizes within 8-12 weeks
  - Regain of lost skills/ restart of development

- CAD deficiency should be added to both the (short) lists of
  - treatable inborn errors of metabolism
  - treatable metabolic epilepsies

- Urgent need for a biomarker >>> new born screening
- Cave: effect of nutritional uridine (e.g. formula, tube feeding)


PURINE
Ribose-5-P
PRPS
neuropathy
PRPP
SAICAR
ADSL
AICAR
(d)ITP
(d)IDP
ITPA
DNA/RNA biosynthesis
DNA
RNA
dATP
ATP
dADP
ADP
Methionine metabolism
ADSL
AMP
IMP
GMP
AMPD1
muscle
AK
liver, hyperinsulinism, dysmorphic
ADA
diarrhoea
Adenosine
Inosine
Guanosine
APRT
NP
HPRT
NP
HPRT
Adenin
Hypoxanthine
Guanine
XDH
Xanthine
XDH
Urate
PYRIMIDINE
Gln-NH3
HCO3-
CPS2
ACT
= CAD
Carbamylphosphate
DHO
DHOD
dysmorphic features
Orotate
UMPS
urea cycle
OMP
UMPS
CDP
CMP
UMP
dTMP
UMPH
UMPH
UMPH
Cytidine
Uridine
Thymidine
TP
Uracil
Thymine
DPD
DPD
ID/DD
Dihydrouracil
Dihydrothymine
DHP
DHP
ID/DD
β-Ureidopropionate
β-Ureidoisobutyrate
Ureidopropionase
β-Alanine
β-Aminoisobutyrate
* ID/DD? neurological (CNS incl. hearing/vision)
* hematological * immunological
* nephrolithiasis/renal *gout
* drug toxicity
? non disease ?
adapted from www.vademetab.org

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CAD PATIENTS?
ITPA PATIENTS?

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SALK
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Technische Universität München