Disorders of metabolism purine and pyrimidine; porphyrias

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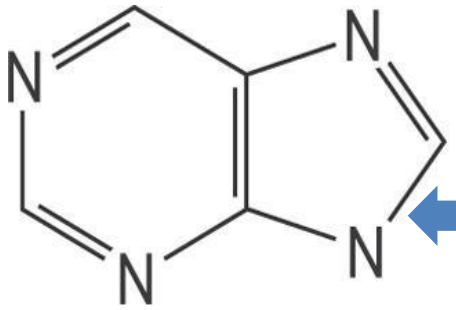
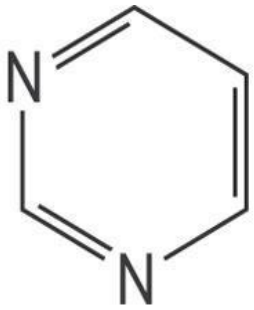
9. 10. 2017 *Pathobiochemistry*

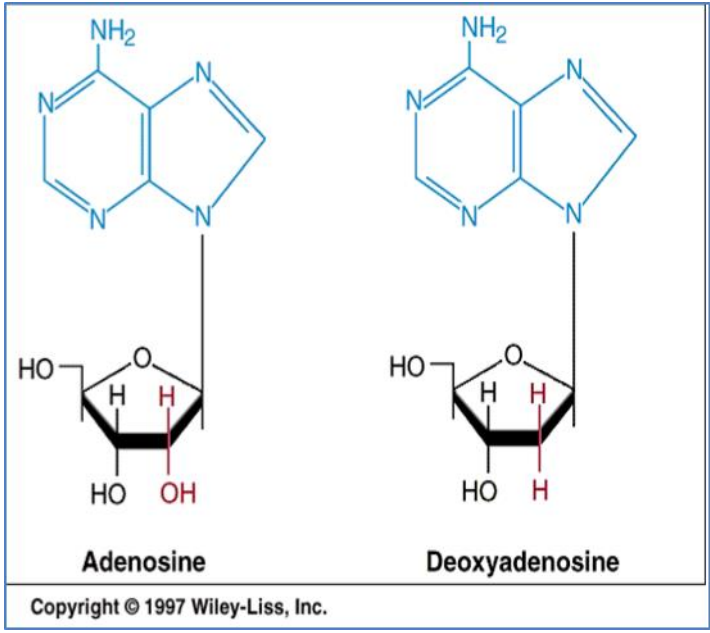


imidazole



Purine

Pyrimidine

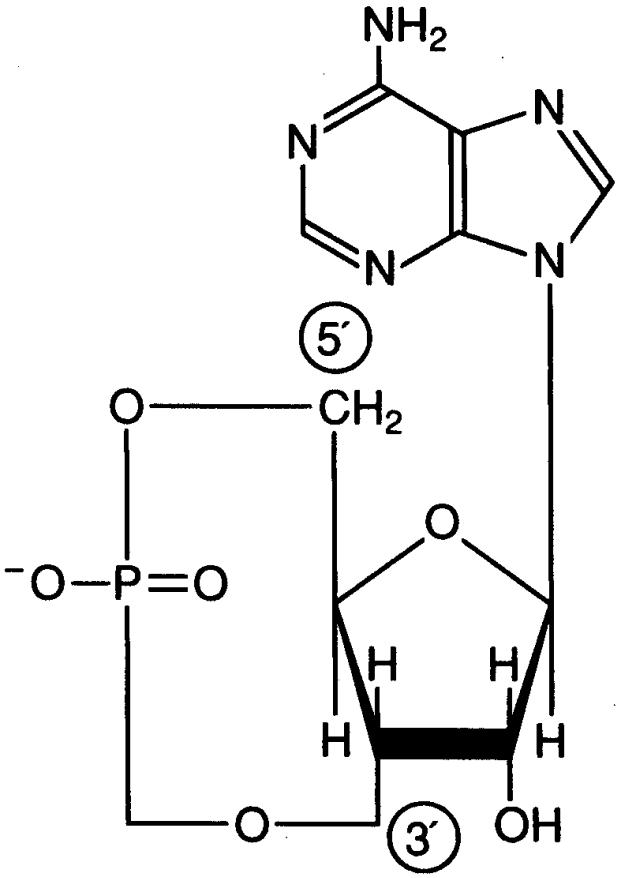


Adenosine

Deoxyadenosine

- purines
- pyrimidines
- nucleoside
- nucleotide

Role of nucleotides

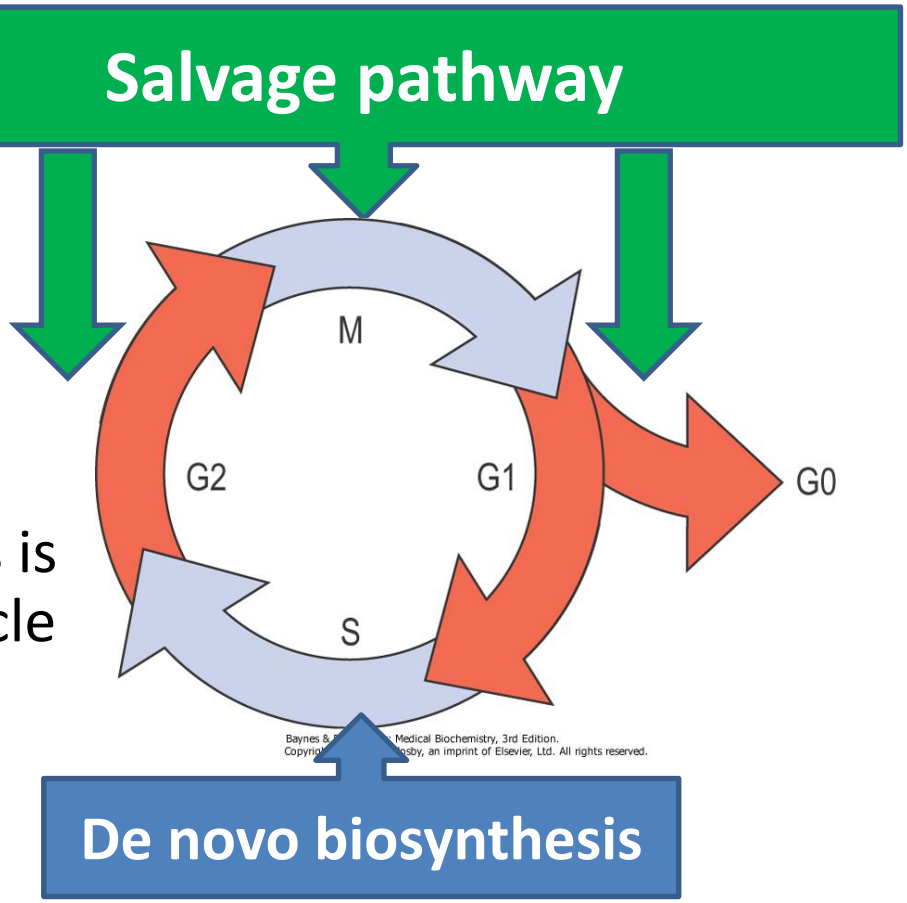


http://www.benbest.com/health/cycAMP.gif

- information carriers (DNA/RNA)
- universal source of energy (ATP 30 kJ/mol)
- second messengers: cGMP and cAMP
- coenzymes and group transfer (e.g. doMet)

Cell cycle and P/P synthesis

- purine nucleotides can be synthesized in two distinct pathways: ***de novo***, **salvage**
- *de novo* purine biosynthesis is closely related to the cell cycle



- purine **salvage pathways** are especially noted for the energy that they save and the remarkable effects of their absence

PURINE

- salwage pathway is not sufficient to meet total body requirements and so some *de novo* synthesis is essential
- d*e novo* synthesis of purines is most active in liver
- non-hepatic tissues generally have limited or even no *de novo* synthesis

PYRIMIDINE

- since pyrimidine are simpler than purines → synthesis simpler
- begins with **carbamoyl phosphate** synthesized in the cytosol of those tissues capable of making pyrimidines (highest in spleen, thymus, gastrointestinal tract and testes)

Synthesis

- *de novo* occurs actively in the cytosol of the liver where all of the necessary enzymes are present as a macro-molecular aggregate

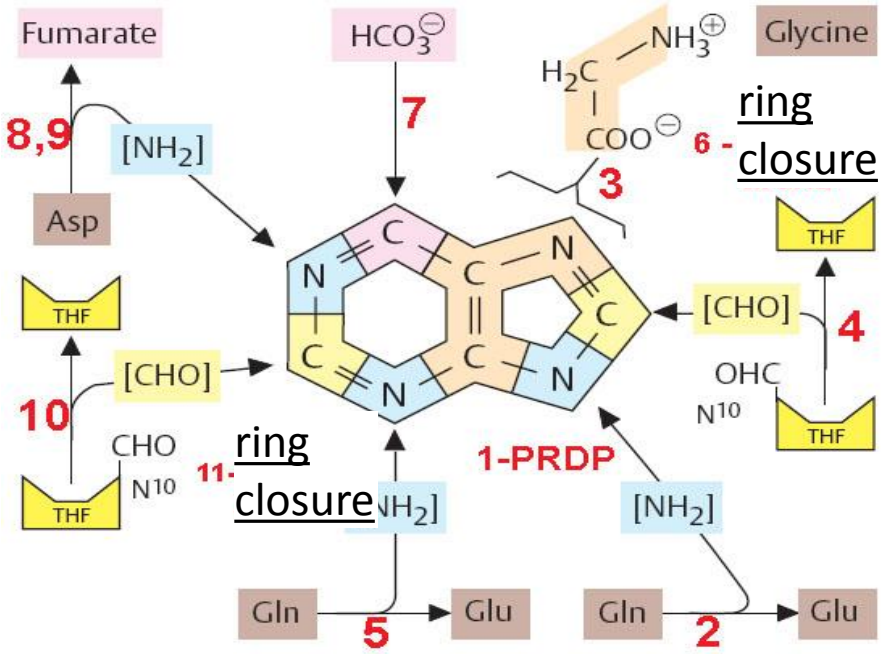
- *de novo* is a complex (11 steps), energy-expensive pathway (ATP)

- relies on six enzymes to catalyze the conversion of phosphoribosyl-pyrophosphate to inosine 5'-monophosphate (IMP)

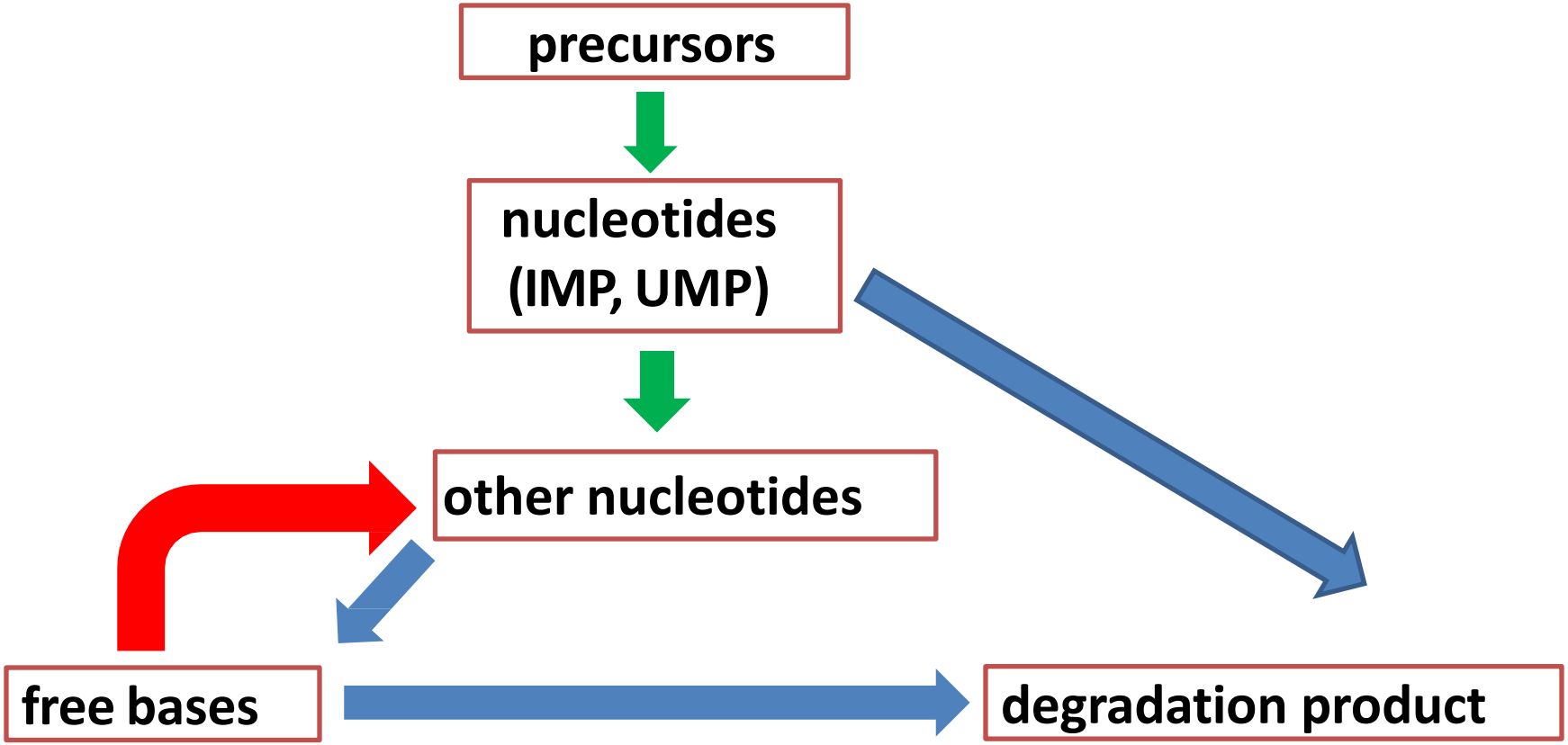
- **substrate:** 5-fosforibozyl-1-difosfate, aa: Gln, Gly, Asp

- tetrahydrofolate, CO_2

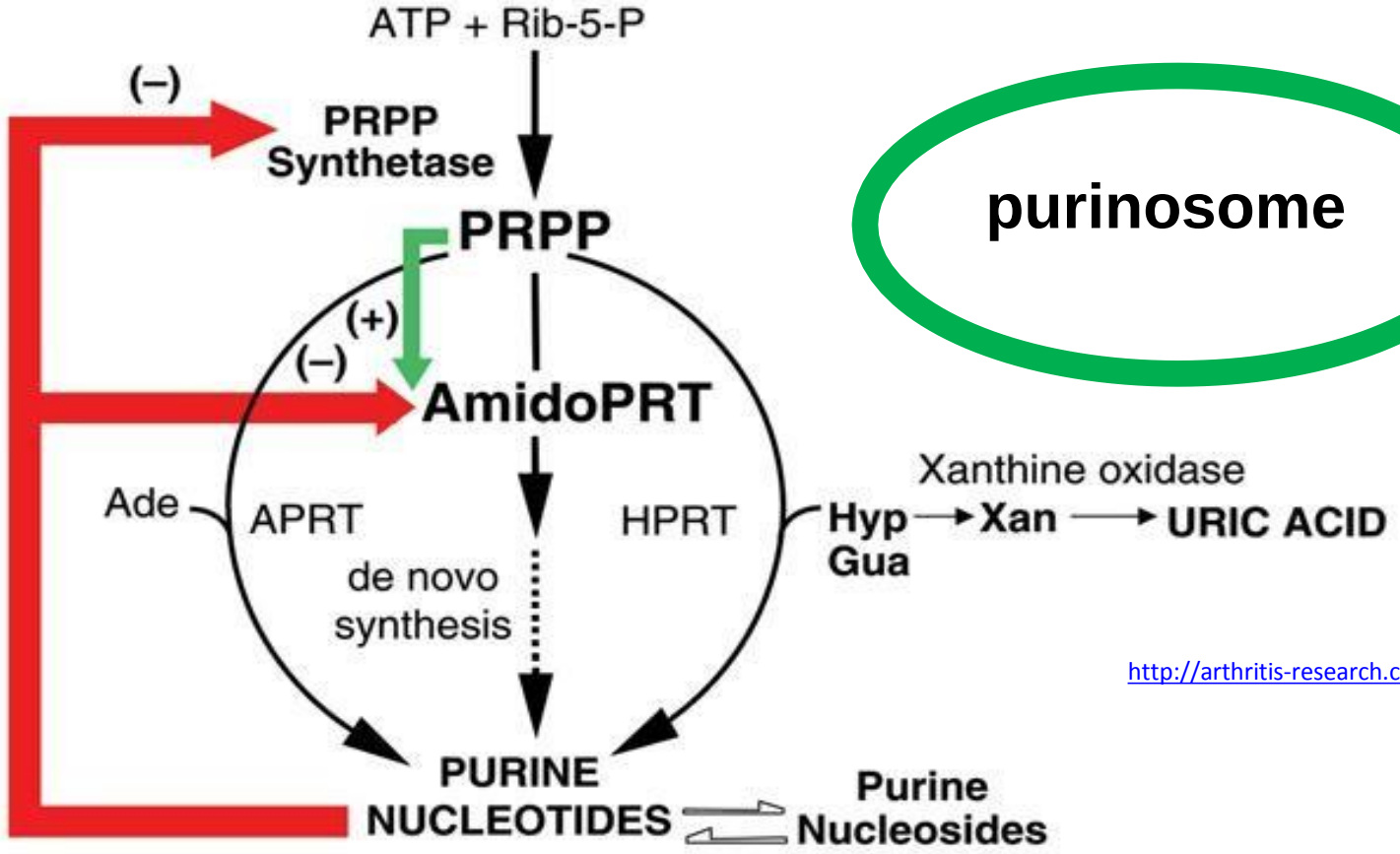
- **coenzyme**



Synthesis and degradation of purine and pyrimidine



- control of the synthesis as a whole occurs at the amidotransferase step by nucleotide inhibition and/or PRPP
- the second phase of control is involved with maintaining an appropriate balance (not equality) between ATP and GTP; each one stimulates the synthesis of the other by providing the energy
- is exerted primarily at the level of carbamoyl phosphate synthetase II



http://arthritis-research.com/content/figures/ar1909-2.gif

- enzymes in the *de novo* purine biosynthetic pathway were shown to organize and reversibly assemble into punctate cellular bodies known as "purinosomes"
- several of the enzymes form a core structure, whereas others appear to interact peripherally

Metabolism of purines and pyrimidines

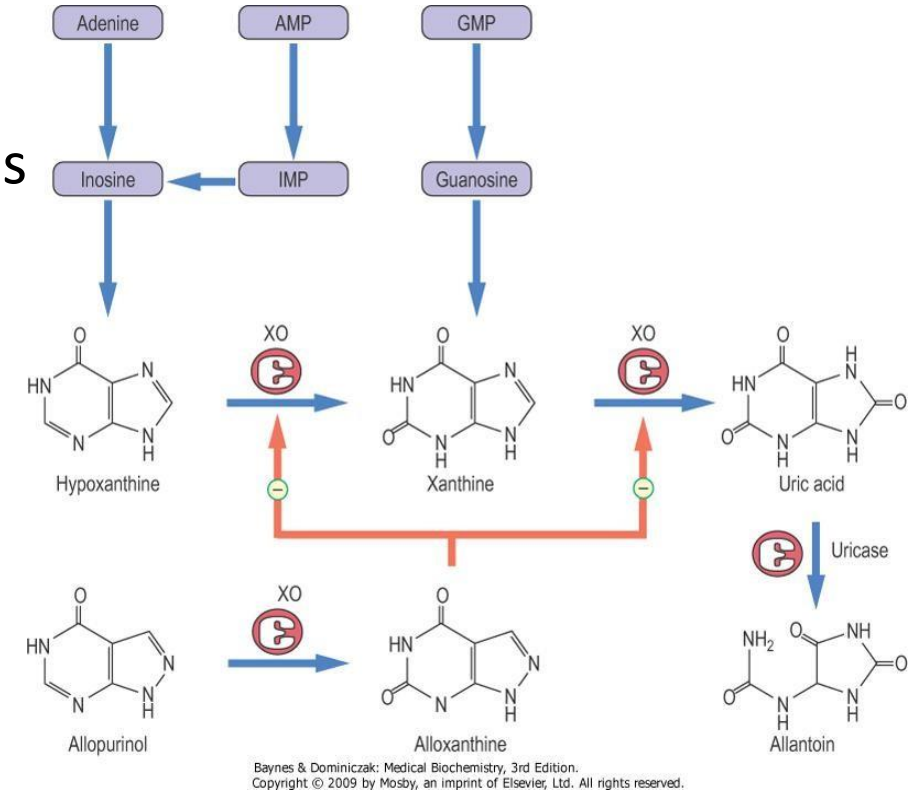
	purines	pyrimidines
PRPP	1st step	last step
product	IMP	UMP
localization	cytoplasm	cytoplasm + 1 enzym in mitochondria
degradation products	uric acid, ammonia	CO_2, NH_4, β-alanine, B-aminoisobutyrate

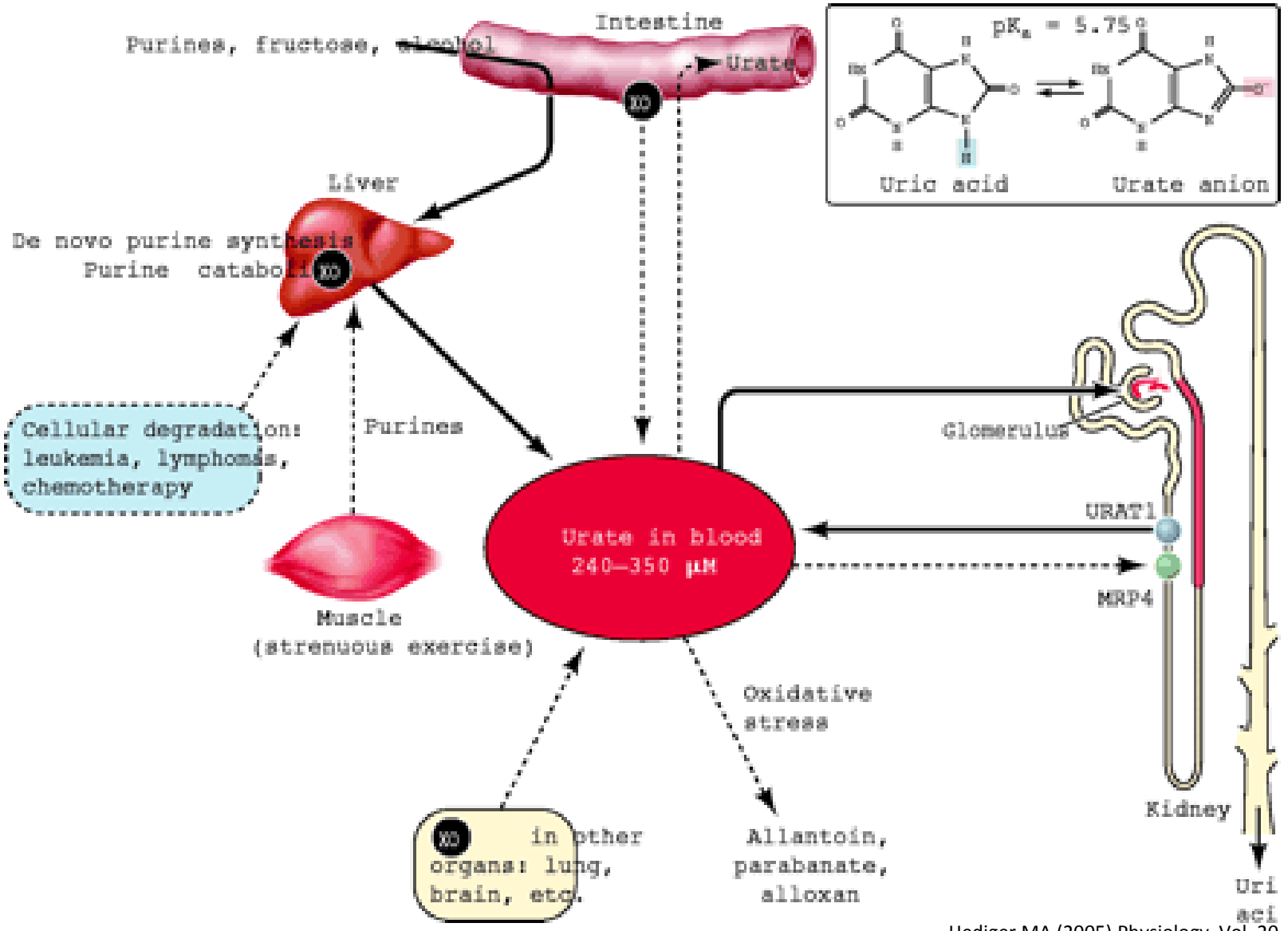
Catabolism

- nucleic acids are constantly being degraded and resynthesized
- purine and pyrimidine bases which are not degraded are recycled
- dietary nucleoprotein is degraded by pancreatic enzymes and tissue nucleoprotein by lysosomal enzymes
- NA are hydrolyzed randomly by nucleases to yield a mixture of polynucleotides → these are further cleaved by phosphodiesterases to a mixture of the mononucleotides

- NT are hydrolyzed by nucleotidases to give the nucleosides and Pi

- in at least some tissues, NS undergo phosphorolysis to yield the base and deoxy/ribose 1-P

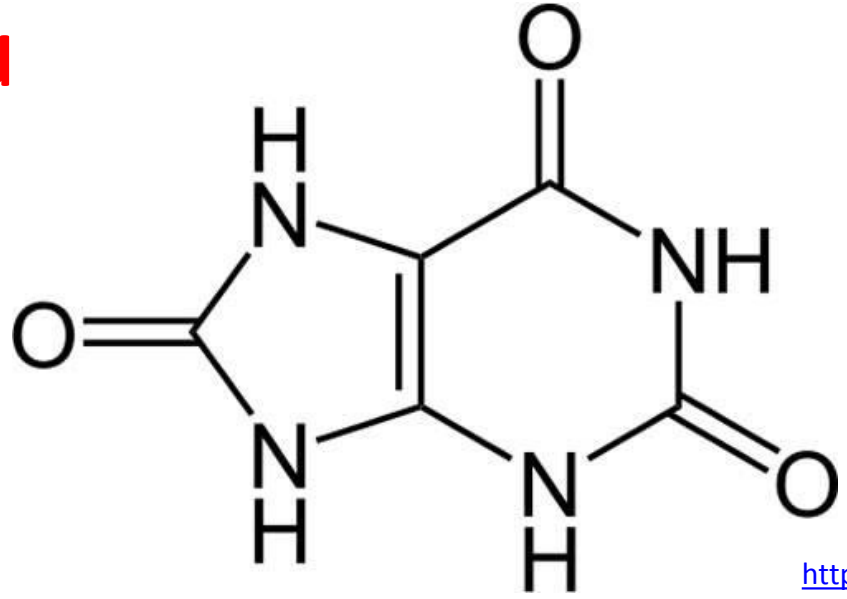




Hediger MA (2005) Physiology, Vol. 20, No. 2, 125-133

- **UA: major end product of purine**

Uric acid



- trioxopurine
- keto/enol form
- physiological pH: monosodium urate
- limited solubility
- free radical scavenger

http://0.tqn.com/d/chemistry/1/0/M/R/1/Uric_acid.jpg

- in humans, the uricase gene is crippled by two mutations that introduce premature stop codons (during the Miocene)
- the absence of hepatic enzyme uricase, combined with extensive reabsorption of filtered urate, results in urate levels in human plasma that are approximately 10 times those of most other mammals dietary
- higher s-UA may be of selective advantage in the evolution of hominids

- *Mammals*→UA→allantoin *Teleostei*→UA→allantoin→allantoic acid

Chondrostei and *Amphibia*→UA→allantoin→allantoic acid→urea

Marinus Invertebrata→UA→allantoin→allantoic acid→urea→NH_3

- **UA** is a powerful scavenger of peroxyl/hydroxyl radicals and singlet oxygen in human biological fluids

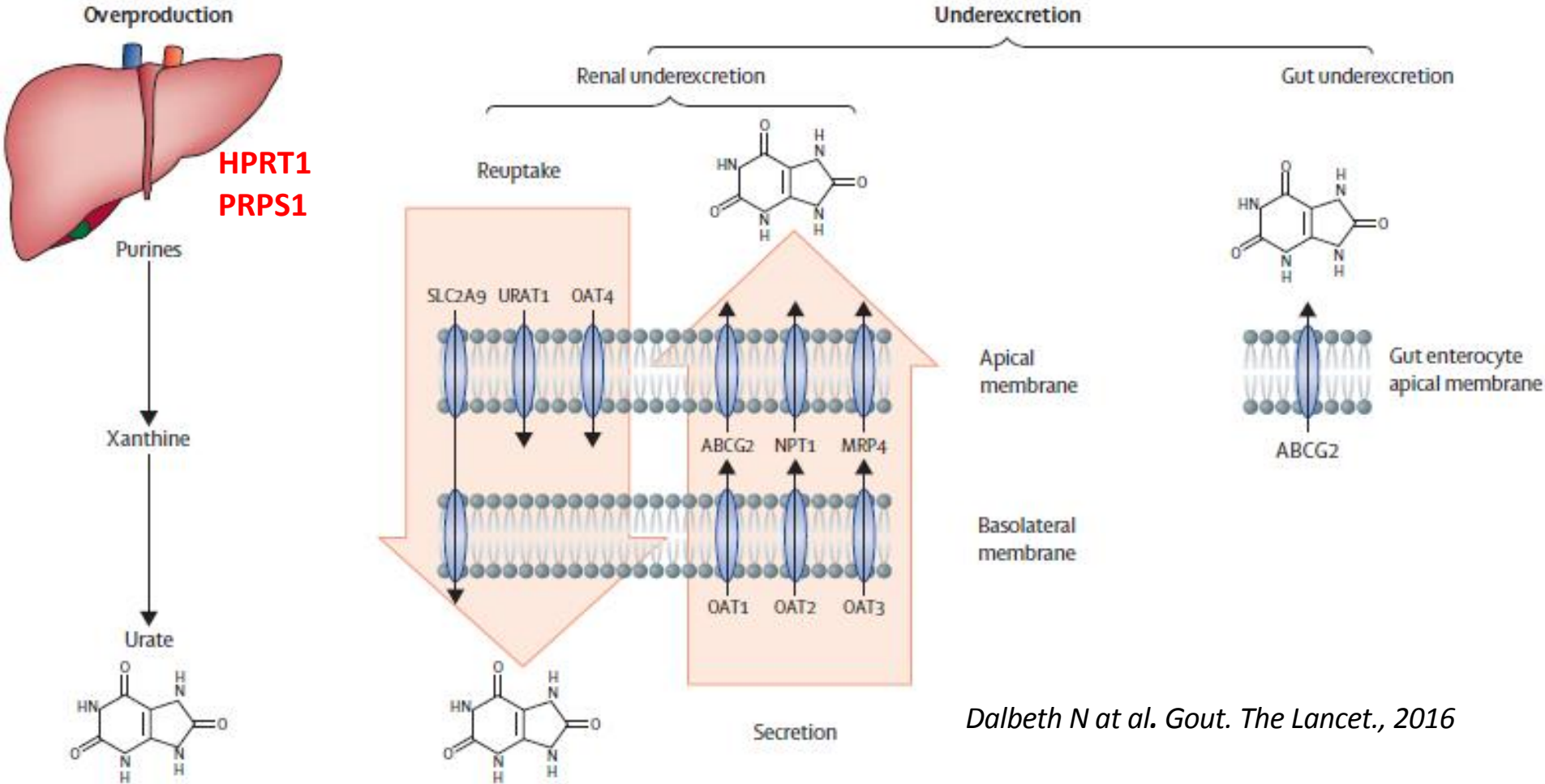
- **UA** accounts for up to 60% of plasma antioxidative capacity and presumably protects not only erythrocytes, but also DNA-contained in long-lived T and B lymphocytes and macrophages

- **UA** has been hypothesized to protect against oxidative stress, a prominent contributor to dopaminergic neuron degeneration in Parkinson's disease → studies have evaluated a potential association between s-UA and the risk of developing Parkinson's disease, finding a lower risk among individuals with higher levels of s-UA

- **UA** maintains blood pressure under low salt conditions

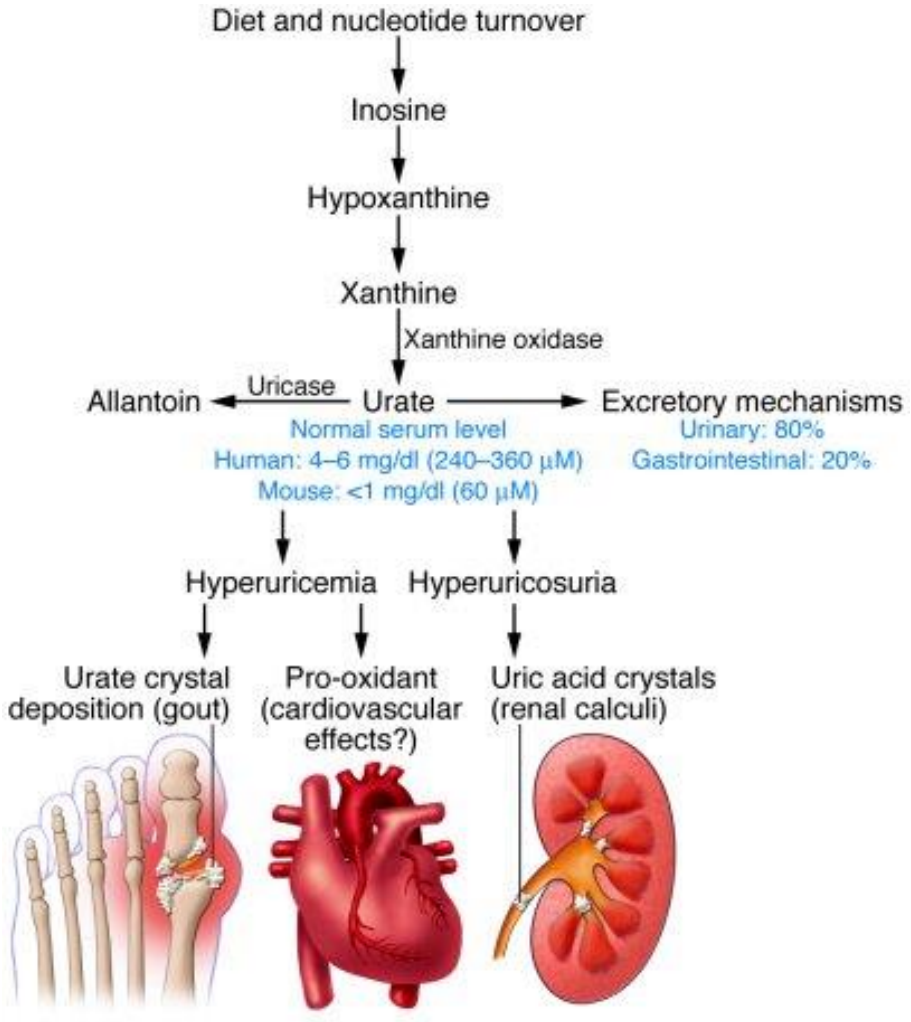
- **UA** may help arrest inflammatory demyelinating diseases such as optic neuritis linked to multiple sclerosis, through scavenging of peroxynitrite in the central nervous system

- balanced endo/exogenous factor: through diet, biosynthesis, excretion, with overproduction or insufficient renal clearance leading to chronic hyperuricemia
- UA is secreted and extensively reabsorbed by specific transporter that reside in the apical and basolateral membranes of prox. tubules
- excreted UA is only 10% of the UA filtered through the glom. memb.



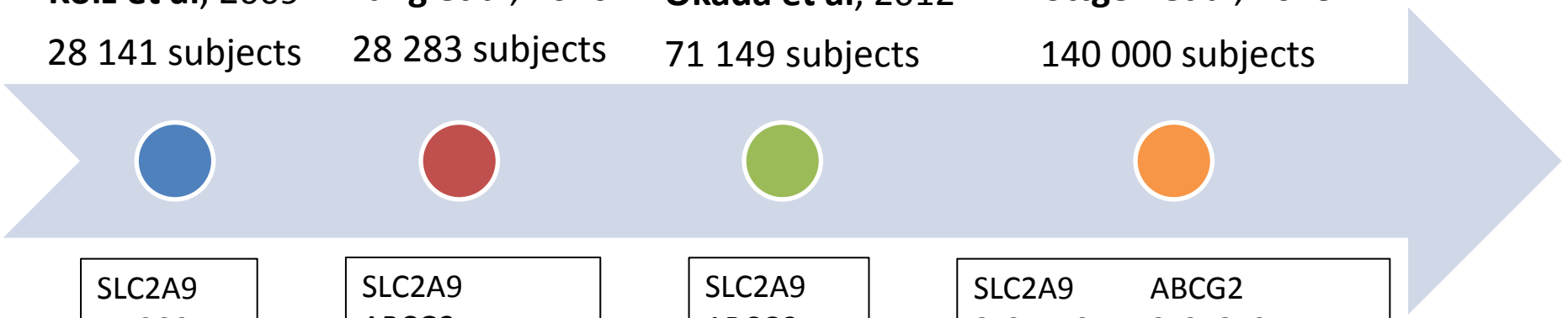
Dalbeth N at al. Gout. The Lancet., 2016

- an elevated concentration of s-UA/hyperuricemia, is a key risk factor for gout and may also be a risk factor for CDV incidence and mortality, hypertension, and chronic kidney disease



http://www.jci.org/articles/view/42344/figure/1

GWAS have uncovered over 30 common sequence variants influencing s-UA/hyperuricemia/gout



Kolz et al, 2009
28 141 subjects

- SLC2A9
- ABCG2
- SLC17A1
- SLC22A11
- SLC22A12
- SLC16A9
- GCKR
- LRRC16A
- PDZK1

Yang et al, 2010
28 283 subjects

- SLC2A9
- ABCG2
- SLC17A1
- SLC22A11
- GCKR
- R3HDM2-INHBC
- RREB1
- PDZK1

Okada et al, 2012
71 149 subjects

- SLC2A9
- ABCG2
- SLC22A12
- MAF

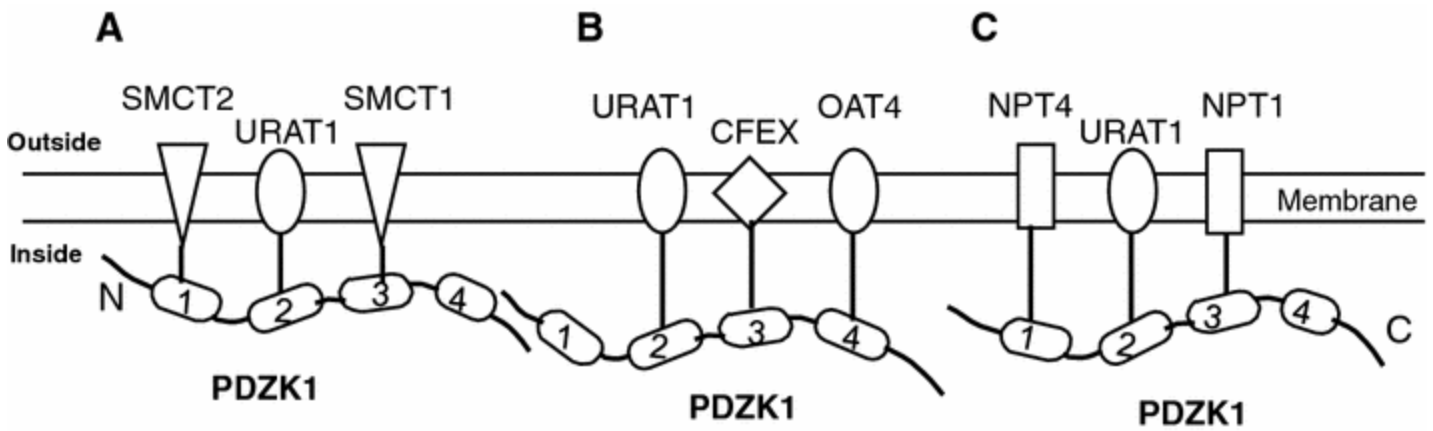
Köttgen et al, 2013
140 000 subjects

- SLC2A9
- SLC17A3
- SLC22A11
- GCKR
- RREB1
- TRIM46
- SFMBT1
- VEGFA
- PRKAG2
- HNF4G
- ATXN2
- IGF1R
- MAF
- B3GNT4
- ABCG2
- SLC16A9
- SLC22A12
- INHBC
- PDZK1
- INHBB
- TMEM171
- BAZ1B
- STC1
- A1CF
- UBE2Q2
- NFAT5
- HLF
- ACVR1B-ACVRL1

dle Merriman et al., Rheum Dis Clin North Am. 2014

Renal reabsorbtion and secretion of UA

- urate transportosome: urate-transporting multimolecular complex



Anzai N et al. *Clin Exp Nephrology,* 16, 1, 89-95.

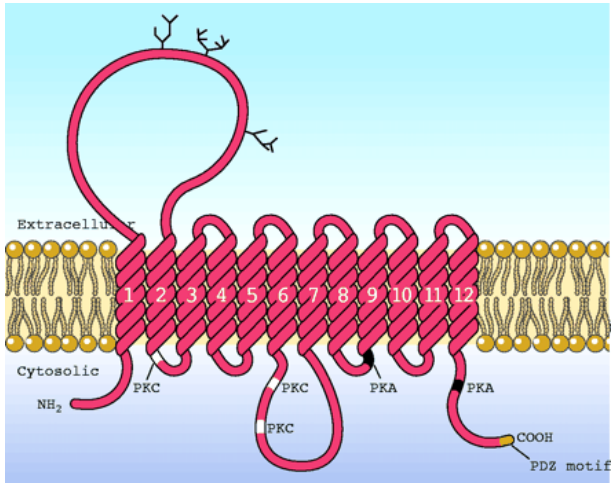
- hyperuricemia
- ↓/normal excretion fraction of uric acid EF-UA
- normal levels of purine and pyrimidine in urine, plasma
- defect in urate transporter *ABCG2, SLC17A3, SLC2A9*

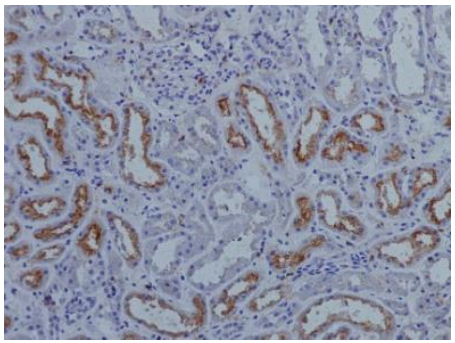
- hypouricemia
- ↑E-UA
- normal levels of purine and pyrimidine in urine, plasma
- defect in urate transporter *SLC2A9, SLC22A12*

SLC22A12 (**URAT1,** OMIM*607096)

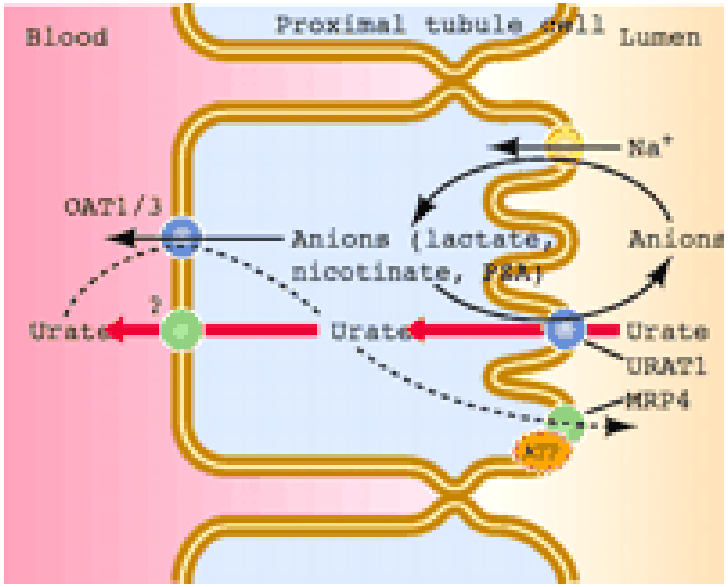
- was identified in 2002 as the crucial transporter involved in UA reabsorption
- regulates blood UA levels and plays a central role in the reabsorption of UA from the glomerular filtrate
- loss-of-function mutations in the SLC22A12 gene cause renal hypouricemia type 1, OMIM #220150

Enomoto, A., et al., Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature, 2002. 417(6887): p. 447-52.





H. Hulkova

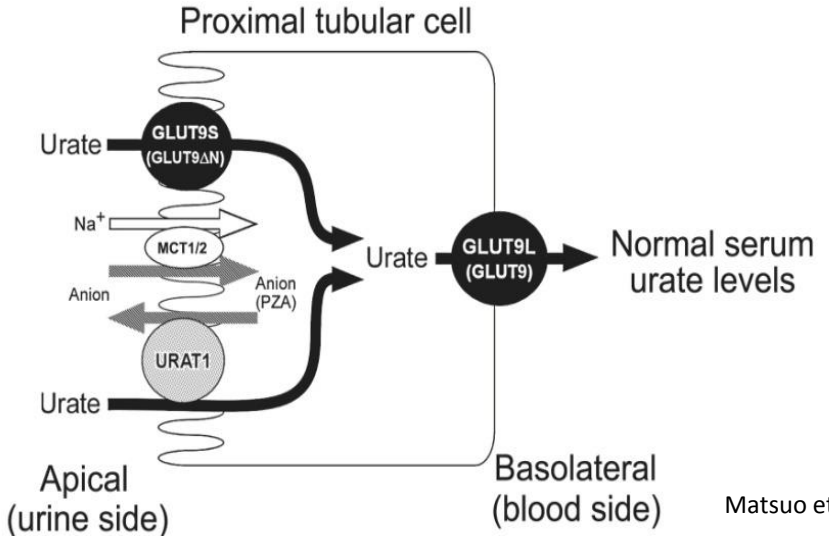


Hediger MA (2005) Physiology, 20, 2, 125-133

SLC2A9 (**GLUT9**, OMIM*606142)

- in 2008, the primary role of *SLC2A9* in UA reabsorption was identified: member of the glucose transporter family, plays a key role in urate reabsorption on both sides of the proximal tubules
- results revealed significant correlations between genetic variants in *SLC2A9* and s-UA levels, the EF-UA, blood pressure, BMI and gout
- the *SLC2A9* variants are responsible for a portion of the variance in s-UA concentrations: 5–6% in females and 1–2% in males
- mutations in the *SLC2A9* cause renal hypouricemia 2, OMIM #612076

Vitart V et al. (2008) Nat Genet, 40(4): p. 437-42. , Anzai N et al (2008) J Biol Chem,Oct 3;283(40):26834-8, Döring A et al. (2008) Nat Genet, 40(4):430-6., Wallace C et al. (2008) Am J Hum Genet, Jan;82(1):139-49.



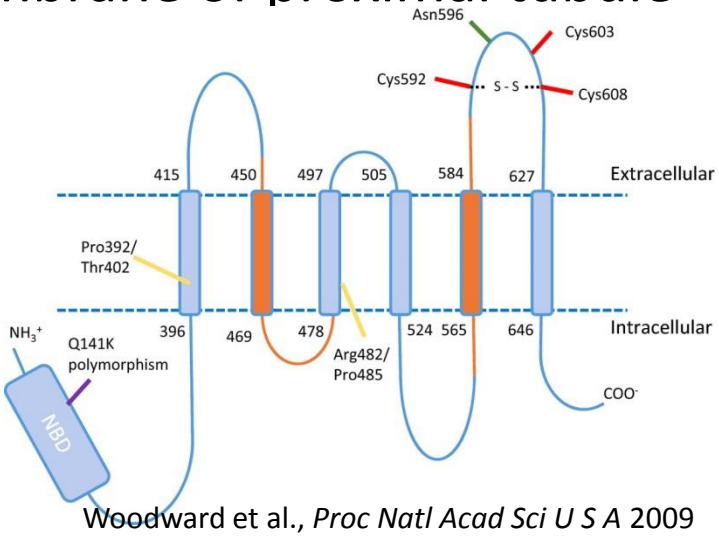
Matsuo et al. 2008

A model of transcellular urate transport it has been proposed in the kidney; urate is taken up via apically located *SLC22A12* and exits the cell via basolaterally located *SLC2A9*.

ABCG2 (**ABCG2**, OMIM*603756)

- membrane transporter belonging to the ATP-binding cassette (ABC) superfamily of membrane transporters
- initially found to be a xenobiotic transporter that plays a role in the multidrug resistance phenotype of a specific human breast cancer and has since been shown to confer multidrug resistance in several cancer cells by actively exporting a wide variety of drugs across the plasma membrane
- a high capacity transporter for UA excretion in the kidney, liver, and gut protein→ to mediate renal urate secretion as a urate efflux transporter in the (luminal) brush-border membrane of proximal tubule

- ABCG2: secretion of UA
c.421C>A (Q141K) 53% reduction
poor response to allopurinol
- **decreased UA excretion caused by ABCG2 dysfunction is a common mechanism of hyperuricemia**



Woodward et al., *Proc Natl Acad Sci U S A* 2009

- s-UA: man < **420** µmol/l, children and woman < **340** µmol/l
- **hypouricemia**
- **hyperuricemia**

- allantoin: only non-enzymatic processes with reactive oxygen species will give rise to allantoin, which is thus a suitable biomarker to measure oxidative stress in chronic illnesses and senescence

- uric acid, a weak organic acid with a pK_a of 5.75, is present principally as monosodium urate at physiological pH values (7,4)

- the two major factors that promote precipitation of UA are a high urine UA **concentration** and an acid urine **pH**

uric acid stones

http://img.medscape.com/pi/emed/ckb/pediatrics_general/980683-983759-669.jpg

HYPOURICEMIA

- serum urate levels < 2 mg/dl (119µmol/l)

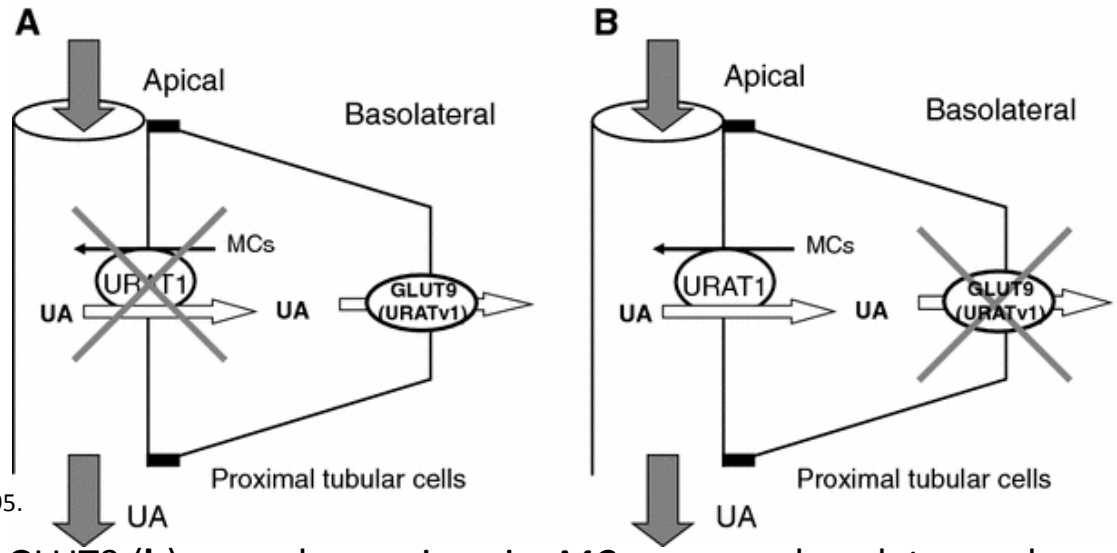
- decreased uric acid production
- decreased renal tubular urate reabsorption

- secondary reduction in uric acid biosynthesis hepatic failure
- acquired causes of the Fanconi renotubular syndrome and its variants
- drugs XDH inhibitor, uricosuric agents, coumarin anticoagulants (warfarin)…
- nutritional deficiencies vitamines B_{12}, C, D…

- inherited disorders - deficiency of purine metabolism, RHUC

RENAL HYPOURICEMIA

- heterogeneous inherited disorder (OMIM #220150 and #612076)
- biochemical markers : hypouricemia, increased EF-UA
- clinical markers : urolithiasis, nephrolithiasis, acute kidney injury
- more than 150/10 patients with a mutation in the *SLC22A12/SLC2A9* have been identified, mainly in Asia
- an uneven geographical and ethnic distribution of *SLC22A12* variants that need to be considered in non-Asian patients: the c.1245_1253del and c.1400C>T var. were present in the Roma population at high frequencies 1.87 and 5.56%, respectively

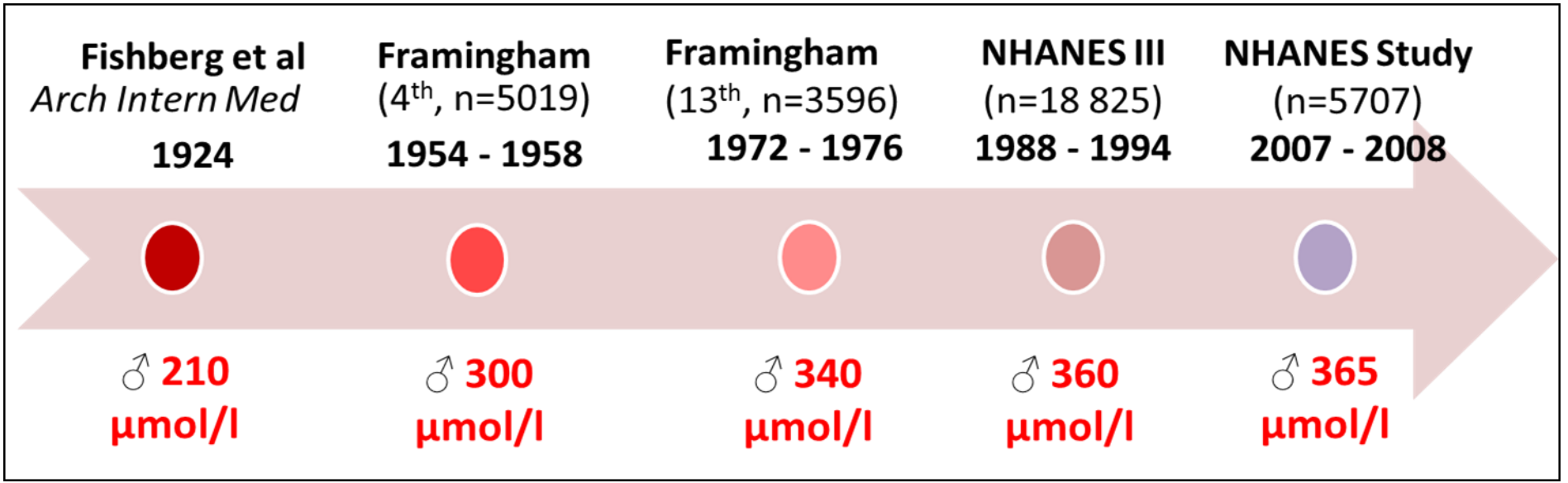


Anzai N et al. *Clin Exp Nephrology* 16, 1, 89-95.

- loss of function variant in URAT1 (**a**) and GLUT9 (**b**) cause hypouricemia, *MCs* monocarboxylates such as lactate

prevalence of hyperuricemia ♂	**24-29%**
prevalence of hyperuricemia ♀	**2,6-20%**
prevalence of gouty arthritis	**1-2%**
heritability of s-UA	**0,38-0,63**

- fructose → ↑ s-UA



- **primary hyperuricemia** → hyperuricemia is considered primary when it exists in the absence of coexisting diseases or drugs that alter uric acid production or excretion
  - purine metabolic disorders
  - kidney disorders
  - increased production of uric acid from purine

- **secondary hyperuricemia** → this refers to excessive urate production or diminished renal clearance occurring as a consequence of another disease, drug, dietary product, or toxin
  - certain cancers, or chemotherapy agents may cause an increased turnover rate of cell death
  - kidney disease
  - medications
  - endocrine or metabolic conditions -certain forms of diabetes, or acidosis can cause hyperuricemia
  - etc

- < 10% of hyperuricemia/gout cases are due to **overproduction**

- enzymopathy of purine metabolism (HPRT, PRPS1)

- deficiency of glucose 6-phosphatase in GSD type I → hyperuricemia results from a combination of increased generation and decreased excretion of UA, which is generated when increased amounts of G6P are metabolized *via* the pentose phosphate pathway → UA competes with lactic acid and other organic acids for renal excretion in the urine

- **hyperuricemia is caused in most patients by inefficient UA excretion**

Gout athritis urica

- chronic hyperuricemia
- a type of arthritis: crystals

of sodium urate form inside/around joints

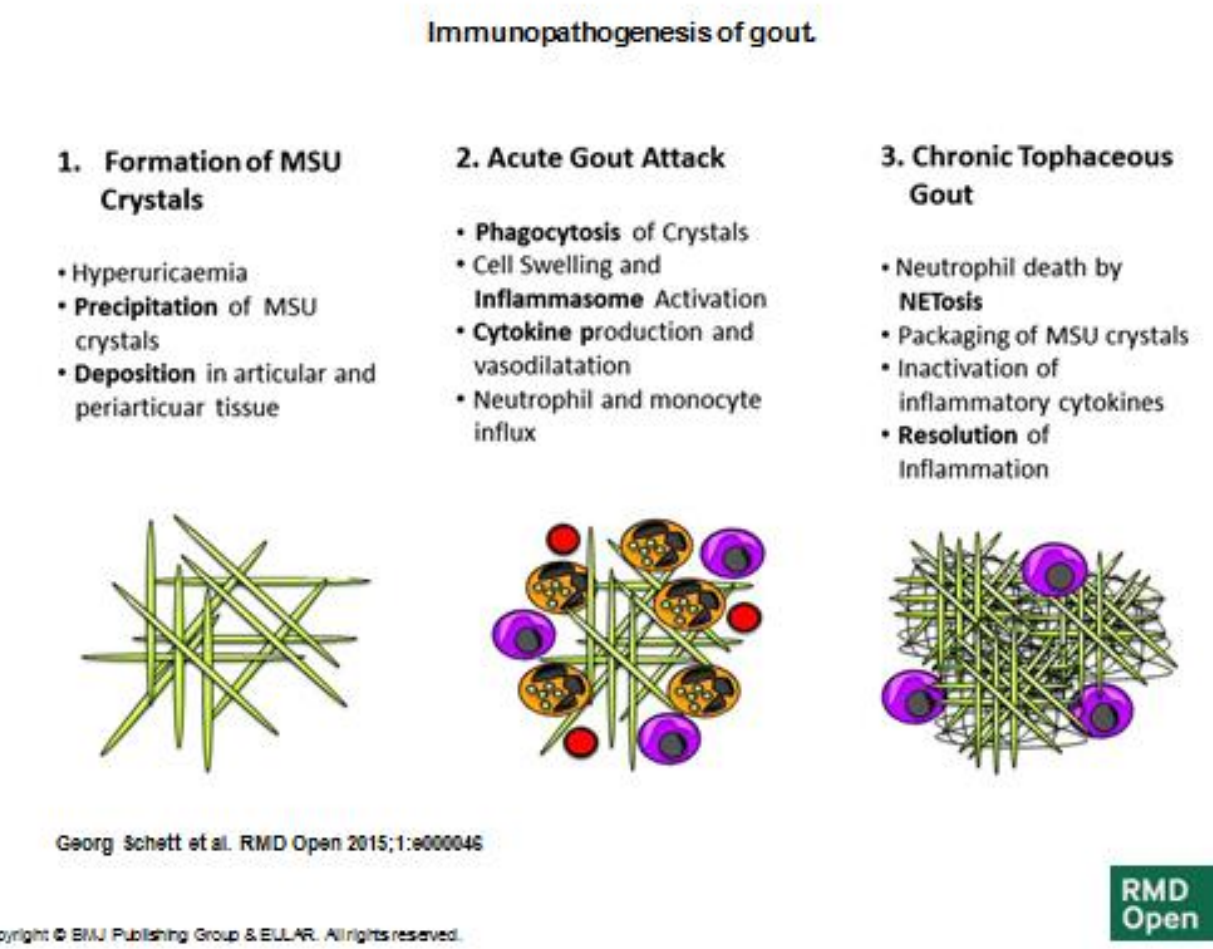
- 2640 BC
- tophy, Galén 2nd century
- recognized gout as an affection of older men and a product of high living long back, Hippocrates 5th c BC
- gout atack, Sydenham 1683
- crystals in tophus, Van Leeuwenhoek 1697
- synovial fluid, McCarter/Hollander 1961
- pathogenesis, overproduction, Nyhan/Lesh 1964

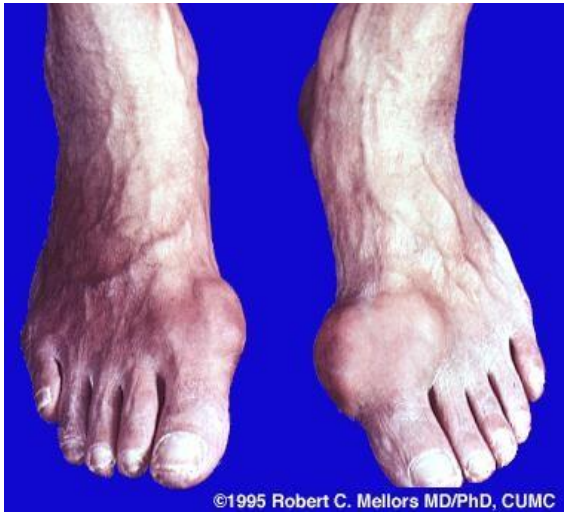
Gout athritis urica

- 9 000 000 Europe
- > 8 000 000 USA
- > 3 000 000 Japan

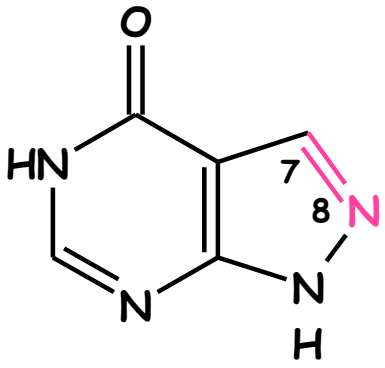
- the most common form of inflammatory arthritis
- ČR 200 000 patients
- more commonly in men than women, although among women the prevalence increases after menopause ?
- prevalence also increases dramatically with age
- hyperuricemia ≠ gout

- oversaturation of serum urate → formation of MSU crystals activates the inflammasome → resulting in the maturation of IL-1β, a proinflammatory cytokine → this begins a cascade of events that culminates in neutrophil influx into the synovium and the highly inflammatory nature of acute gouty arthritis
- clinical signs: acute arthritis, tenosynovitis, bursitis uratica

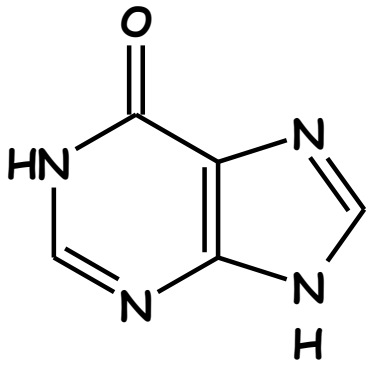




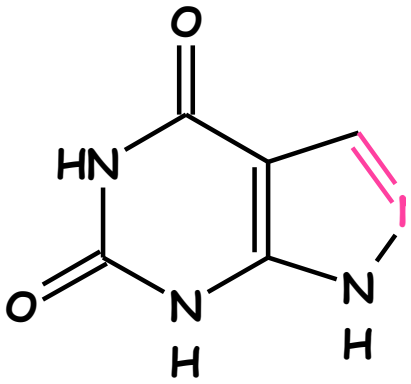
- allopurinol: xanthine oxidase/dehydrogenase inhibitor
- febuxostat: non purine analog, XDH/XO inhibitor
- probenecid: uricosuric agent which blocks tubular reabsorption of UA
- peglocytase: pegylated uricase enzyme



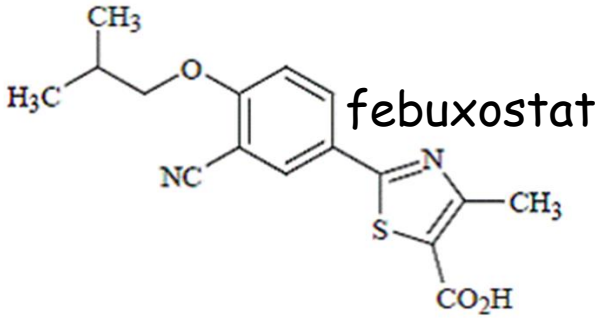
Allopurinol



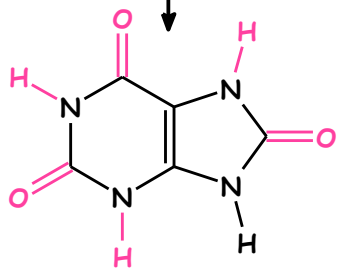
Hypoxanthin



Alloxanthin



- allopurinol inhibits XDH/XO, the enzyme which catalyses the oxidation of hypoxanthine to xanthine, and of xanthine to urate/uric acid

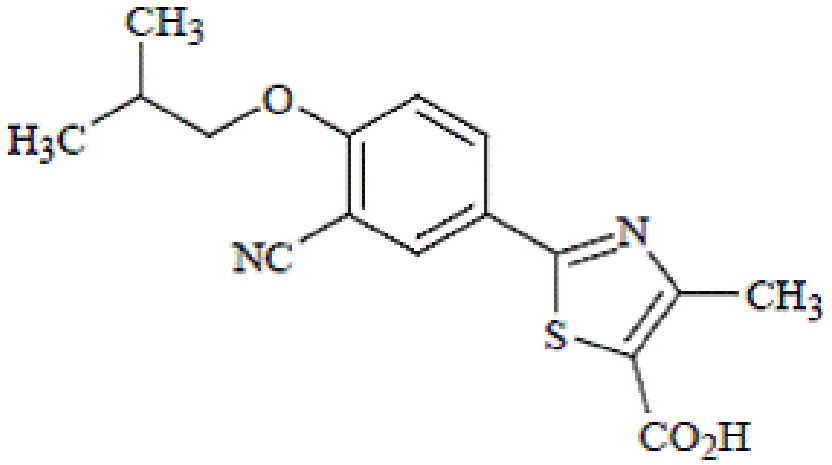


uric acid

Lesinurad

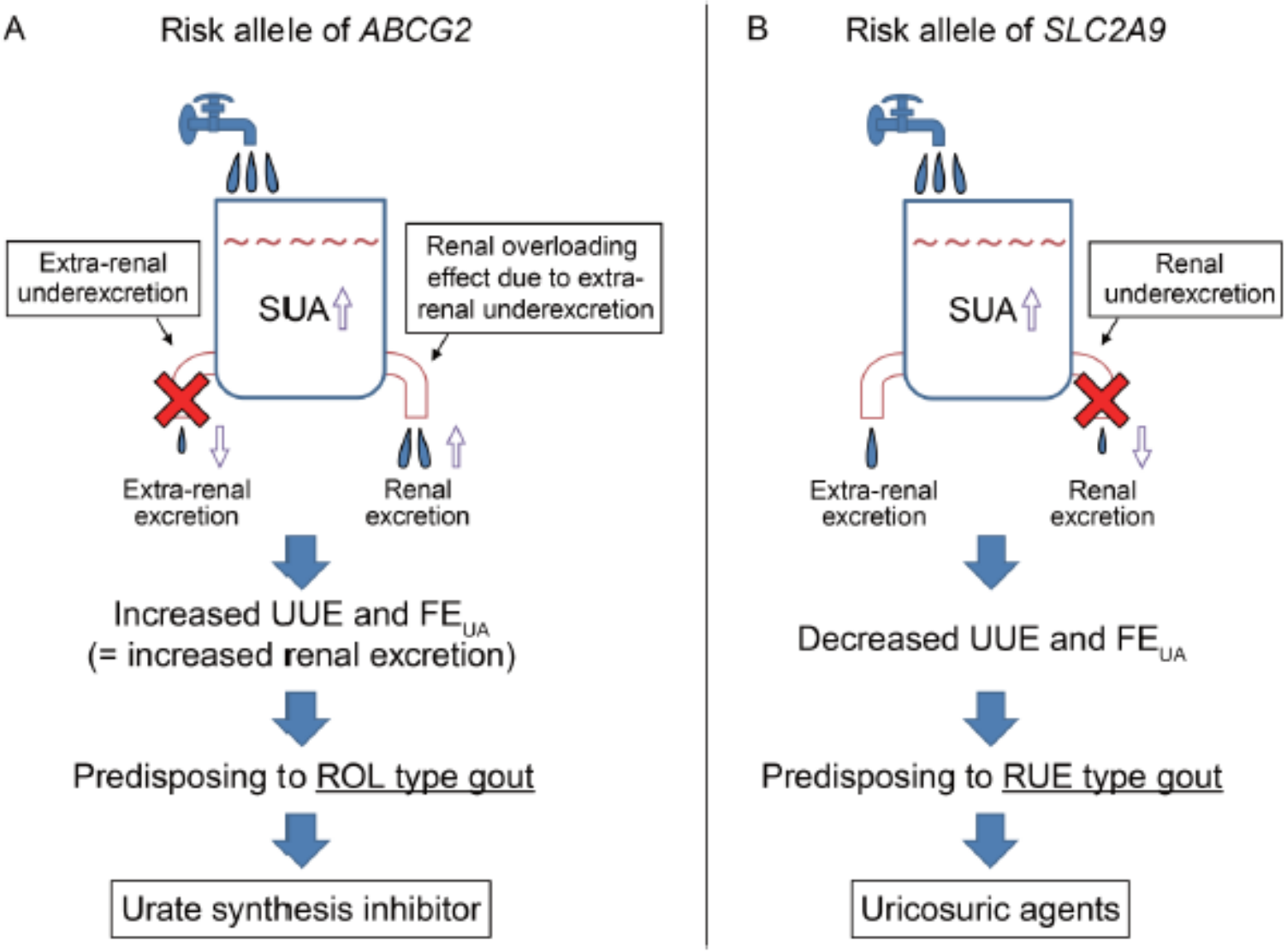
ZURAMPIC® lesinurad 200mg tablets

- a selective uric acid reabsorption inhibitor that inhibits the URAT1 (non-nucleoside reverse-transcriptase inhibitor)
- USA 12/2015, CZ 2/2016
- allopurinol, febuxostate
- AKI



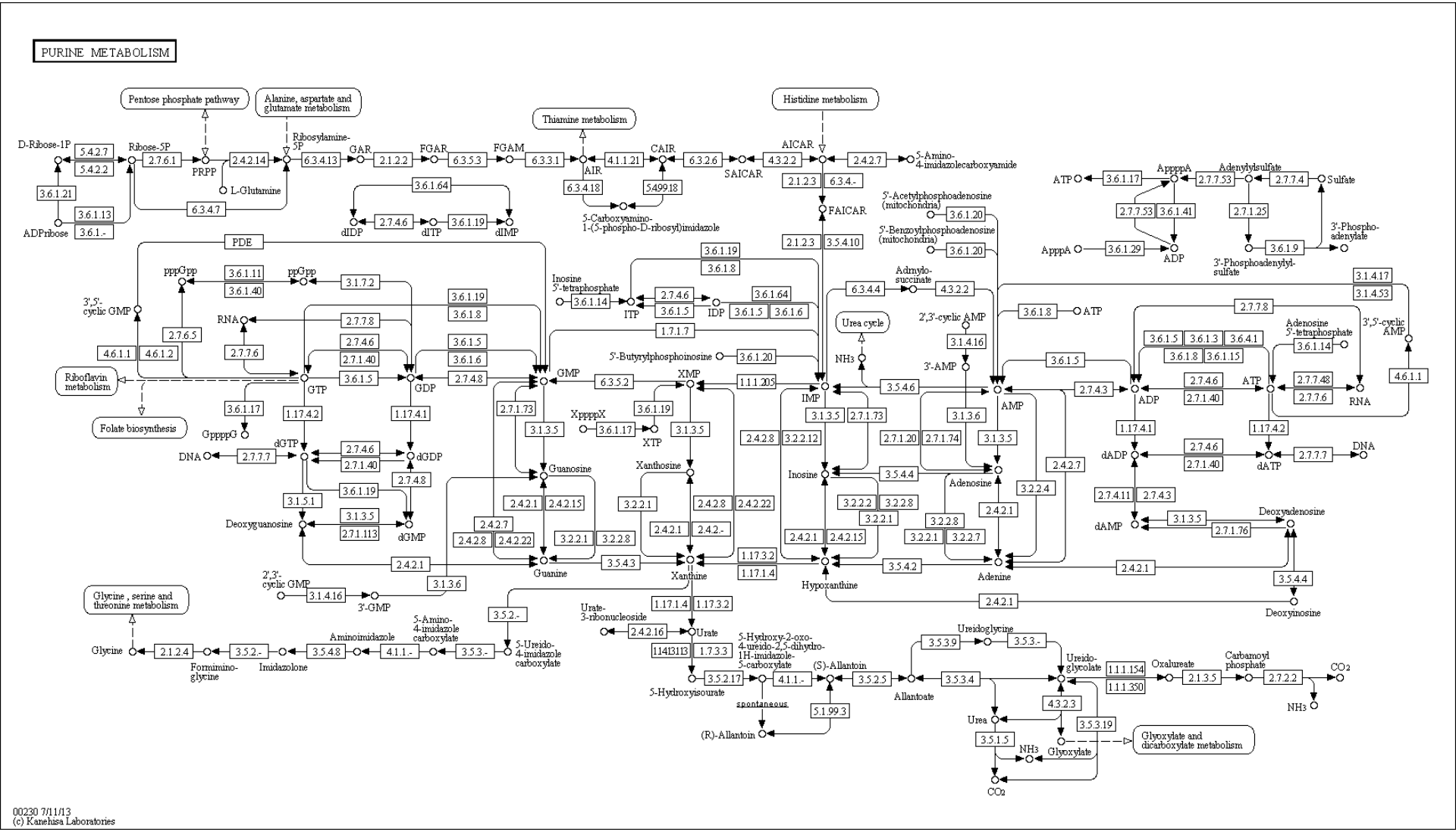
http://www.med-chemist.com/2016_03_01_archive.html

- **gout is increasingly recognized as a heterogeneous disease requiring individualized treatment**



Matsuo et al., *Ann Rheum Dis.* 2014

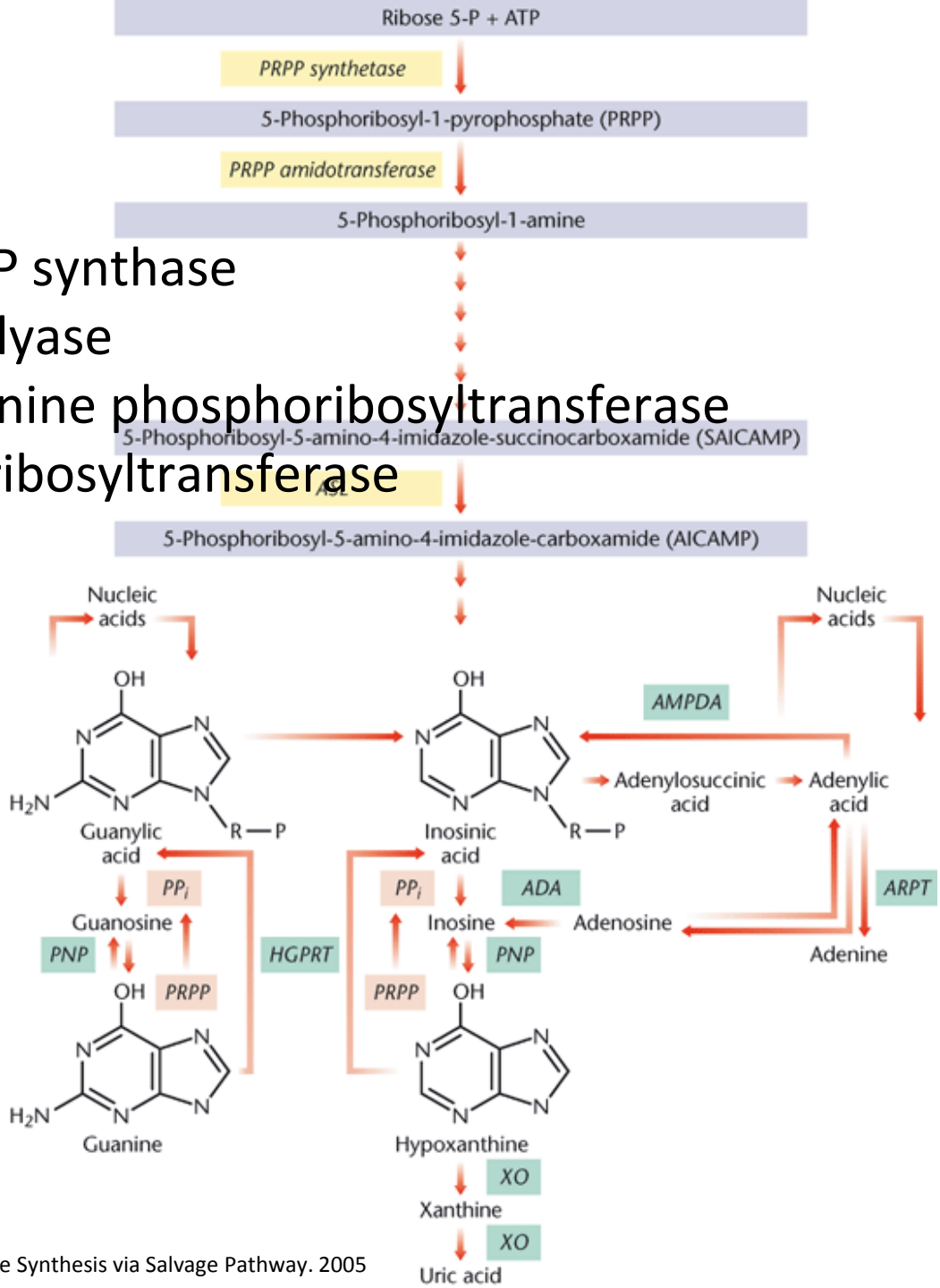
Inherited metabolic disorders of purine metabolism



- inherited metabolic disorders of purine metabolism: *de novo* synthesis, salvage pathway and catabolism

De novo synthesis
Salvage pathway

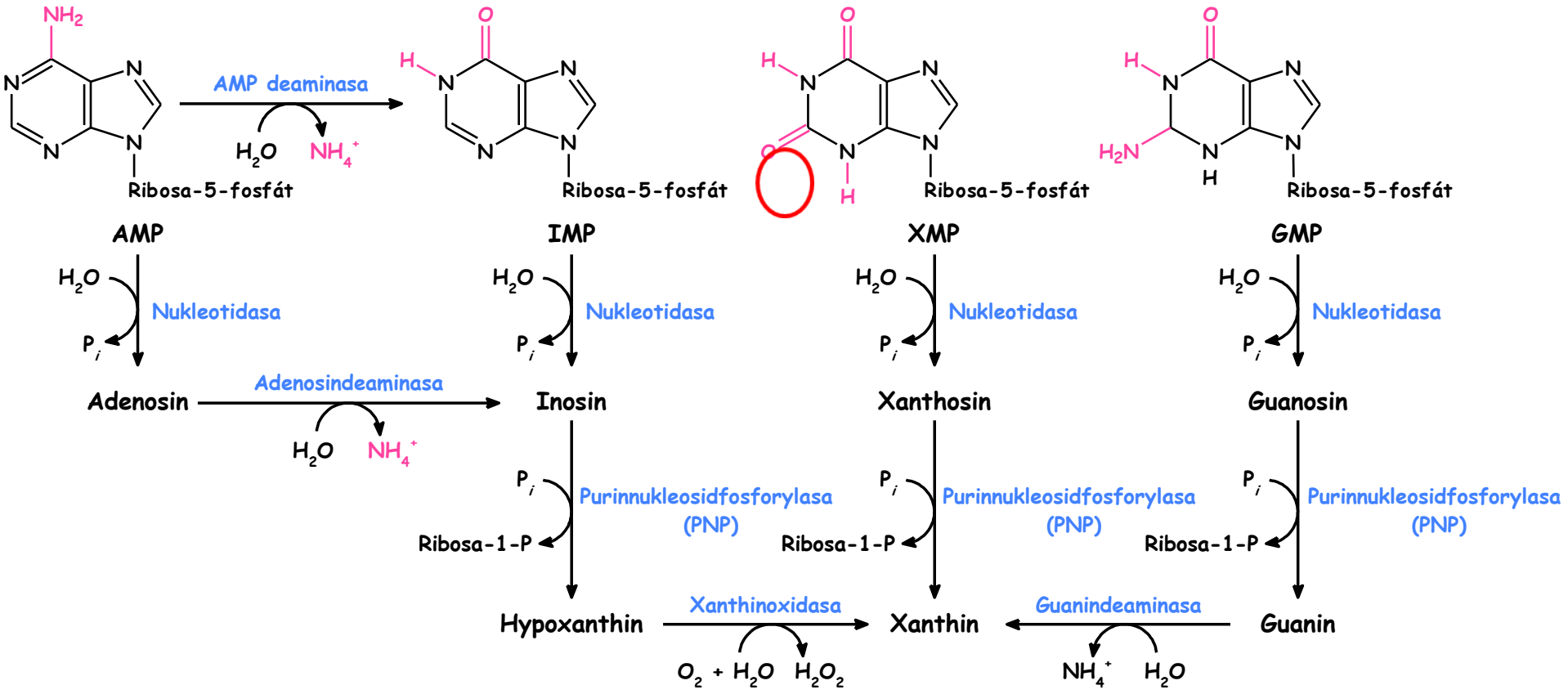
- deficiency/superactivity PRPP synthase
- deficiency adenylosuccinate lyase
- deficiency hypoxanthine guanine phosphoribosyltransferase
- deficiency adenine phosphoribosyltransferase



Nyhan WL, Nucleotide Synthesis via Salvage Pathway. 2005

Catabolism of purines

- adenosine deaminase deficiency
- adenosine deaminase superactivity
- purinnucleoside fosforylase deficiency
- xanthin oxidase/dehydrogenase deficiency



Deficiency of purine synthesis

PRPS1 syntetasa

- phosphoribosylpyrophosphate synthetase, an enzyme that catalyzes the synthesis of PRPP

- X-linked

- *PRPS1* (MIM 311850)

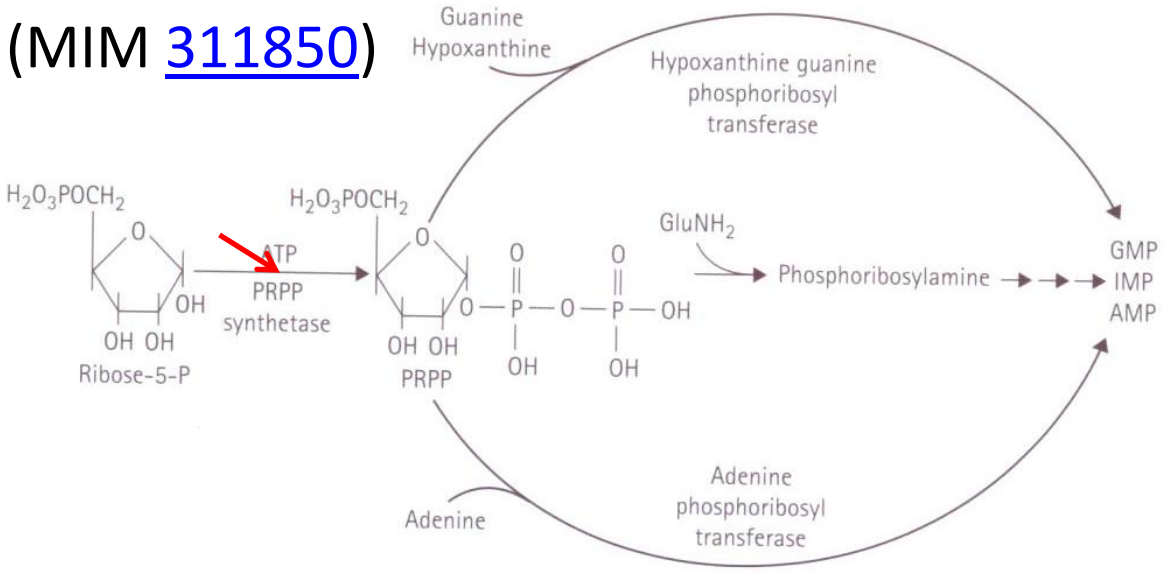


Figure 67.1 *PRPP synthetase. The role of the product PRPP is central in the interrelation of purines and their nucleotides.*

William N Nyhan, Bruce A Barshop, Pinar T Ozand (eds). Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

PRPS1 superactivity

- regulatory defects and ↑ expression of PRS-I, normal kinetic enzyme properties
- 30 patients, 7 point mutation in *PRPS1* has been identified
- variable neurological findings, neurological symptoms, sensorineural hearing loss, PM
- **severe superactivity** phenotypes with purine overproduction accompanied by neuropathy, PRPS1 is not truly "superactive" because it does not have a higher V_{max} than the normal protein, but rather it lacks regulatory control of its
- **milder phenotype**: ↑ transcript levels, but no genetic defects have been identified, ↑ expression, that manifest as purine overproduction without any neuropathy
- overexpression has been shown to be accompanied by raised intracellular levels of PRPP in all cell types examined, i.e., fibroblasts, lymphoblasts, and erythrocytes
- ↑ *de novo* purine synthesis causes accelerated nucleotide degradation to UA

Charcot-Marie-Tooth disease-5 (MIM 311070)

- part of the spectrum of *PRPS1*-related disorders, is characterized by peripheral neuropathy, early-onset (prelingual) bilateral profound sensorineural hearing loss, and optic neuropathy
- the onset of peripheral neuropathy is between ages five and 12 y

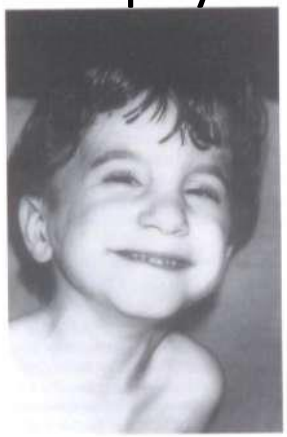
X-linked nonsyndromic sensorineural deafness (MIM 304500)

- vestibular and cochlea hair cells in early developing and postnatal mice and in the spiral ganglion cells in mice at P6, a role in inner ear development and maintenance

Arts syndrome (MIM 301835)

- mental retardation, early-onset hypotonia, ataxia, delayed motor development, hearing impairment, and optic atrophyneurological problems and immune dysfunction

PRPS-I superactivity (MIM 300661)



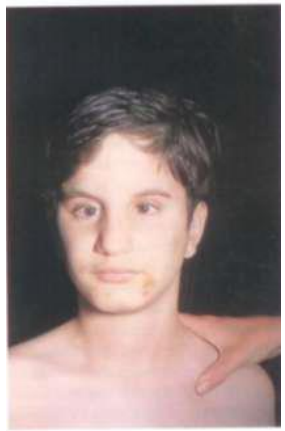


Figure 67.2 S.M., a 3-year-old with an abnormal PRPP synthetase. The odd grimace was characteristic. (Reprinted with permission from the Journal of Pediatrics [5]).

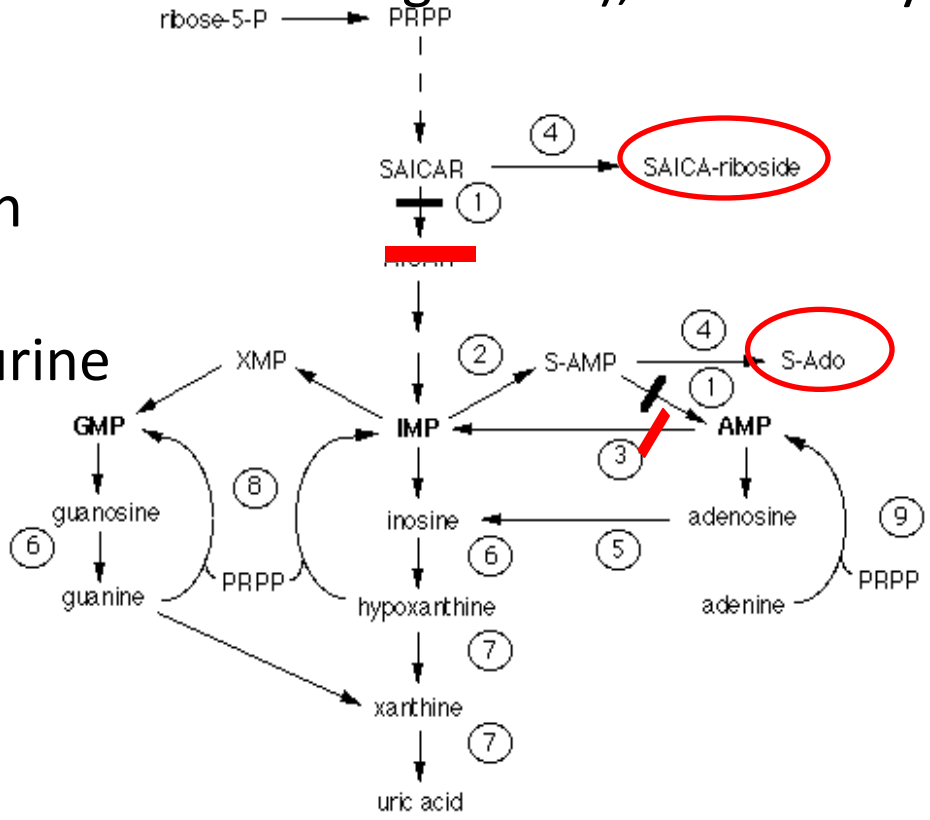
S.M., at 14 years-of-age.

WN Nyhan et al. Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

Adenylosuccinate lyase deficiency (ADSL)

- ADSL is a defect of purine metabolism affecting purinosome assembly and reducing metabolite fluxes through purine *de novo* synthesis and purine nucleotide recycling pathways

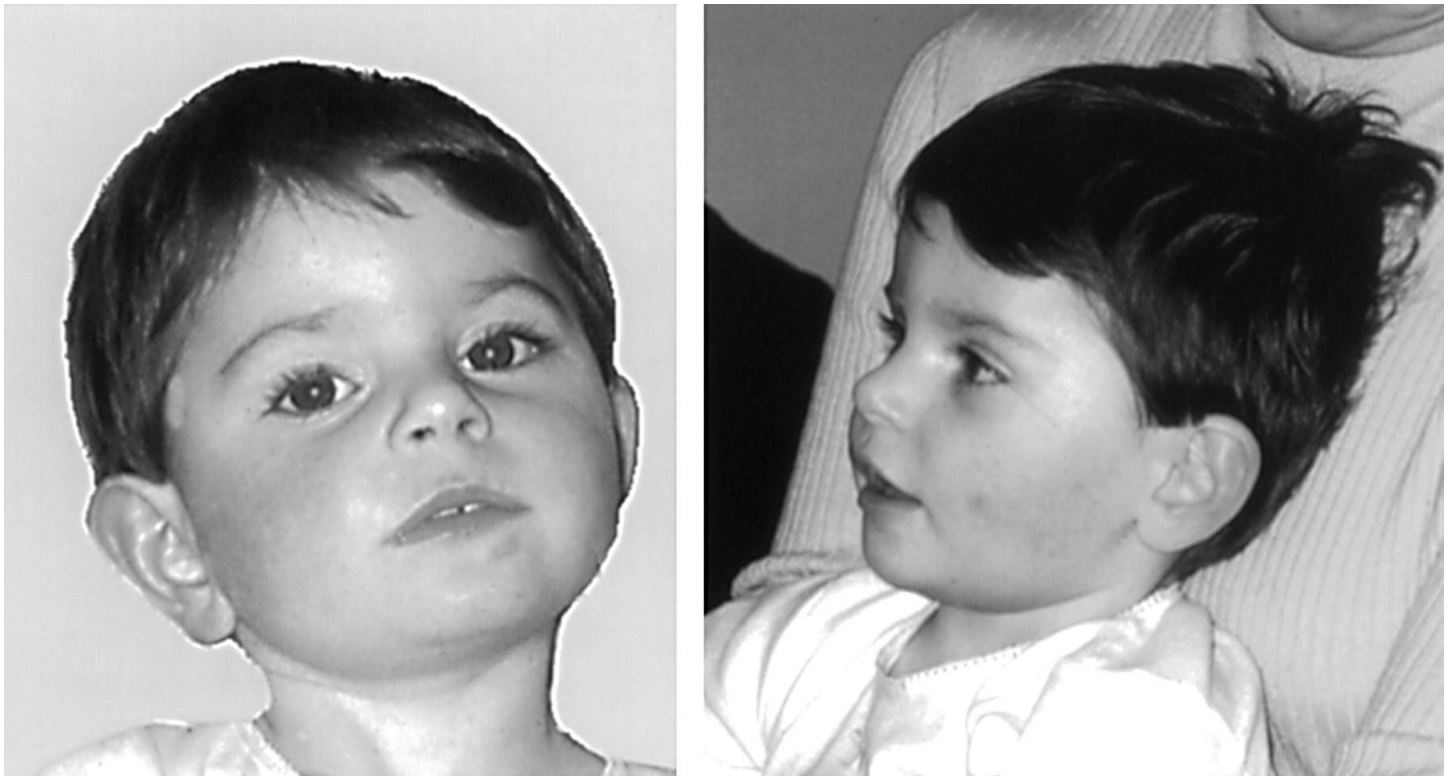
- AR inheritance, OMIM 608222
- SAICAR toxic for neurons (impaired utilization of glucose), S-Ado may be protective
- uncertain role of purine depletion
- biochemical markers: SAICAR in urine
- treatment N/A



- ADSL covers a continuous clinical spectrum with three major forms
  - **fatal neonatal**
  - **severe** (type I)
  - **mild to moderate form** (type II)

- clinical variability is found, even in patients from the same family
- onset is generally between birth and early childhood
- cases ranging from fatal neonatal encephalopathy (presenting with hypokinesia, intractable seizures and respiratory failure) to mild intellectual disability have been reported
- intellectual disability is found in all patients, epilepsy of various types in most, and autistic features in about one third (failure to make eye contact, hypersensitivity to noise and light, repetitive behavior, agitation, temper tantrums, autoaggression and self-mutilation)
- prenatal manifestations are also reported: impaired intrauterine growth, microcephaly, fetal hypokinesia, and loss of fetal heart rate variability

Facial dysmorfia in ADSL deficiency

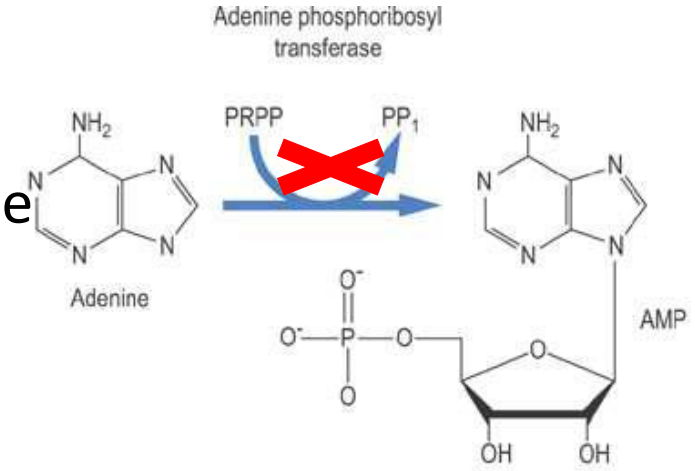


Holder-Espinasse M et al. J Med Genet2002;39:440-442

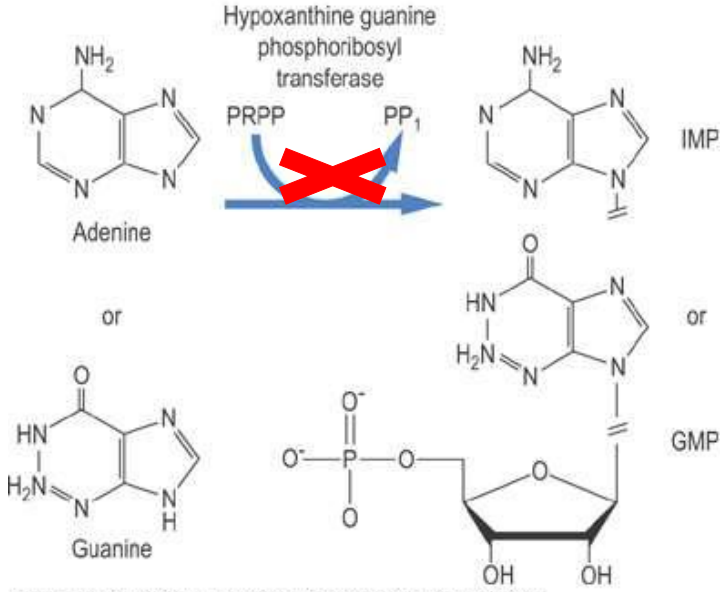
- brachycephaly, prominent metopic sutures, small nose with anteverted nostrils, long, smooth philtrum, and thin upper lip

Salwage pathway defects

deficiency adenine phosphoribosyl transferase



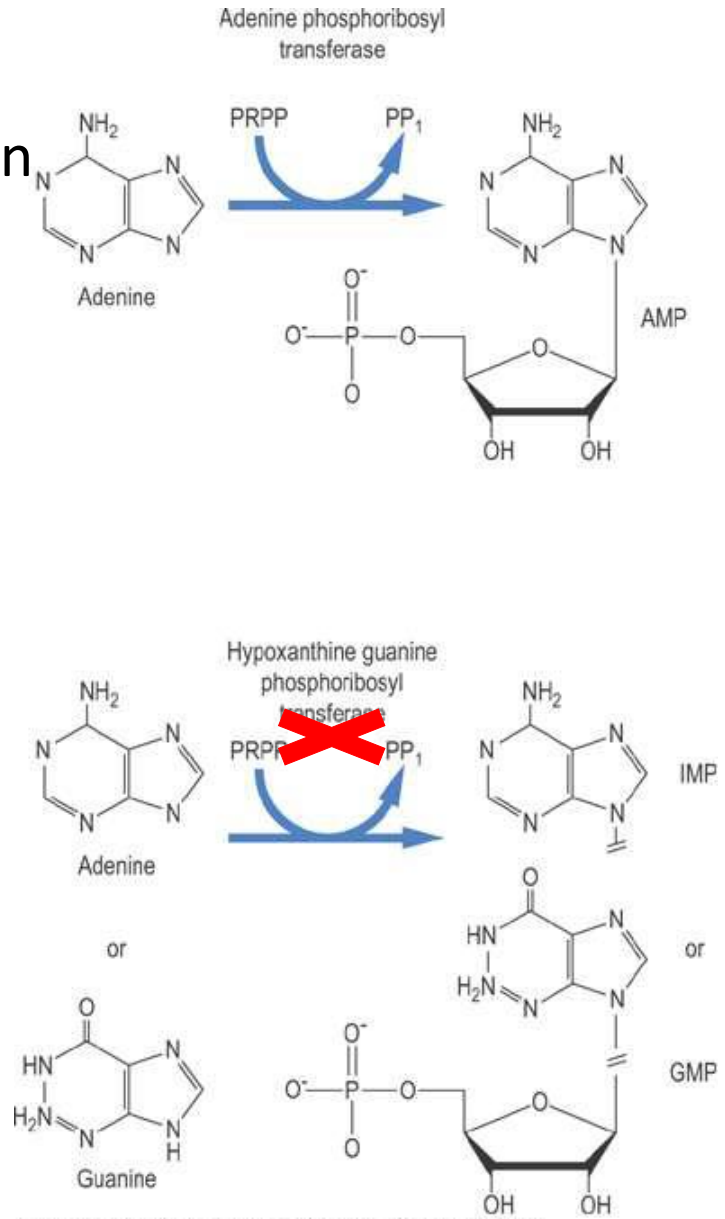
deficiency hypoxanthine guanine phosphoribosyl transferase



Hypoxanthine guanine phosphoribosyl transferase

- X-linked disease, OMIM 308000
- the HPRT defect results in the accumulation of its substrates, hypoxanthine and guanine
- the increased availability of PRPP for PRPP amidotransferase increases purine synthesis
- on the other hand, there is decreased formation of PRPP amidotransferase feedback inhibitors, IMP and GMP
- this dual mechanism results in an increased *de novo* synthesis of purine ntd

- the combination of deficient recycling of purine bases with increased synthesis of purine nucleotides explains marked UA



- HPRT deficiency classified into distinguished forms
- **partial** HPRT deficiency, also known as Kelley–Seegmiller syndrome (#300323), is usually associated with the clinical manifestations of purine overproduction which results in increased uric acid synthesis (hyperuricemia/gout, urolithiasis, nephrolithiasis and kidney stones); however, a variable spectrum of neurological manifestations, such as motor disability and intellectual impairment, is available (Lesch–Nyhan variants)
- classical features of severe deficiency, **Lesch–Nyhan syndrome** (#300322), are moreover characterized by psychyatrics aspects: self-injurious behavior

- the diagnosis of HPRT is determined by hyperuricemia and hyperuricosuriawith urinary hypoxanthine and xanthine elevation
- secondly, HPRT deficiency is confirmed by low HPRT activity in erythrocytes
- finally, the results are confirmed by molecular genetics

Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. *Am J Med.* Apr 1964;36:561-70.

- boy 4 y, PMR, urinary infection, urinary stones, miss-diagnosed cystinuria

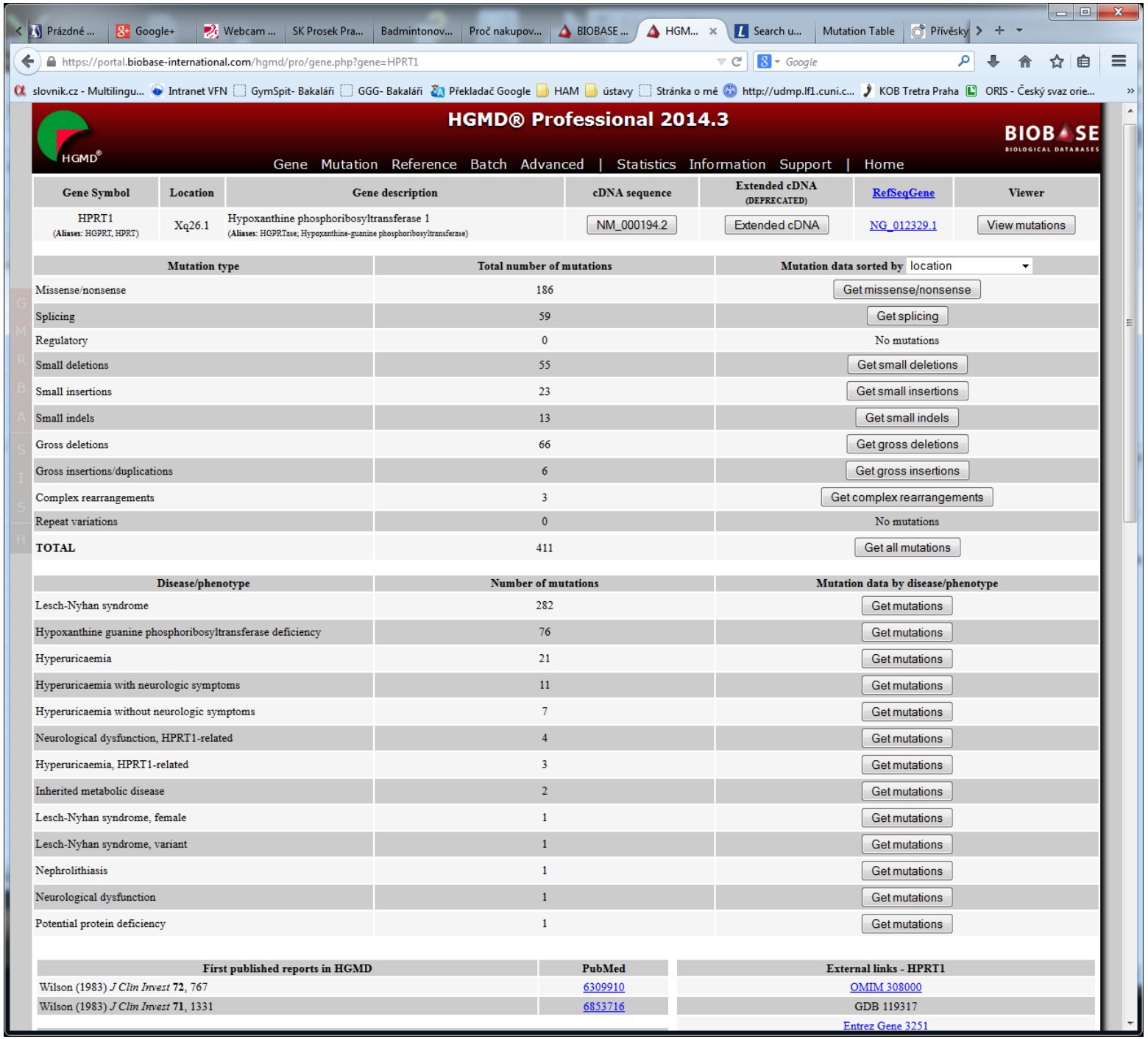
- urinary urate crystals
- brother of proband, 8 y, PMR, self-injurious

M Lesch

WL Nyhan

"the idea of a potential new disease with all its ramifications seemed so great that we immediately quit"

"Mike worked full time and essentially did 100 % of the lab work documenting that this was an inborn error of purine metabolism"



HGMD® Professional 2014.3

BIOBASE BIOLOGICAL DATABASES

Gene Mutation Reference Batch Advanced | Statistics Information Support | Home

Gene Symbol	Location	Gene description	cDNA sequence	Extended cDNA (DEPRECATED)	RefSeqGene	Viewer
HPRT1 (Aliases: HGPRT, HPRT)	Xq26.1	Hypoxanthine phosphoribosyltransferase 1 (Aliases: HGPRTase, Hypoxanthine-guanine phosphoribosyltransferase)	NM_000194.2	Extended cDNA	NG_012329.1	View mutations

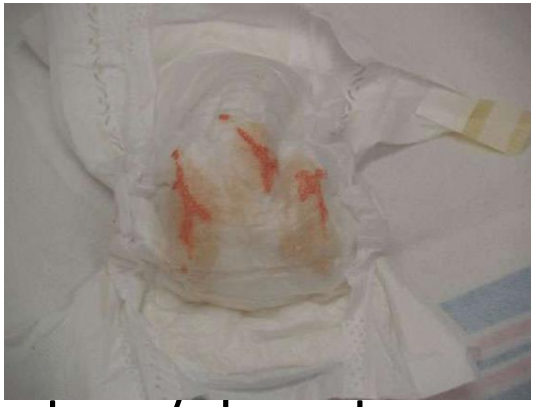
Mutation type	Total number of mutations	Mutation data sorted by location
Missense/nonsense	186	Get missense/nonsense
Splicing	59	Get splicing
Regulatory	0	No mutations
Small deletions	55	Get small deletions
Small insertions	23	Get small insertions
Small indels	13	Get small indels
Gross deletions	66	Get gross deletions
Gross insertions/duplications	6	Get gross insertions
Complex rearrangements	3	Get complex rearrangements
Repeat variations	0	No mutations
TOTAL	411	Get all mutations

Disease/phenotype	Number of mutations	Mutation data by disease/phenotype
Lesch-Nyhan syndrome	282	Get mutations
Hypoxanthine guanine phosphoribosyltransferase deficiency	76	Get mutations
Hyperuricaemia	21	Get mutations
Hyperuricaemia with neurologic symptoms	11	Get mutations
Hyperuricaemia without neurologic symptoms	7	Get mutations
Neurological dysfunction, HPRT1-related	4	Get mutations
Hyperuricaemia, HPRT1-related	3	Get mutations
Inherited metabolic disease	2	Get mutations
Lesch-Nyhan syndrome, female	1	Get mutations
Lesch-Nyhan syndrome, variant	1	Get mutations
Nephrolithiasis	1	Get mutations
Neurological dysfunction	1	Get mutations
Potential protein deficiency	1	Get mutations

First published reports in HGMD	PubMed
Wilson (1983) *J Clin Invest* **72**, 767	6309910
Wilson (1983) *J Clin Invest* **71**, 1331	6853716

External links - HPRT1
OMIM 308000
GDB 119317
Entrez Gene 3251

- patients with HPRT deficiency are normal at birth, one of the first signs of the disease may be the observation of orange crystals in the diapers, or crystalluria with obstruction of the urinary tract
- psychomotor delay, when present, becomes evident within 3 to 6 m
- a delay in the acquisition of sitting and head support with hypotonia and athetoid movements may lead to neurological consultation
- self-mutilation, in the form of lip biting or finger chewing, can appear as soon as teeth are present



http://newborns.stanford.edu

WN Nyhan et al. *Atlas of metabolic diseases*, 2005

- variability: no correlation genotype/phenotype
- hyperuricuria (300 - 850 µmol/kg/24 hours)
  hyperuricemia, ↑ hypoxanthine
  ↓ activita HPRT in erythrocytes/fibroblast
- **hyperuricemia:** the only treatable feature of disease, prevents the development of gouty manifestations and urate nephropathy

- various theories for neurological anormalities incl. purines depletion, possibly secondary dopamin synthesis defect (decreased DOPA-decarboxylase)

- X-linked recessive inheritance pattern
- female carriers are usually asymptomatic; fewer than ten clinically affected females were described previously
- carrier diagnosis is an important issue for most families with HPRT deficiency and carrier status cannot be confirmed by biochemical and enzymatic methods in most of the cases
- accurate carrier diagnosis can be performed by molecular genetics; however, in about 5% of patients, no molecular defect is found

- treatment controlling UA overproduction with allopurinol/febuxostat
- however, allopurinol has not usually been considered to cause behavioral and neurological symptoms

HGPRT activity in fibroblasts

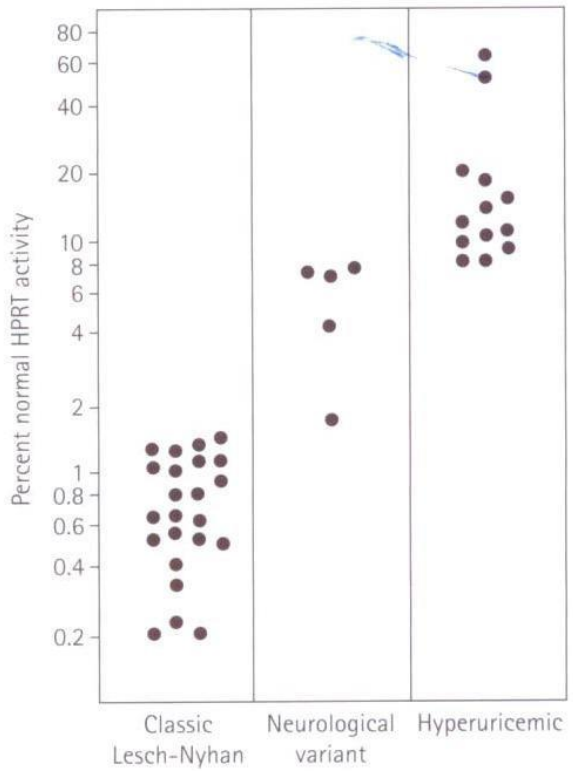


Figure 65.21 *Activity of HPRT in intact fibroblasts. The level of enzyme activity was roughly inversely proportional to the degree of clinical severity. Actually, the values fell into three groups, correlated with phenotype: the Lesch-Nyhan; the neurologic variant, and the classic partial variant.*

Lesch-Nyhan syndrome < 1.5%

- less than 1.5 % of residual enzyme activity, leads to neurologic impairment and impulsive, self-injurious behaviours along with overproduction of UA

Kelly-Seegmiller syndrome 1.5 – 8%

- residual activity is responsible for milder neurologic disabilities, such as minor clumsiness or even extrapyra-midal and pyramidal motor dysfunction

HPRT-related hyperuricemia > 8%

- patients with at least 8 % of residual activity suffered only from the clinical consequences of UA overproduction, such as nephrolithiasis and gout.

William N Nyhan, Bruce A Barshop, Pinar T Ozand (eds). Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

Deficiency HGPRT- urate tophus

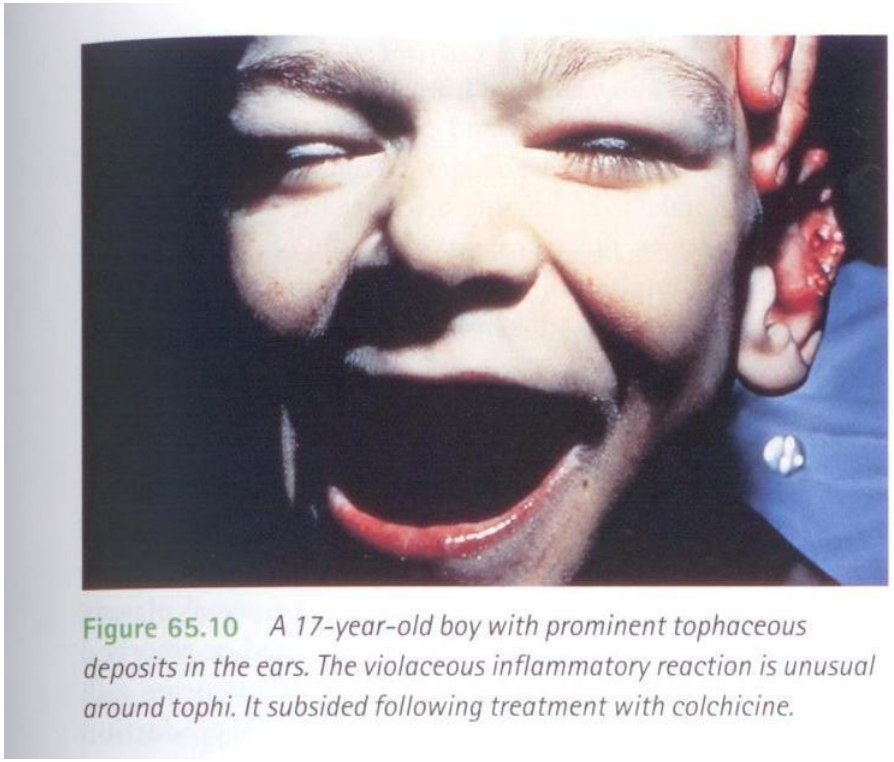
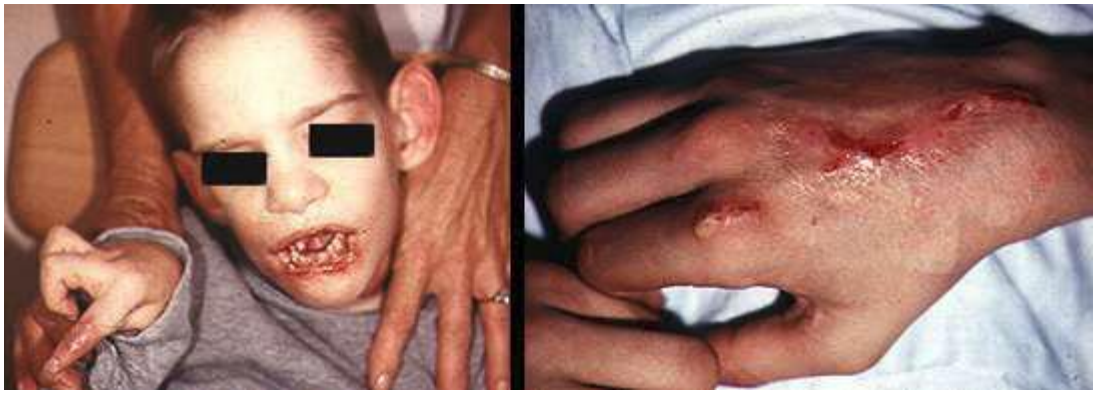


Figure 65.10 *A 17-year-old boy with prominent tophaceous deposits in the ears. The violaceous inflammatory reaction is unusual around tophi. It subsided following treatment with colchicine.*

William N Nyhan, Bruce A Barshop, Pinar T Ozand (eds). Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

- hyperuricemia: the only treatable feature of disease

- compulsive self-injurious behaviour is the most striking feature of Lesch-Nyhan syndrome and is only present in patients with the complete enzyme defect, although some Lesch-Nyhan patients never show auto-destructive behaviour
- the patients begin to bite their lips, tongue or fingers and, without restrictions, important auto-mutilating lesions can develop
- the mutilation is not the result of a lack of sensation (the patients feel pain and are relieved when protected from themselves) and recently it has been ascribed to an obsessive-compulsive behaviour



http://www.dent.ucla.edu/pic/visitors/teethloss/images/PreFig9.jpg

X-inactivation

- the mechanistic aspects of the primary cause of symptomatic females were highlighted by X-inactivation studies

- **lyonization,** discovery by Mary Frances Lyon, 1961

- process by which one of the two copies of the X chromosome present in female mammals is inactivated

- gene dosage: if there were no X inactivation, women would make twice as much of all 1100 or so proteins encoded by X genes

- inactivation is random and stable

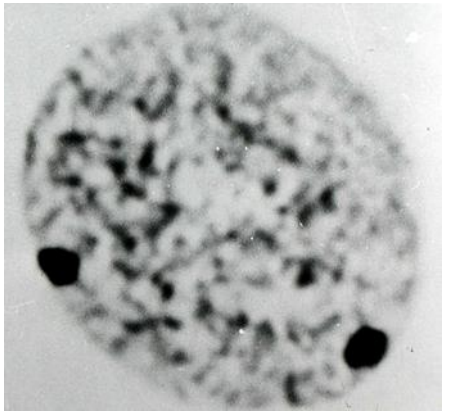


foto K. Barták

- X chromosome inactivation is widely believed to be random in early female development, resulting in a mosaic distribution of cells

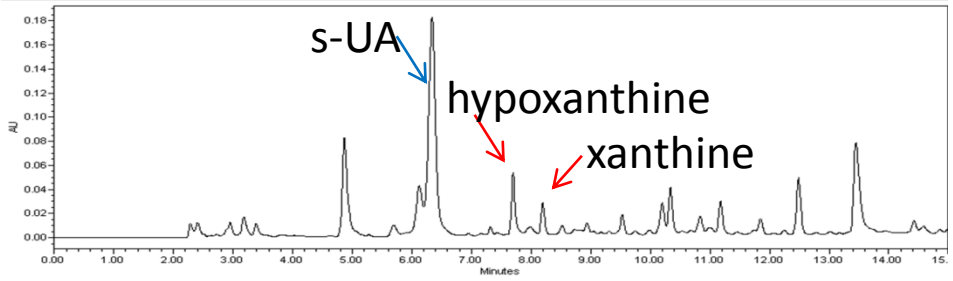
- females are thus expected to have varying X inactivation ratios: as the proportions of cells expressing alleles from one or the other X chrom

- ratios can range from a completely skewed ratio of 0:100, where the same X chrom is active for all cells, to a 50:50 ratio, where each X chrom is active in an equal number of cells

- **asymptomatic heterozygotes**
- **symptomatic heterozygotes,** mild phenotype
- **complete symptomatic heterozygotes,** very rare

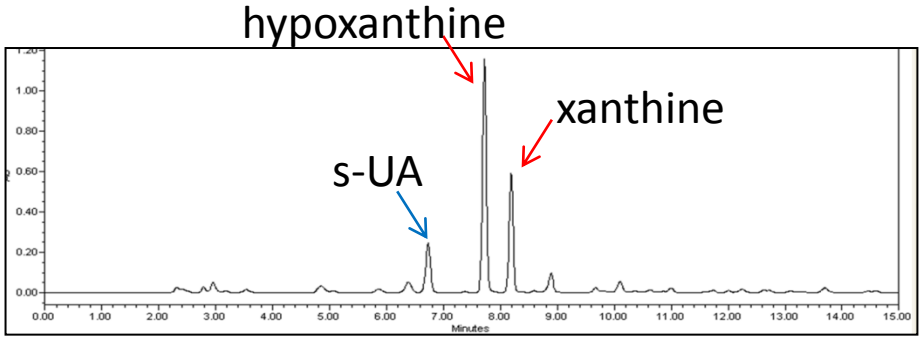
- investigations in asymptomatic family members of subjects with LND variants, and a greater awareness of this disorder is needed for an efficient diagnosis (prenatal diagnosis, pre-implantation diagnosis)

AII.1, 39 y woman, hyperuricemia stardted in 19 y, 8 gouty atacks, MTP 1

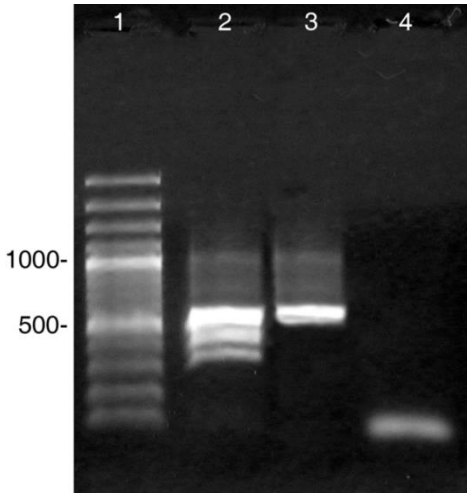


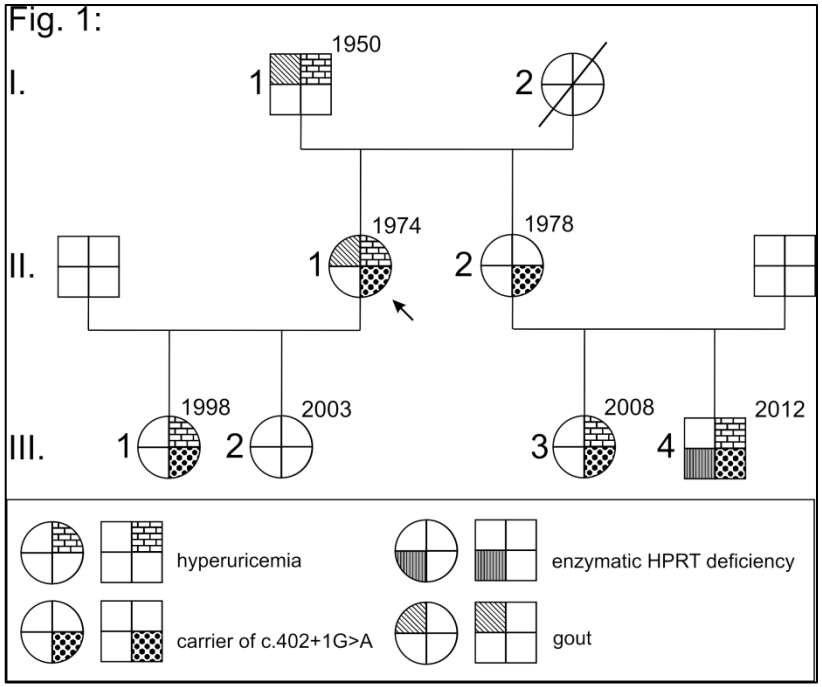
HPRT deficiency: case report 1

AIII.4 8-m boy, hypotonia 3 m, dystonia, urate crystals in diapers



c.402+1G>A HPRT



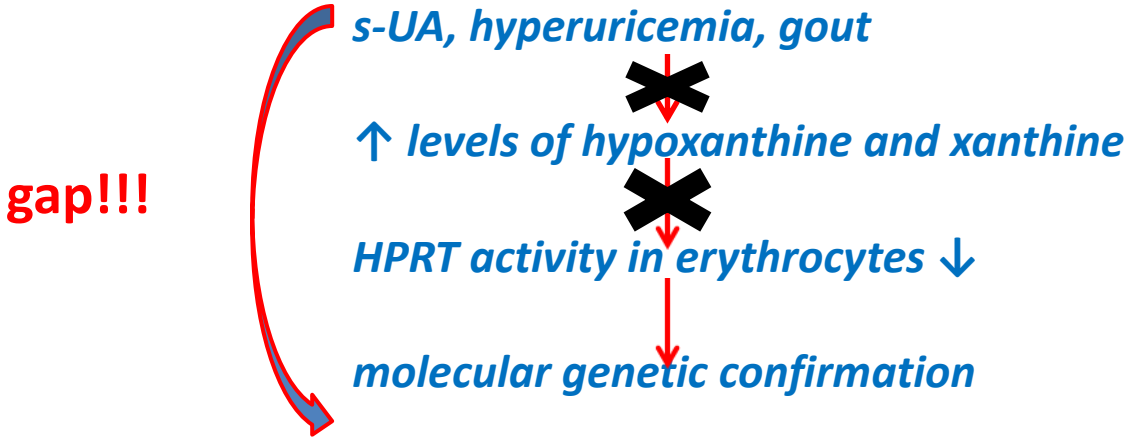


Differential diagnosis of deficiency HPRT

- hyperuricemia, gout
- normal urinary excretion of hypoxanthine and xanthine
- normal enzyme activity of HPRT

- it highlights the fact that HPRT deficiency may present as hyperuricemia and/or gout and that the presence of non-articular symptoms and increased s-UA in females should alert the rheumatologist to its possible presence

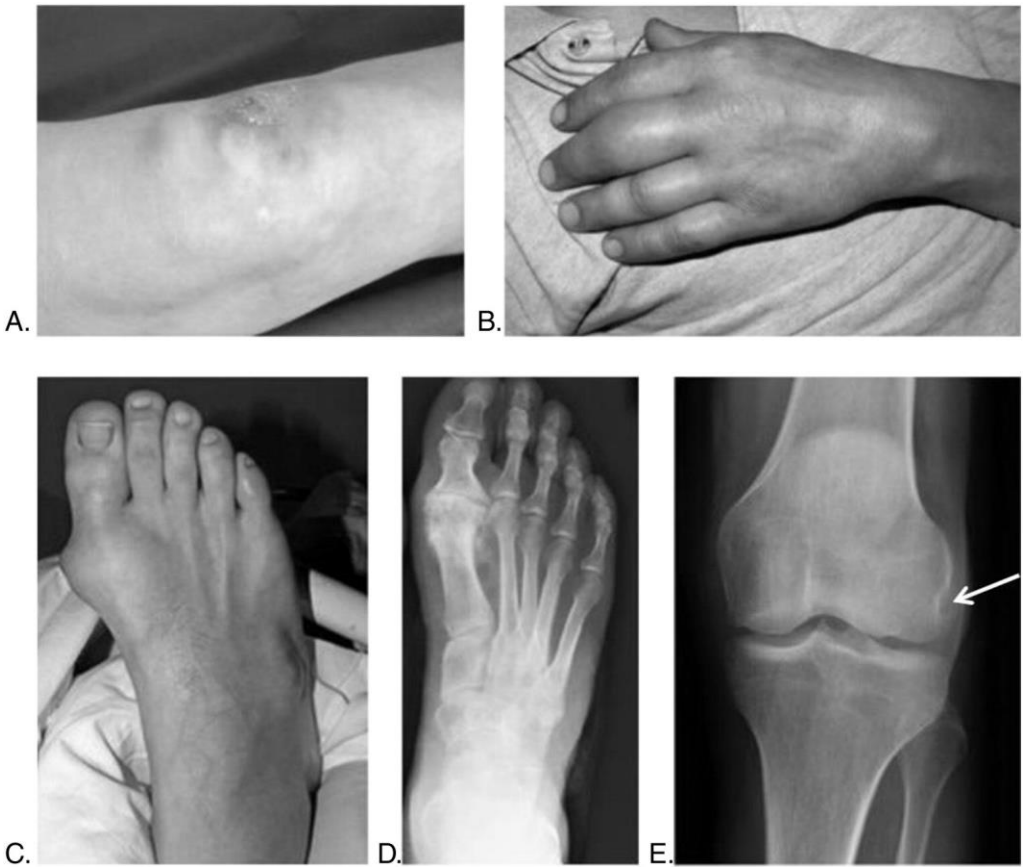
- HPRT deficiency should also be considered in females with hyperuricemia and normal excretion of xanthine and hypoxanthine



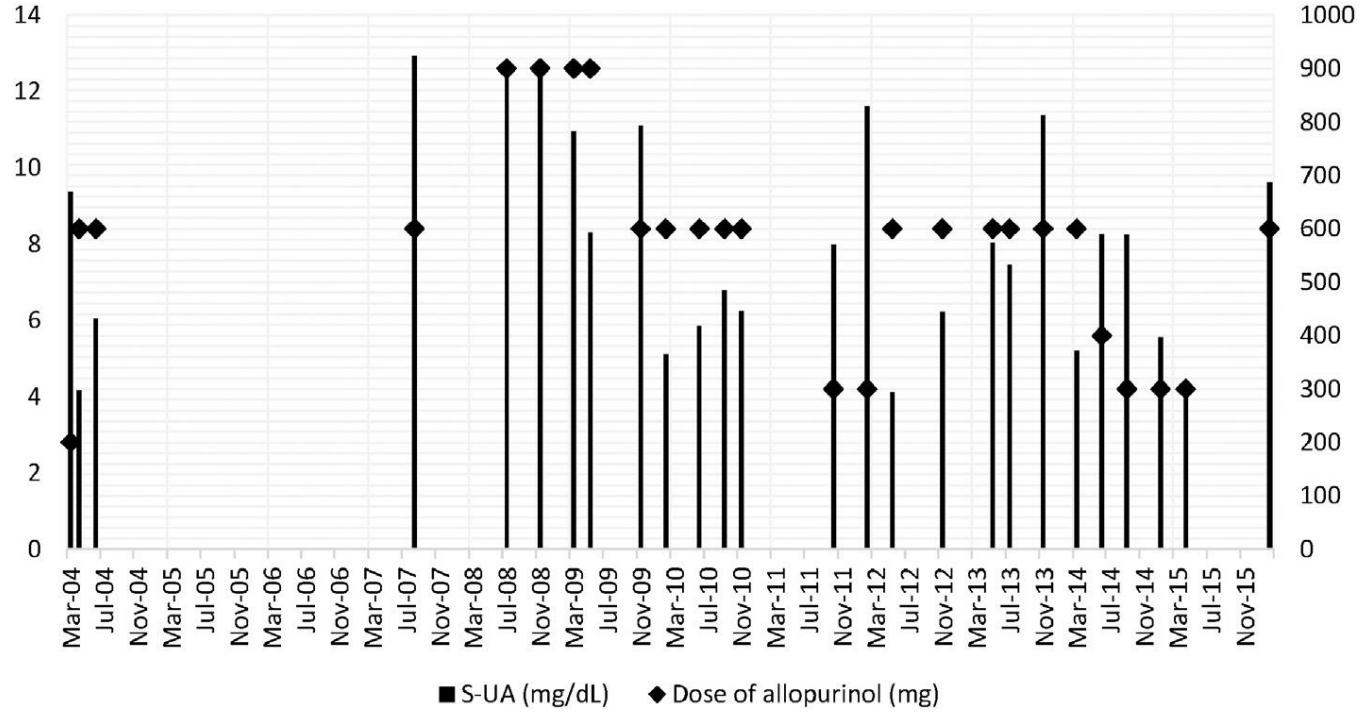
familiar hyperuricemia and/or gout, hyperuricemia and/or gout namely in children and young woman, are an important clue and should always be further investigated

HPRT deficiency: case report 2

- 41-year-old man,who suffered from severe chronic tophaceous gout
- the first episode of acute podagra at the age of 13, nephrolithiasis developed at age 22
- his mother had gout and nephrolithiasis (+ 55 pyelonephritis)
- 13 siblings; all his brothers suffer from renal disease
- at the age of 29, the patient was examined at the UDMP

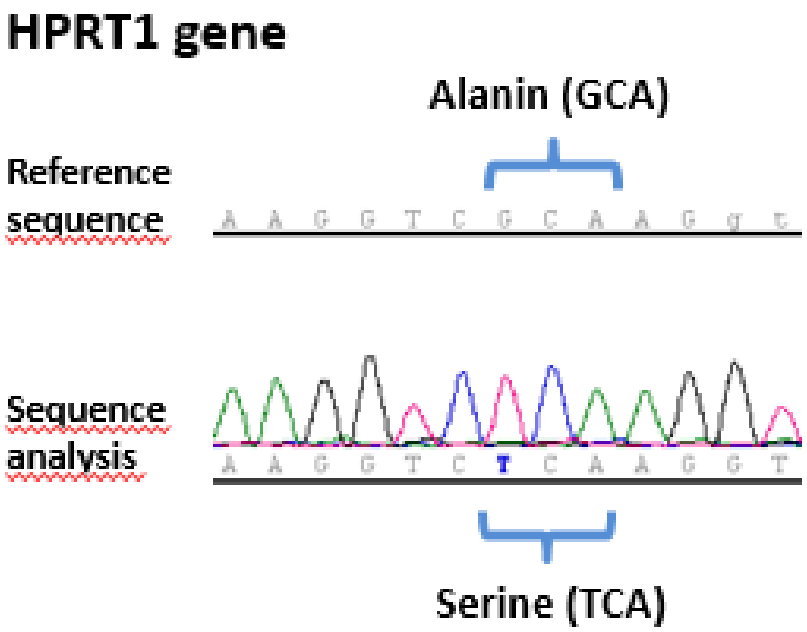


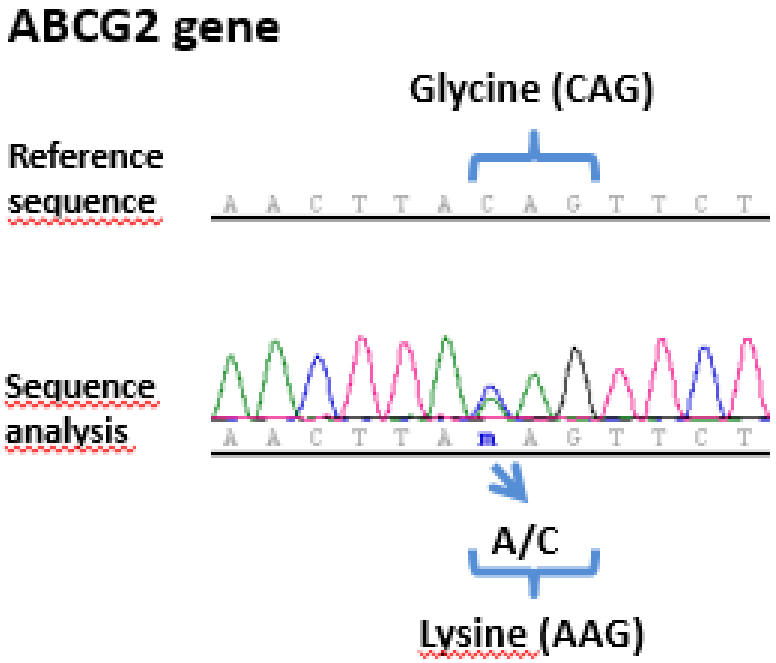
- allopurinol since the age of 13 years



- despite treatment with full doses of allopurinol, long-term serum UA levels were poorly controlled and TG eventually developed
- recently he was admitted to hospital because of his worsening condition: s-UA 9.6 mg/dl, tophi on his right metatarsus and left knee drained spontaneously, renal ultrasound showed progression of urate nephropathy, s-creatinine 1.32 mg/dl

- the cause of TG in our patient with long term treatment with high doses of allopurinol**?**
- c.421C>A: 53% reduction in transport of UA and has been hypothesized to cause at least 10% of all gout cases in Caucasians
- significant association of c.421C>A with an increased risk of a poor response to allopurinol

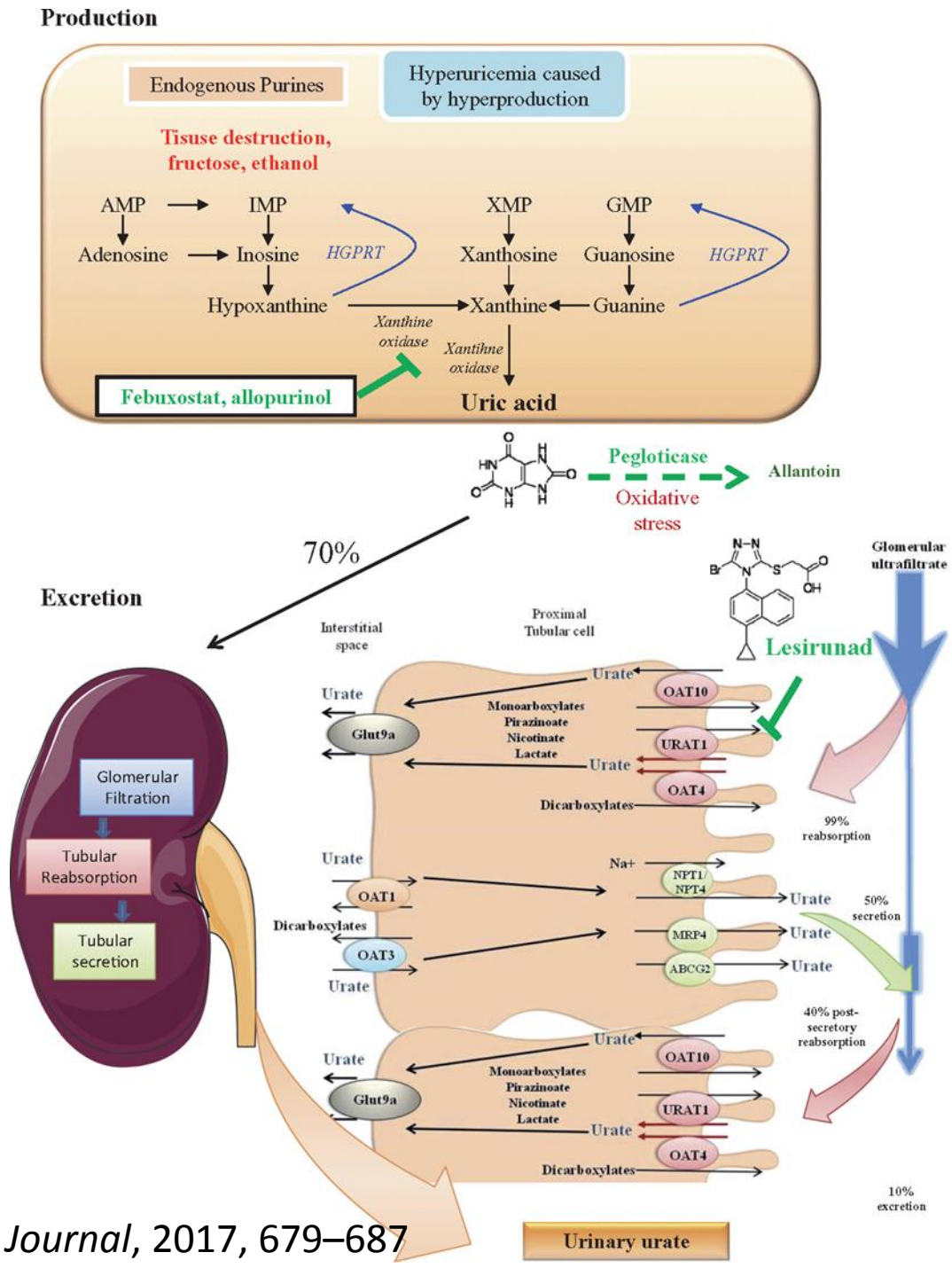




Clin Chim Acta. 2016;460:46-9.

- clinical manifestations of purine overproduction can coexist with common and/or rare variants of proteins that have been shown to transport urate in the proximal tubules
- genetic analysis: wider selection of effective treatments comprehension of treatments failures
- treatment with febuxostat had a significant effect in reducing s-UA in this patient

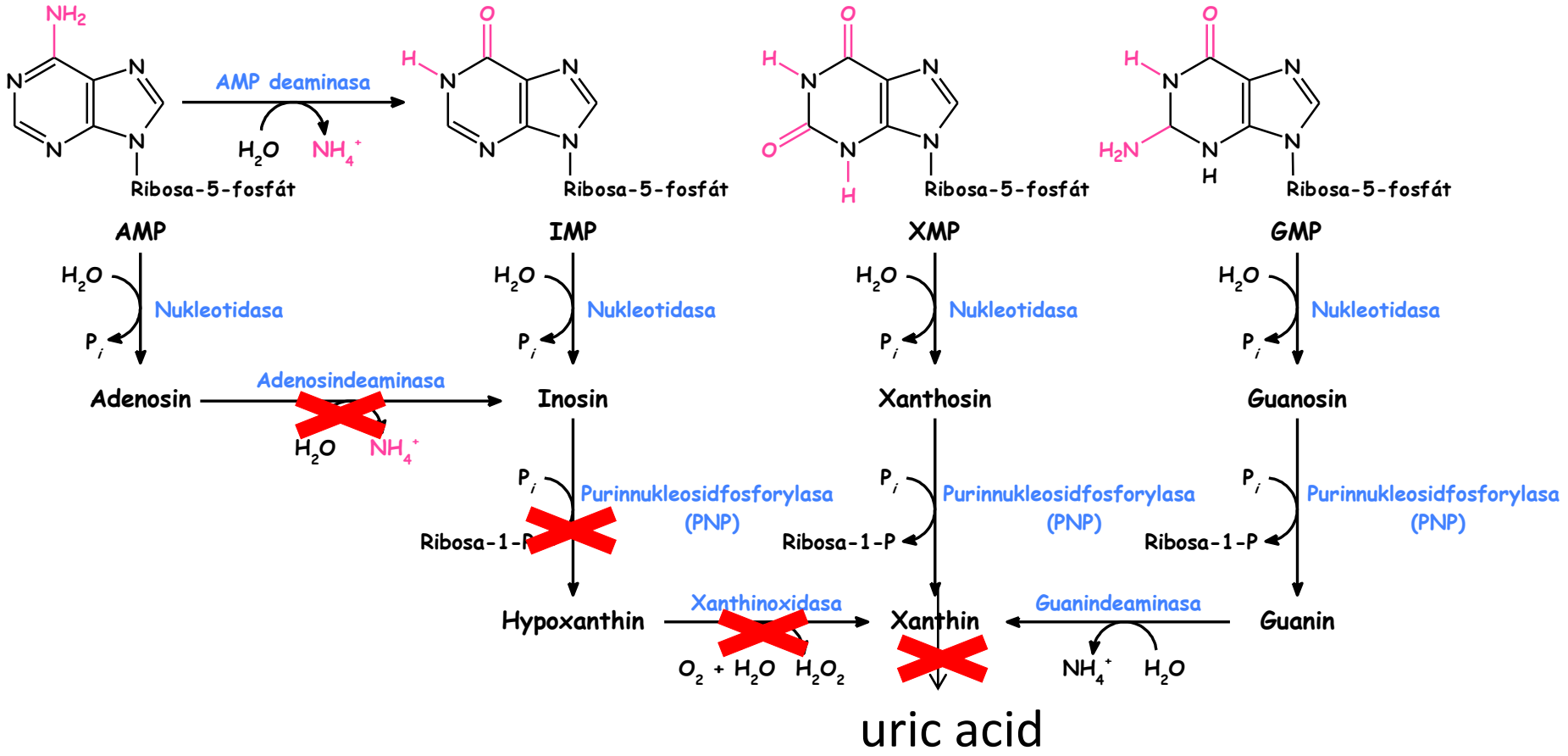
- **significance of genetic background**



Clinical Kidney Journal, 2017, 679–687

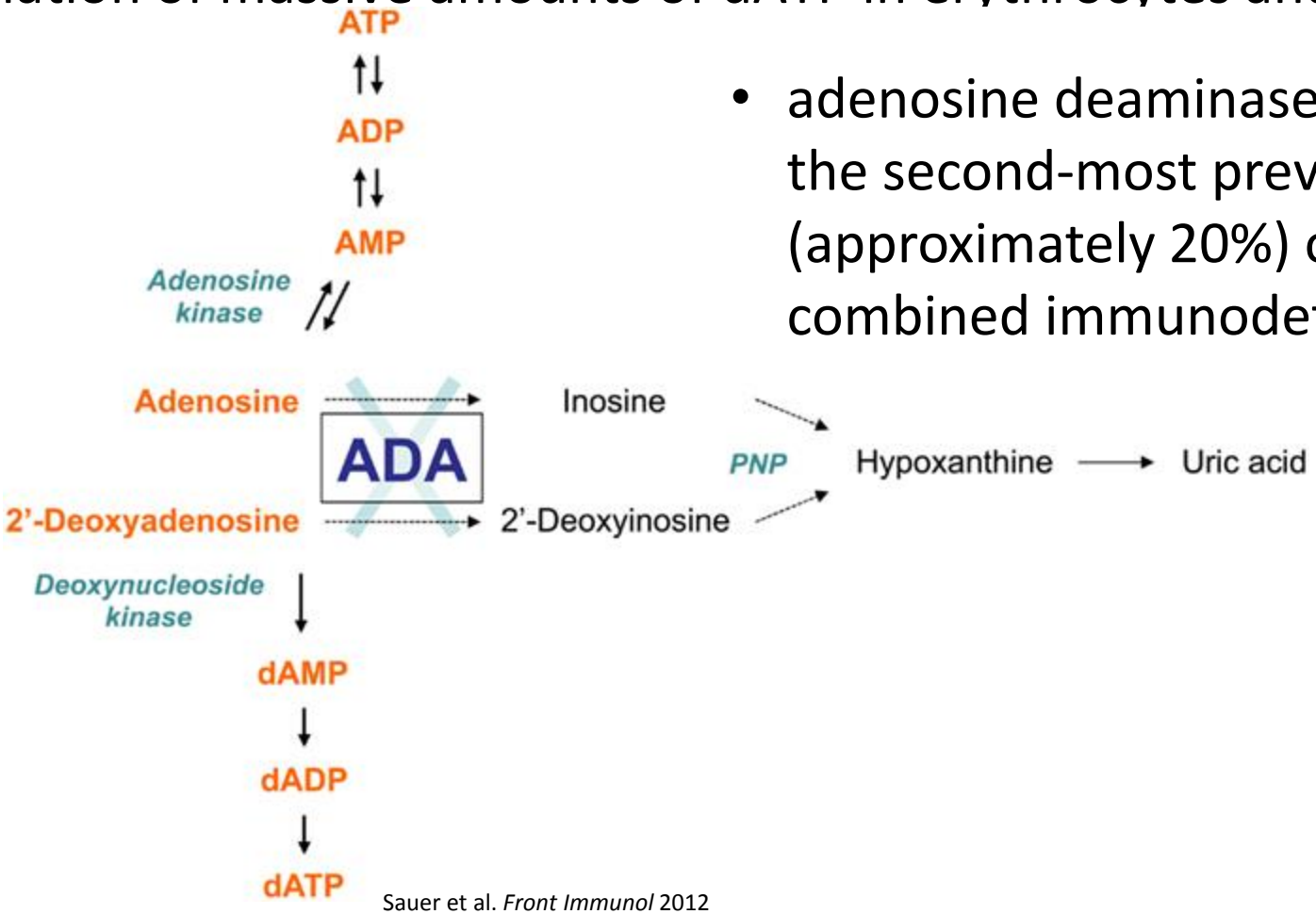
Defects in catabolism of purines

- adenosine deaminase deficiency
- adenosine deaminase superactivity
- purinnucleoside fosforylase deficiency
- xanthin oxidase/dehydrogenase deficiency



Adenosine deaminase deficiency

- 20q13.12, OMIM 608958
- irreversible deamination of adenosine and deoxyadenosine in the purine catabolic pathway
- the most striking metabolic alteration in ADA deficiency is the accumulation of massive amounts of dATP in erythrocytes and lymphocytes



- adenosine deaminase deficiency is the second-most prevalent form (approximately 20%) of severe combined immunodeficiency SCID

Sauer et al. *Front Immunol* 2012

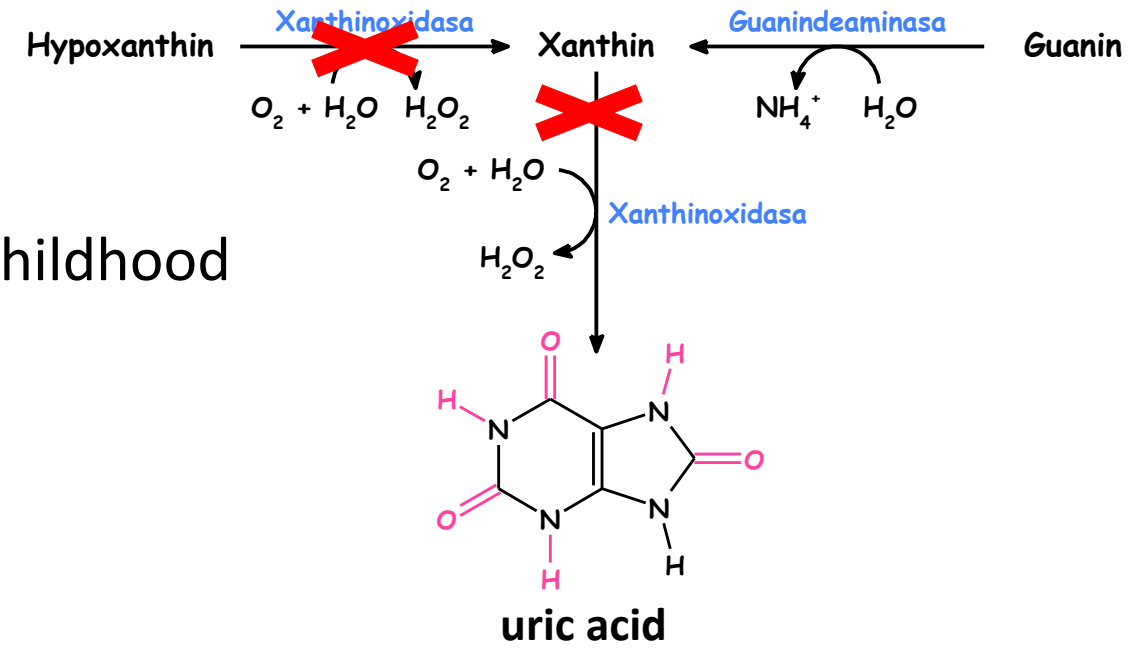
Adenosine deaminase deficiency

- ↑ adenosine and deoxyadenosine → UA stones
- ↑ plasma adenine
- elevated adenosine levels, as occurring in ADA deficiency contribute to apoptosis and block in the differentiation of thymocytes, causing severe T lymphopenia in humans
- ↑ deoxyadenosine and dATP in lymphocytes, inhibition ribonucleotide reductase essential for synthesis of DNA
- lymphopenia and attrition of immune function over time are the two findings common to all presentations of ADA deficiency
- rapidly fatal course due to infections with fungal, viral, and opportunistic agents are characteristic of early onset forms of ADA def → w/m
- variable progressive neurological symptoms (movement, spasticity)

- treatment: bone marrow transplantation, enzyme replacement therapy with bovine ADA, or hematopoietic stem cell gene therapy

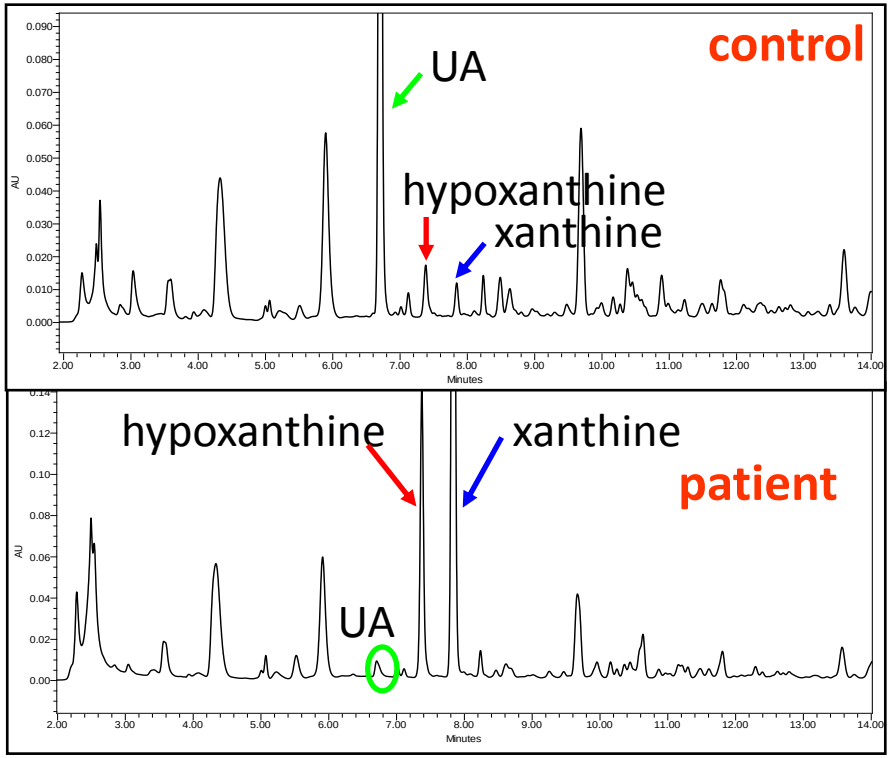
Xanthine oxidase/dehydrogenase deficiency

- XDH/XO catalyzes the two terminal steps of the purine degradation pathway - the oxidation of hypoxanthine to xanthine or xanthine to UA
- AR
- type I and II are collectively coined as classical xanthinuria
- type I (OMIM 278300) is caused by XO/XDH deficiency
- type II (OMIM 603592) results from a combined def of XO/XDH and aldehyde oxidase and/or molybden cofactor sulfurase (MOCOS)
- a third type, clinically distinct, molybdenum cofactor def. (252150) is characterized by the lack of sulfite oxidase activity as well as XO/XDH and AOX → neonatal neurological abnormalities : epilepsy, encephalopathy, hypertonia → death in early childhood



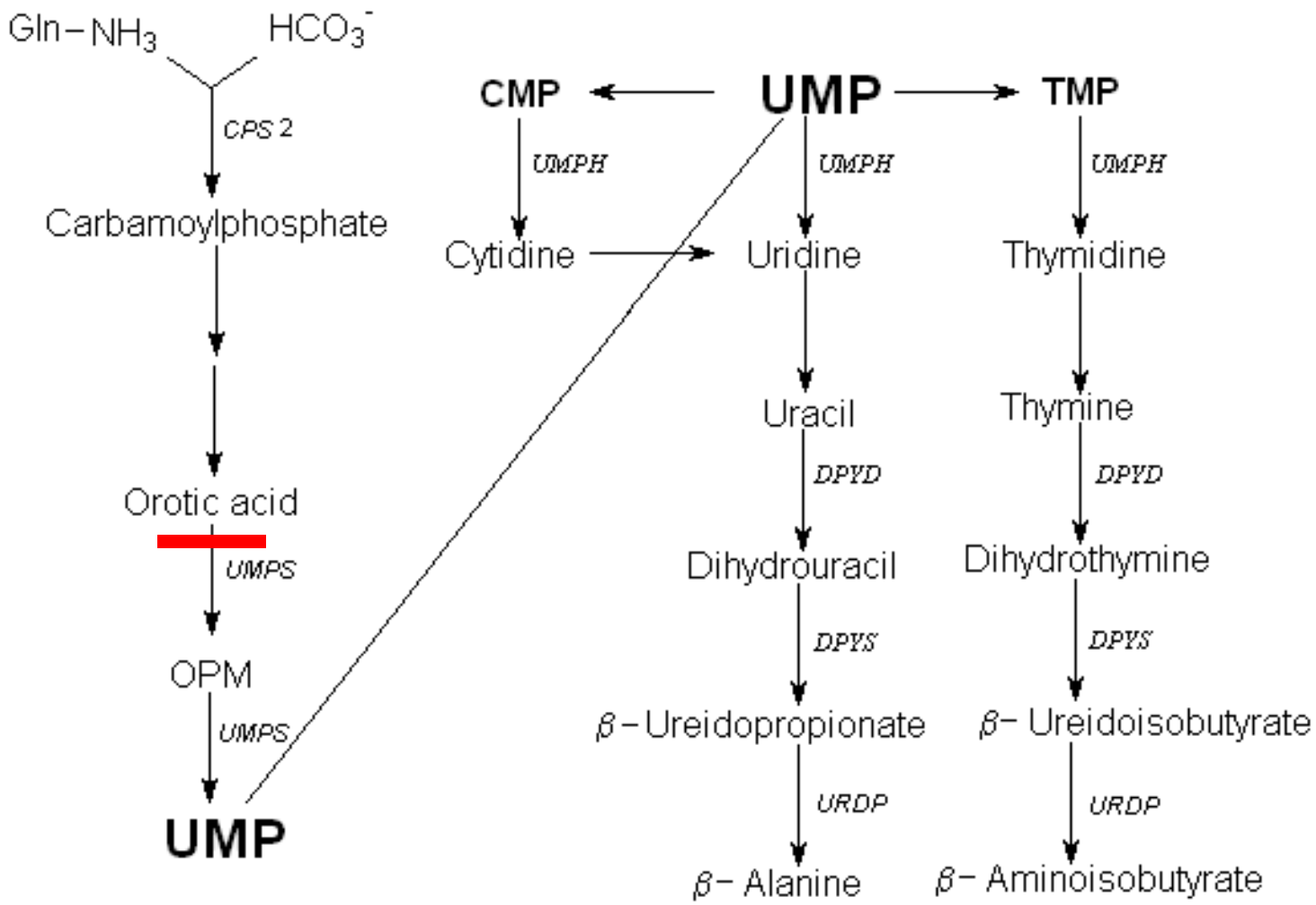
- about 150 patients with classical xanthinuria have been described
- ↓ s-UA and ↑excretion of u-xanthine and hypoxanthine
- confirmation and/or identification of the type: allopurinol loading test, molecular analysis and the xanthine oxidase assay in plasma
- large clinical variability
- only about half of all patients have urolithiasis
- calculi in the urinary tract, ARF, arthropathy and myopathy due to deposits of xanthine crystalls
- treatment: fluid intake

http://www.tamilspider.com/attachments/Resources/3322-71129-xanthine.jpg



HPLC chromatograms of urine samples

Inherited metabolic disorders of pyrimidine metabolism

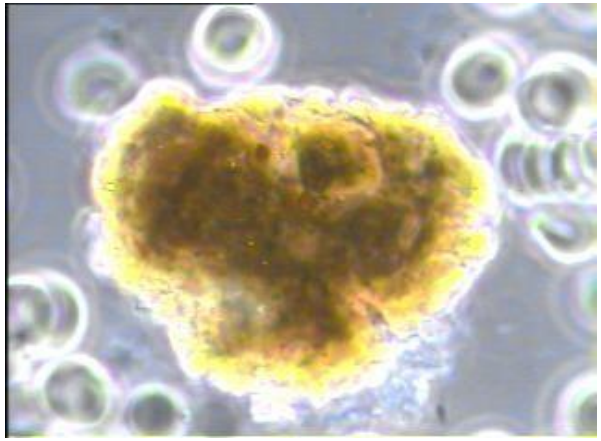


Orotic aciduria

- deficiency in the gene for uridine monophosphate synthase
- a bifunctional enzyme with orotate phosphoribosyltransferase and orotidylic decarboxylase which catalyze the last 2 steps in uridine monophosphate biosynthesis

- AR, OMIM 613891

- appears in the first year of life: growth failure, developmental retardation, megaloblastic anemia
- large amounts of orotic acid in the urine → crystaluria
- lack of CTP, TMP and UTP → decreased pyrimidine synthesis → decreased erythrocyte formation



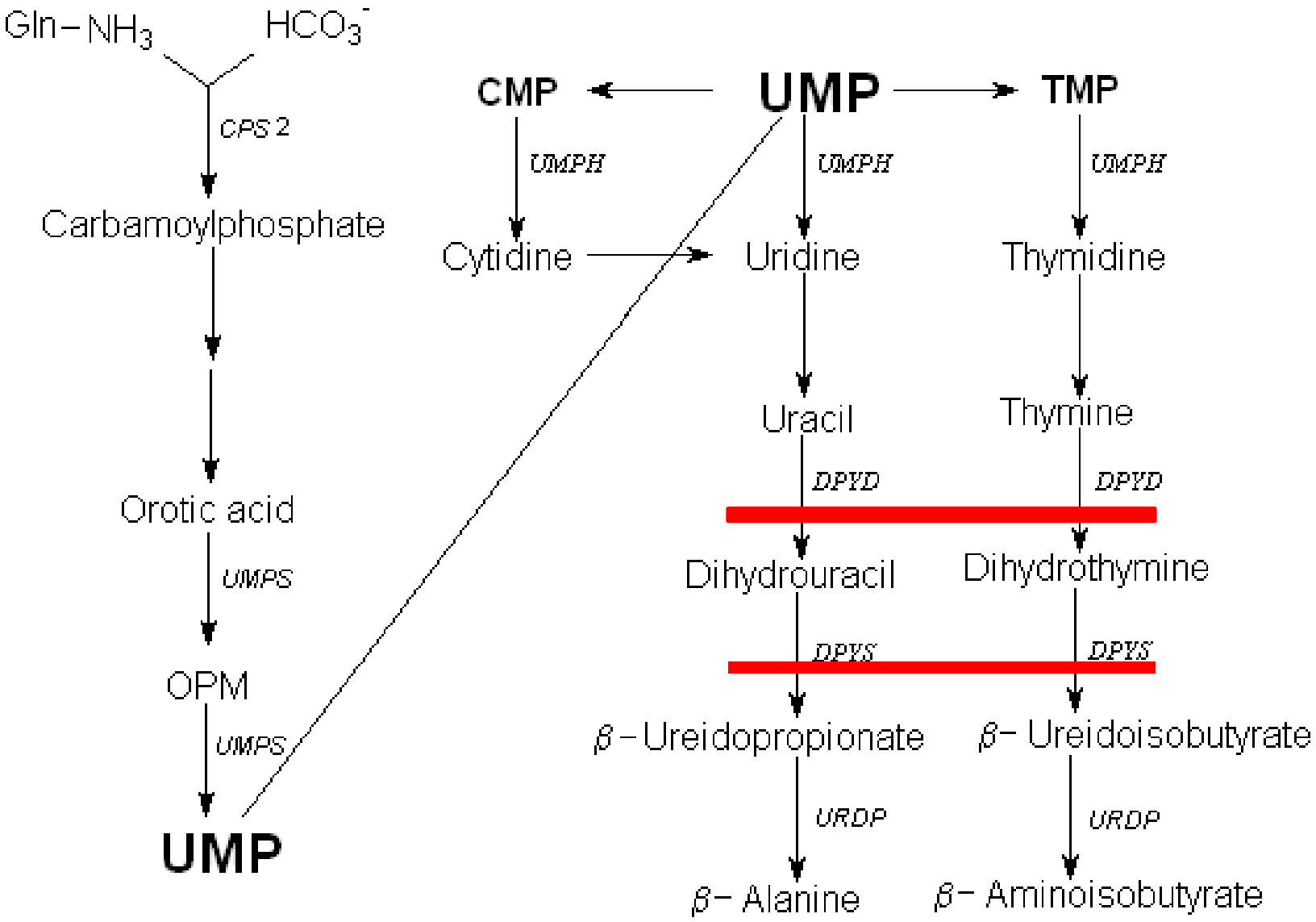
http://www.prohealthdynamics.com/images/orotic_and_sulphuric_acid_ojrx.jpg

- the phenotypic features of orotic aciduria is megaloblastic anemia that is **unresponsive** to vitamin B12 and folic acid

- frequently associated with some degree of PMR

- respond to appropriate pyrimidine replacement therapy, and most cases appear to have a good prognosis → treatment: uridine (kinase converts to UMP)

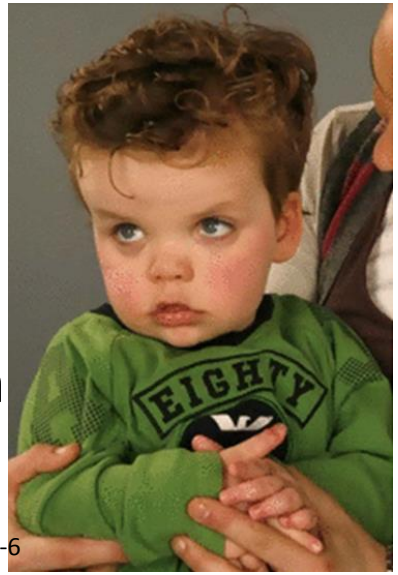
- a minority of cases have additional features, particularly congenital malformations and immune deficiencies, which may adversely affect this prognosis



- defect in degradation pathway of pyrimidines: **dihydropirimidine dehydrogenase deficiency**, dihydropyriminidase deficiency, thymidine phosphorylase deficiency

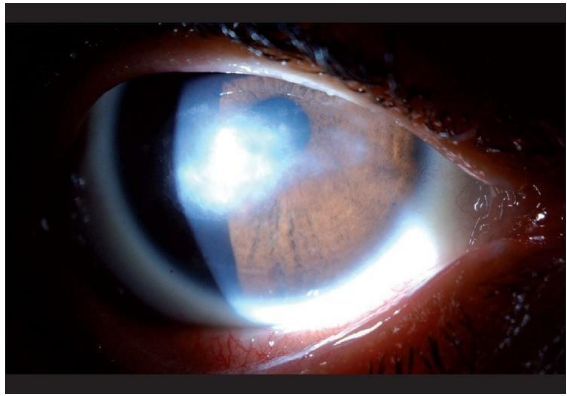
Dihydropyrimidine dehydrogenase deficiency

- the rate-limiting step in the degradation of the pyrimidine bases thymine and uracil → NADPH-dependent reaction converts the bases of thymine and uracil into dihydrothymine and dihydrouracil, respectively
- AR, OMIM 274270
- excessive accumulation of thymine and uracil in urine, blood, and cerebrospinal fluid but ↓ levels of metabolites downstream of DPD
- wide clinical spectrum, ranging from asymptomatic to severe neurological manifestations, including intellectual disability, seizures, microcephaly, autistic behavior, and eye abnormalities
- partial/complete def.: childhoot onset, recurrent seizures, intell. disability, microcephaly, dysmorphy
- macrocephaly, prominent forehead, low nasal bridge, ante-verted nares, open mouth appearan
- no effective therapy



http://link.springer.com/article/10.1007%2Fs00439-009-0653-6

neurotrophic keratitits



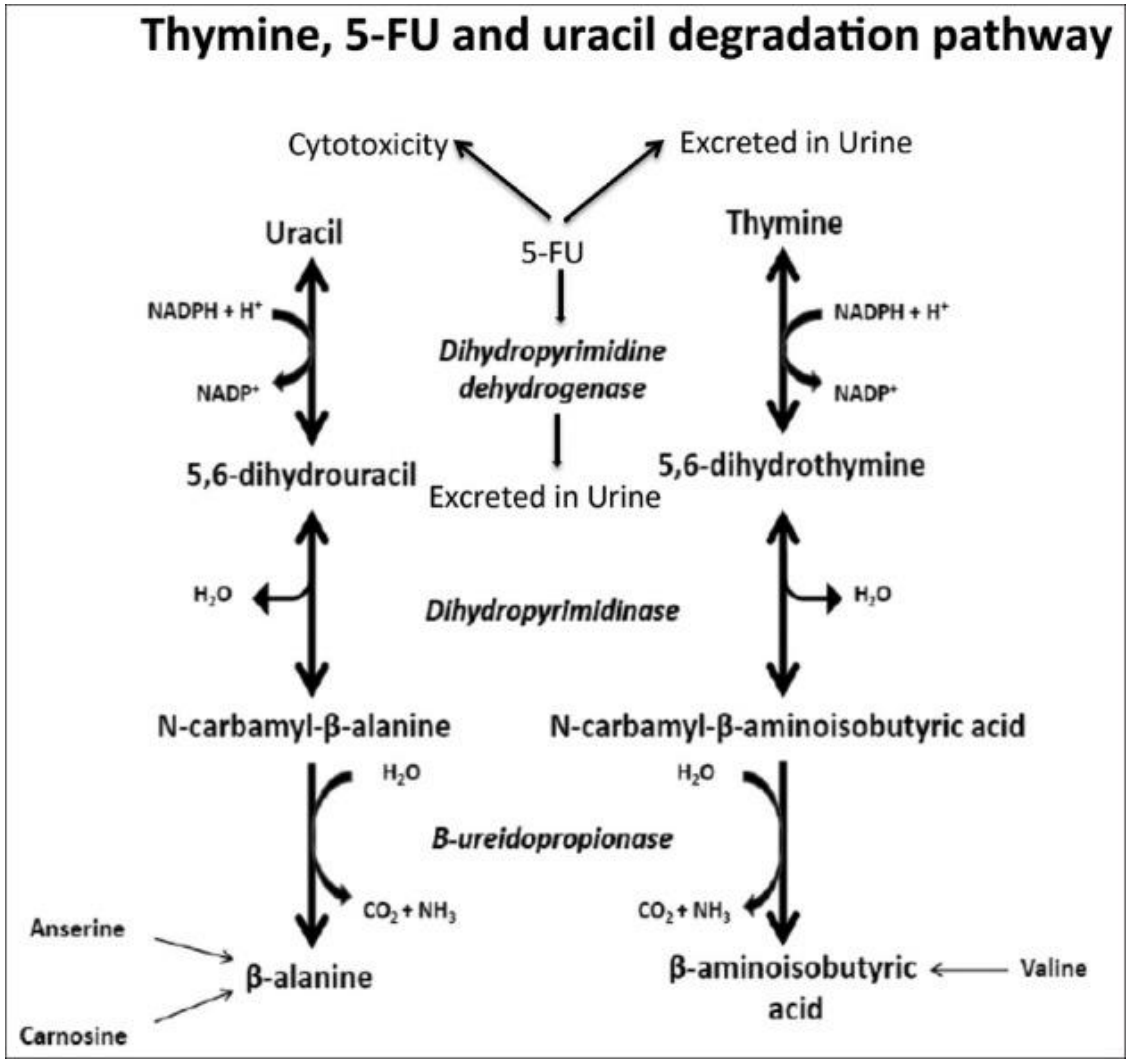
http://www.ijo.in/articles/2008/56/4/images/IndianJOphthalmol_2008_56_4_336_41422_1.jpg

- fluoropyrimidines: in oncology for treating solid tumors

- DPD plays an important role in the catabolism of >80% of the administered dose of 5-fluorouracil

- patients with a partial or complete enzyme deficiency can suffer from severe and potentially lethal toxicity following 5-FU administration

- neutropenia, stomatitis, neurological symptoms



http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897149/

Mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE)

- multisystem disorder, AR, OMIM 603041

- start in 1st to 5th decade (60% pacients before 20 y)

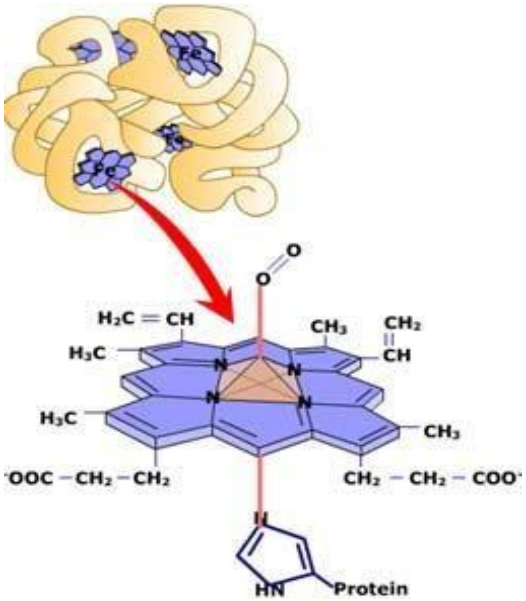
- progressive degeneration of the muscles of the gastrointestinal tract causing gastrointestinal dysmotility, weakness of extra-ocular muscles (ophthalmoparesis), degeneration of peripheral nerves causing altered sensation and weakness the distal arms and legs, and cachexia

- the specific symptoms associated with MNGIE variable: vomiting, nausea, diarrhea, reflux, abdominal pain …

- progressive GIT dysmotility

- ↑ plasma and urine thymidine and deoxyuridine concentration
- lactic acidemia, lactic acidosis
- thymidine phosphorylase enzyme activity in leukocytes is less than 10% of the control mean
- molecular genetic testing of the thymidine phosphorylase gene, detects pathogenic variants in approximately 100% of affected individuals
- no genetype/phenotype correlations
- treatment is supportive
- alel patients have peripheral neuropathy → the neuropathy is demyelinating
- the segmental demyelination is hypothesized to be caused by the uneven distribution of mtDNA abnormalities along the nerve

Porphyrias

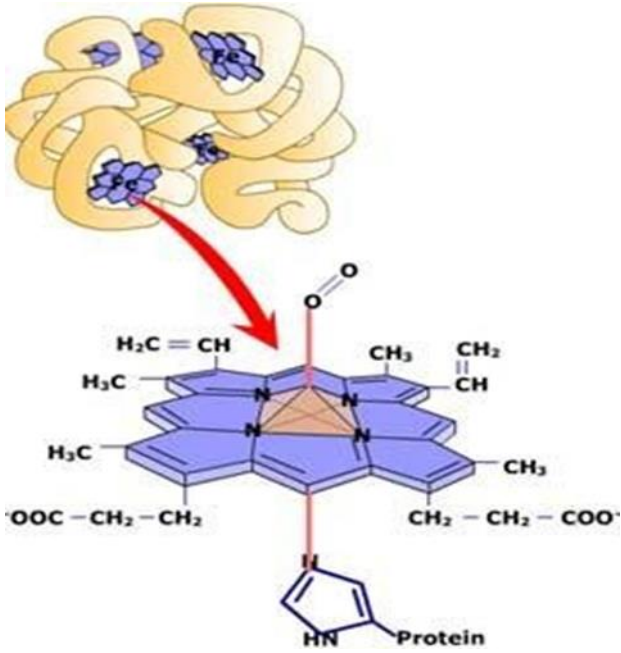


http://www.home-air-purifier-expert.com/images/heme.jpg
http://devoid.blogs.heraldtribune.com/files/2009/10/werewolf.jpg
http://th01.deviantart.com/fs21/300W/f/2007/258/a/5/Vampire_Caitlin_Deadly_Beauty_by_VampHunter777.jpg

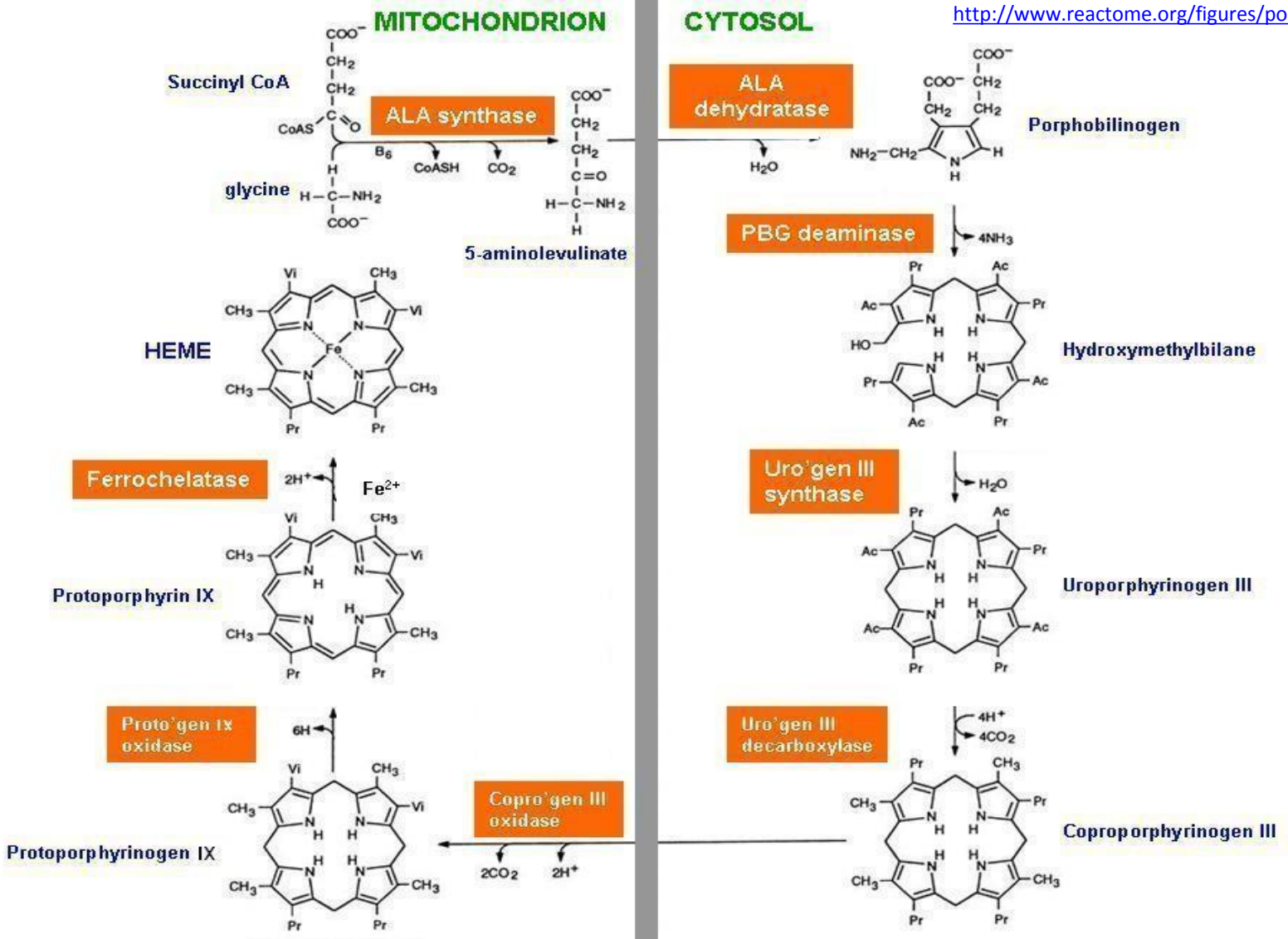
- **porphyrins:** any of a class of water-soluble, nitrogenous biological pigments (biochromes), derivatives of which include the hemoproteins (porphyrins combined with metals and protein)
- all porphyrin compounds absorb light intensely at or close to 410 nanometres (Soret maximum)

- **heme** (metaloporfyrin) is the prosthetic group of hemoglobin, myoglobin, and the cytochromes: Fe2+ contained in the centre of a four pyrrolic groups joined together by methine bridges
- the iron atom and the attached protein chain modify the wavelength of the absorption and gives hemoglobin its characteristic colour

- hemes are most commonly recognized as components of **hemoglobin**, but are also found in a number of other biologically important **hemoproteins**: myoglobin, cytochrome (Fe2+ ↔Fe3+), catalase…



http://www.home-air-purifier-expert.com/images/heme.jpg



- heme is produced in the bone marrow and liver through a complex process regulated by eight different enzymes
- **porphyrias**: a group of at least eight disorders that differ considerably from each other

Porphyrias

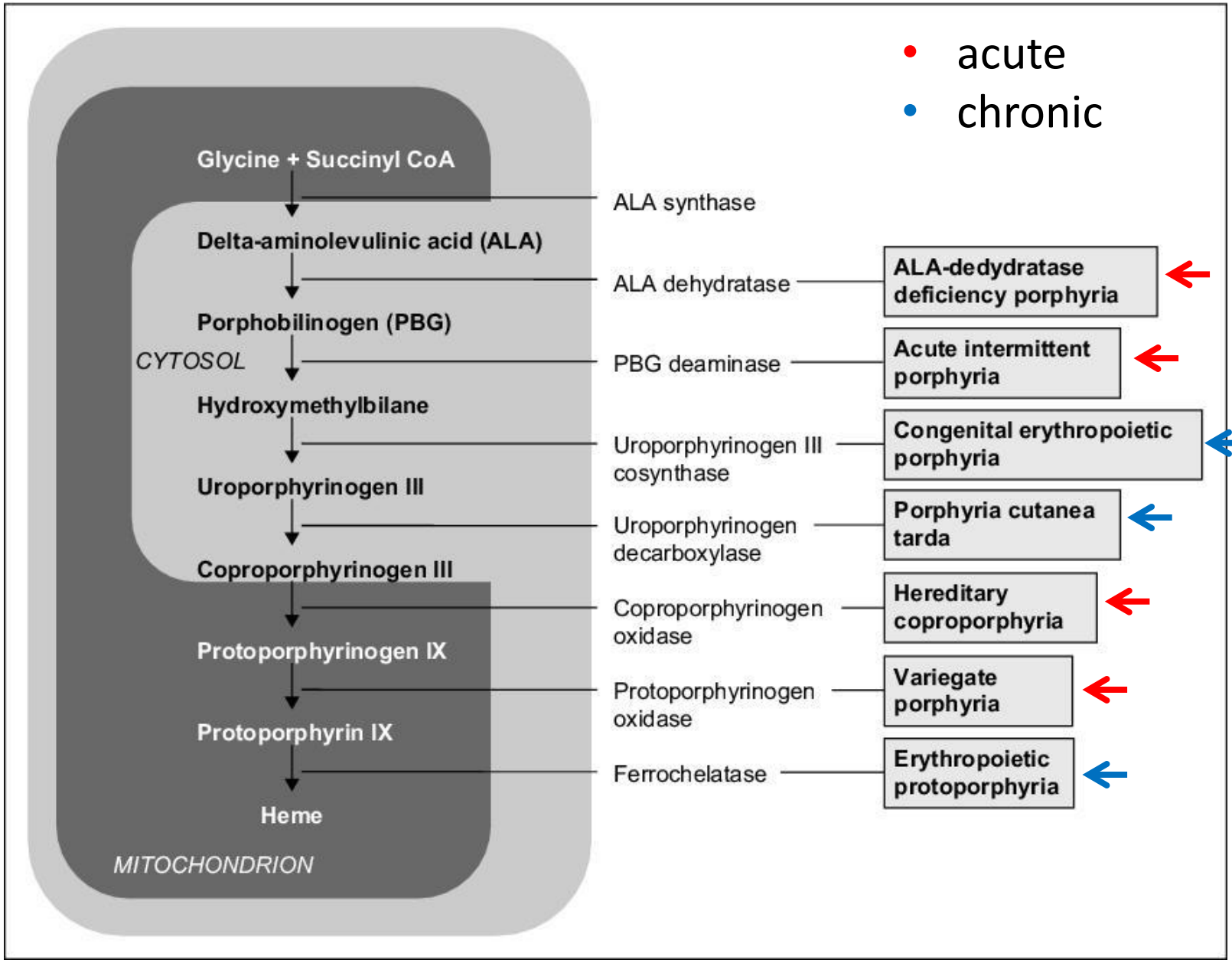
- genetic diseases resulting in decreased activity of one of the enzymes involved in heme synthesis
- *Porphyrus*
- symptoms vary depending on the enzyme, the severity of the deficiency and whether heme synthesis is affected primarily in liver or in developing erythrocytes
- a common feature in all porphyrias is the **accumulation** of porphyrins or porphyrin precursors

- often AD inheritance, some AR inheritance
- usually onset in adulthood
- common manifestation only after exposure (fasting, menses, drugs, sunlight)

- porphyrias can be classified according to their classification-symptoms:
    - skin (PCT, EPP, CEP, také VP a HCP)
    - hepatic (AIP, ADP, VP, HCP)

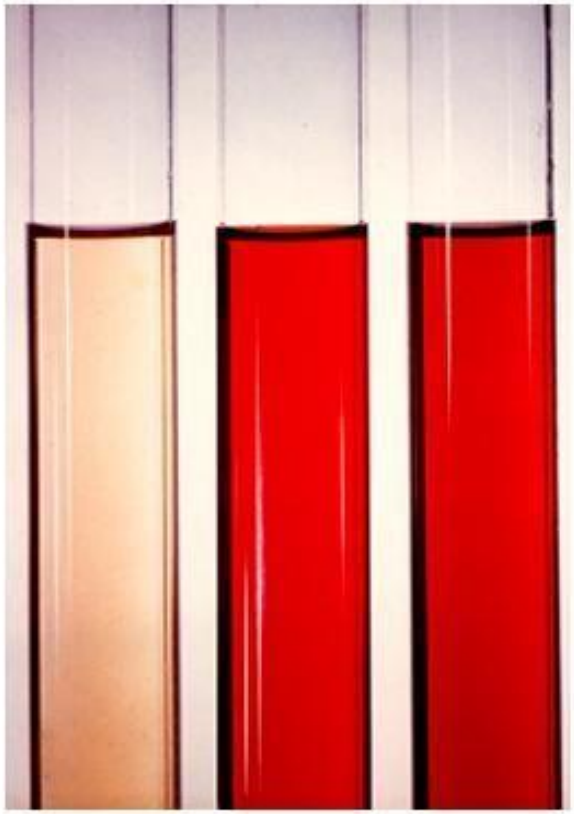
- classified according to their clinical types:
    - acute (AIP, PV, HCP, ADP)
    - chronic (PCT, EPP, CEP)

- another classification uses the site where most of the haem precursors arise from and accumulate in:
    - erytropoetic (AIP, PCT, HCP, VP, ADP
    - hepatic (CEP)
    - erytrohepatic (EPP)

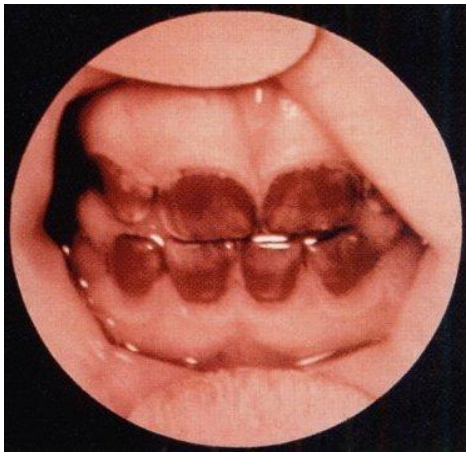


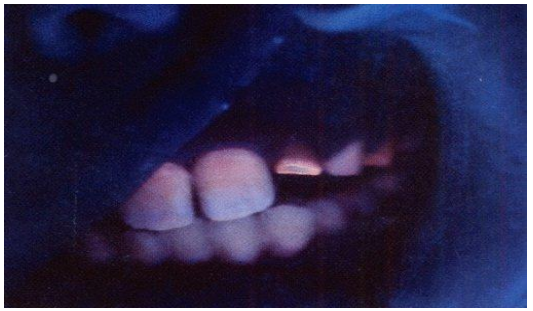
http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

How to detect porphyria by eye?



http://terrycomeau.com/Porphyria/Porphyria.htm

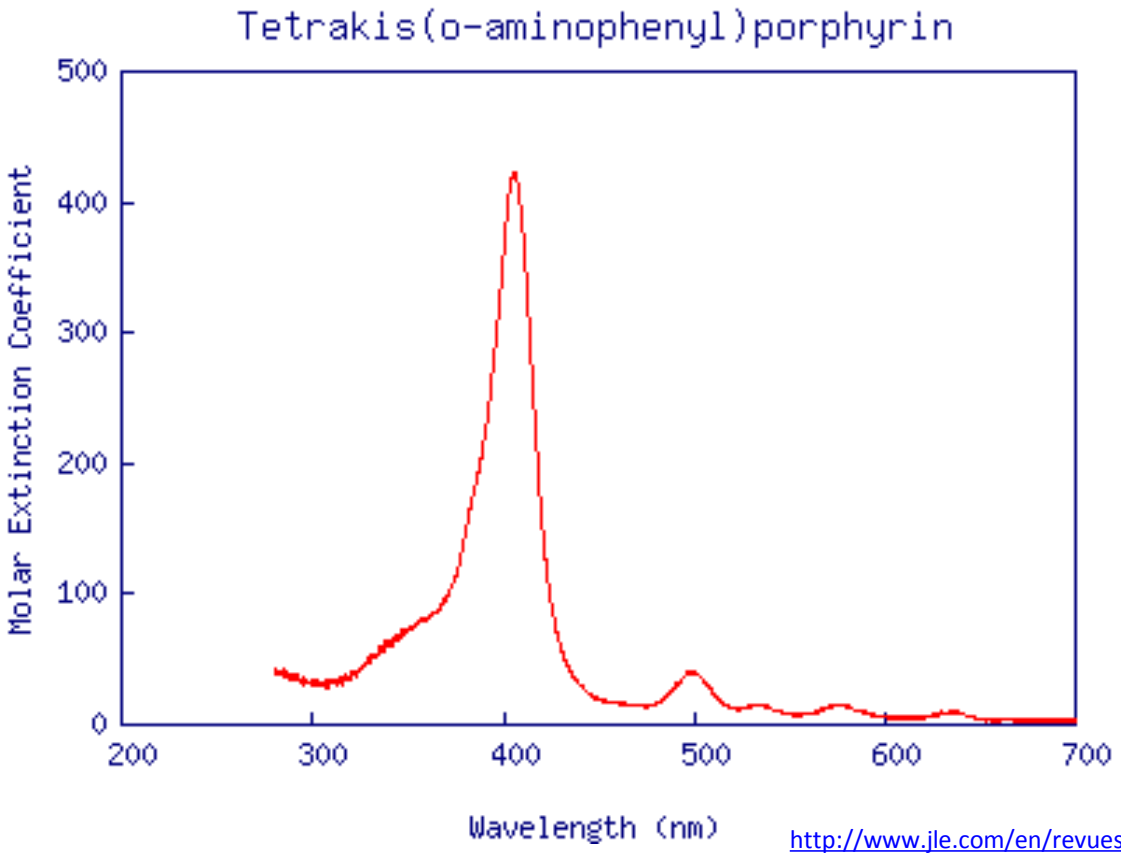


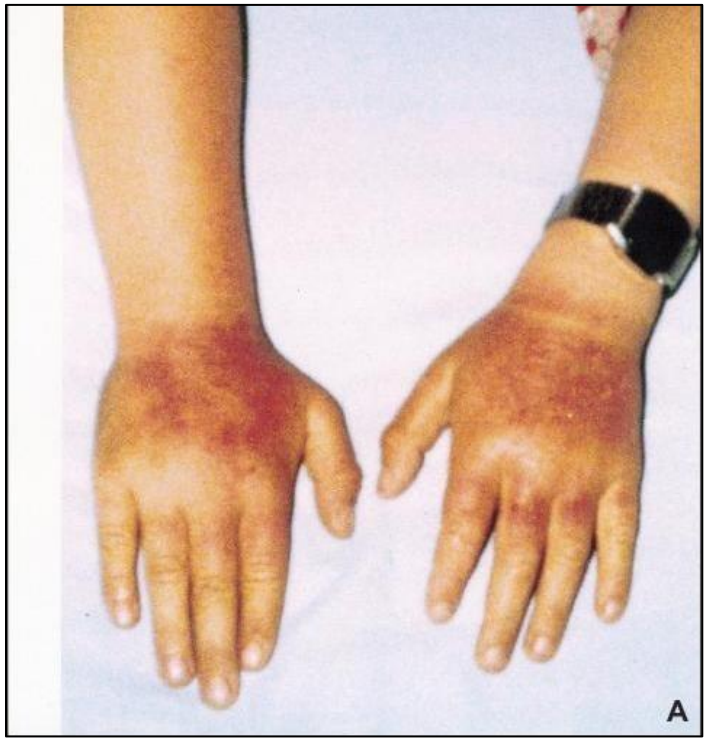


http://www.pathguy.com/lectures/erythrodontia.jpg

- many of the porphyrias of both types, the urine may take on a red or reddish brown discoloration, sometimes the discoloration appears only after the urine has stood in light for about 30 minutes
- reddish-brown color of the teeth (erythrodontia)

Absorption spectrum of porphyrins





http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

- excitation of excess porphyrins in the skin by long-wave ultraviolet light leads to generation of singlet oxygen and cell demage → development of inflammation (rush at start)

Neurological symptoms in porphyrias

- peripheral NS
  - increased activity of sympathicus: tachycardia, hypertension
  - abdominal pain-nonlocalised but also colic
  - parestesias
  - peripheral neuropathy- muscle weaknes

- central NS
  - aggitation
  - psychotic episodes

- mechanisms: synaptic function interference (GABA vs. ALA similarity), heme depletion (NOS, Trp pyrrolase)

Porphyrias producing acute neuropsychiatric features

- frequency and severity of attacks vary widely between people

- between attacks the patient is usually healthy

- acute attacks are precipitated by metabolic, hormonal and environmental factors that induce hepatic delta-aminolaevulinic acid synthase (ALA synthase) activity

- this increased activity causes the haem precursors delta-amino-laevulinic acid and porphobilinogen to increase→ **pathological accumulation**

- rarely an acute attack may be life-threatening **!!!**

Drugs that are considered to be **SAFE** for use in the acute porphyrias

This safe list was produced jointly by staff at Welsh Medicines Information Centre (WMIC) and Cardiff Porphyria Service and is supported by the National Acute Porphyria Service (NAPS). This safe list provides guidance on first choice medication and is not intended to be comprehensive.

N.B. Some drugs may be included under their group name and not their individual drug name.

Abciximab	Cycloserine	Lacosamide	Phenylephrine
ACE Inhibitors	Dabigatran	Lamotrigine	Phosphate salts
Acetazolamide	Desferrioxamine	Laxatives	Pramipexole
Acetylcysteine	Desflurane	Leflunomide	Pregabalin
Aciclovir	Desloratadine	Lercanidipine	Prilocaine
Adenosine	Dextromethorphan	Levetiracetam	Primaquine
Adrenaline	Diamorphine	Levomepromazine	Prochlorperazine
Alfentanil	Diazepam	Levothyroxine sodium	Proguanil
Alginate	Dicycloverine	Lidocaine[2]	Promethazine
Allopurinol	Digoxin	Linezolid	Propofol[3]
Almotriptan	Dihydrocodeine	Lithium	Propylthiouracil
Aluminium salts	Dinoprostone	Loperamide	Pseudoephedrine
Amiloride	Diphenhydramine	Loratadine	Pyrazinamide
Aminoglycosides	Dipyridamole	Lorazepam	Pyridostigmine
Amisulpride	Dobutamine	Magnesium salts	Quinine
Amitriptyline	Domperidone	Mebeverine	Quinolones[5]
Amlodipine	Dopamine	Mefloquine	Ranitidine
Amphotericin	Doxazosin	Melatonin	Remifentanil
Angiotensin II inhibitors	Doxycycline	Meloxicam	Retigabine
Antimuscarinic bronchodilators	Duloxetine	Memantine	Rivaroxaban
Articaine	Epinephrine	Mepivacaine	Rivastigmine
Aspirin	Eplerenone	Mesalazine	Selective beta$_2$ agonists
Atomoxetine	Epoetin & analogues	Metformin	Sevelamer
Atovaquone	Etanercept	Methadone	Sildenafil
Atropine	Ethambutol	Methotrexate	Sodium bicarbonate
Azathioprine	Etoricoxib	Methylphenidate	Sodium fusidate
Azithromycin	Ezetimibe	Metoclopramide	Solifenacin
Aztreonam	Famciclovir	Metronidazole	SSRIs
Baclofen	Felodipine	Midazolam[3]	Statins
Balsalazide	Fentanyl	Mirabegron	Strontium
Barium sulphate	Fexofenadine	Mirtazapine	Sulpiride
Bendroflumethiazide	Fibrates[1]	Mizolastine	Suxamethonium

Acute hepatic porphyria

- the occurrence of neuro-visceral attacks with or without cutaneous manifestations

- all acute hepatic porphyrias can be accompanied by neuro-visceral attacks that appear as intense abdominal pain (in 85-95% of cases) over one to two weeks, neurological symptoms (muscular weakness, sensory loss or convulsions) and psychological symptoms (irritability, anxiety, auditory or visual hallucinations, mental confusion)

- acute intermittent porphyria (the most common)
- variagate porphyria
- hereditary coproporphyria
- hereditary deficit of delta-aminolevulinic acid dehydratase (ext. rare)

Hepatic – acute - induced porphyrias

- AIP, porhyria variegata, hereditary koproporphyria AD
- Doose porphyria AR

- in addition to genetic risks, environmental factors may trigger the development of signs and symptoms
- 80% of individuals who carry a gene mutation remain asymptomatic, and others may have only one or a few acute attacks throughout life
- in most of these cases the levels of delta-aminolevulinic acid (ALA), porphobilinogen, and porphyrins are normal
- severe neuropathic abdominal pain, the most frequent symptom, is diffuse and is often accompanied by nausea, vomiting, distention, constipation, and sometimes diarrhea
- insomnia (often an early symptom), heart palpitations, seizures, restlessness, hallucinations, and other acute psychiatric symptoms

Chronic porphyrias

- manifest in adulthood (porphyria cutanea tarda) or in childhood (hepatoerythropoietic porphyria)

- cutaneous lesions (fragility, bullae, scars) on the surface of skin exposed to the sun (hands, face) and, unlike in cases of acute hepatic porphyrias (see this term), don't present with acute neuro-visceral attacks

- the acquired forms of the diseases may be triggered by risk factors (alcohol, hepatitis C, estrogen, iron overload)

Acute intermittent porphyria (AIP)

- AD, deficiency of porphobilinogen deaminase (PBG-D; the third enzyme in the heme biosynthesis pathway) → accumulation of the precursors of porphyrins in the liver (delta-aminolevulinic acid, ALA and porphobilinogen, PBG)
- the **most frequent** and the **most severe** form of the acute hepatic porf.

- manifests after puberty (20 – 40y) and preferentially affects women **2:1**
- neuro-visceral attacks without cutaneous manifestations, attacks can persist for several days and that repeat over several weeks, manifest as intense abdominal pain (>95% of cases) and neurological and/or psychological symptoms
- **psychological symptoms** variable: irritability, emotionality, depression, considerable anxiety and, more rarely, auditory and visual hallucinations, disorientation, mental confusion
- **neurological manifestations:** the central nervous system as much as the peripheral nervous system (myalgia, paresis,…)

• **diagnosis**: the observation of urine that is pink orred after exposure to light evokes the diagnosis of the disease

• the evidence of elevated concentrations of delta-aminolevulinic acid, and porphobilinogen in the urine and residual PBG-D activity in 50% of red blood cells (not always found during attacks)

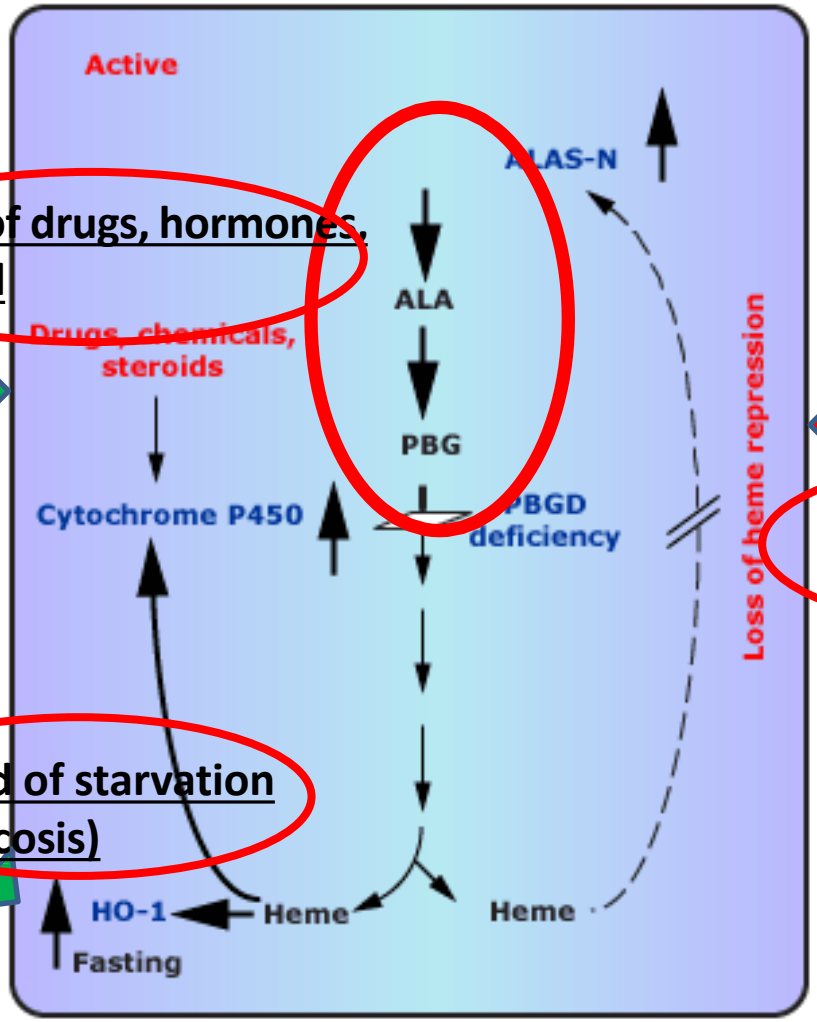
• confirmed by the identification of a causal mutation of the *HMBS* gene

• treatment: human hemin and/or perfusion of carbohydrates

• management includes the suppression of triggering factors, relief from pain (opiates), vomiting and anxiety, and the prevention of attacks (by avoiding triggering factors, particularly drugs)

Treatment of AIP

Increased need of heme synthesis



avoid of drugs, hormones, alcohol

increased turnover of xenobiotics

increased degradation of heme HO-1

avoid of starvation (glucosis)

heme heminarginate

lack of feedback decrease in heme synthesis

http://terrycomeau.com/Porphyria/Porphyria.htm

Hereditary coproporphyria (HCP)

- AD, coproporphyrinogen oxidase (CPOX)

- clinical presentation similar to AIP, except that some patients (about 20%) develop blistering photosensitivity resulting in cutaneous lesions that resemble those in PCT, neuro-psychiatric symptoms

- attacks are generally milder than those seen in patients with AIP

- urinary delta-aminolevulinic acid and porphobilinogen ↑, especially during acute attacks, but generally to a lesser degree than in AIP

- the diagnostic finding: significant ↑ urine PBG and coproporphyrin, plasma porphyrin levels are usually normal but may be increased in patients with skin lesions

- treatment, complications, and preventive measures for HCP are the same as for AIP

Porphyria variegata

- AD, a deficiency of protoporphyrinogen oxidase (PPOX)
- both neurologic and/or cutaneous symptoms
- the presenting signs and symptoms during acute attacks are identical to those in AIP though generally milder
- recommendations for treatment and management are the same as AIP
- blistering skin lesions with sun exposure are much more common than in HCP, and are indistinguishable from those of PCT and may be chronic→ there is no remedy for VP photosensitivity other than use of protective clothing and avoidance of prolonged sun exposure
- urine delta-aminolevulinic acid and porphobilinogen are ↑ during attacks, but as in HCP, these may increase to a lesser degree and decrease more rapidly than in AIP
- in contrast to AIP and HCP, plasma porphyrins are frequently increased in VP and display a distinctive fluorescence peak at ~626nm

Doss porhyria

- AR, δ-Aminolevulinic Acid Dehydratase Porphyria (ADP)

- ADP is the least common of all the porphyrias with less than 10 cases

- all of the reported cases have been males, in contrast to the other acute porphyrias which are more prevalent in females

- a severe deficiency of the enzyme δ-aminolevulinic acid dehydratase causes an increase of 5'-aminolevulinic acid in the liver, other tissues, blood plasma, and urine

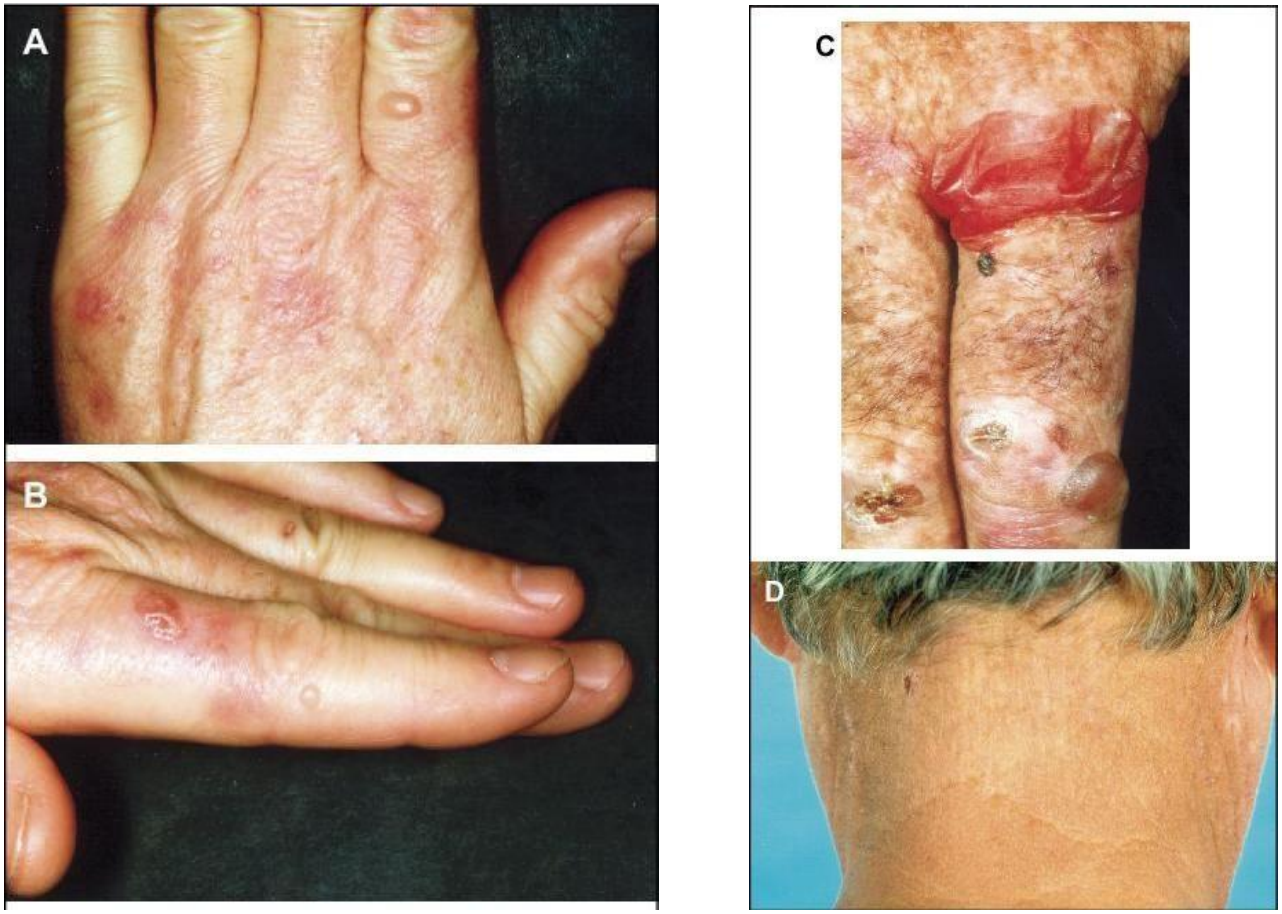
- ↑ urine coproporphyrin and erythrocyte protoporphyrin

- treatment is the same as in the other acute porphyrias

Porphyria cutanea tarda

- the most common type of porphyria
- PCT is due to a deficiency of the uroporphyrinogen decarboxylase
- the development of symptoms requires the enzyme deficiency in the liver to be less than 20% of normal activity
- liver disease is common, 35% cirrhosis, 7-24% liver cancer
- excess porphyrins produced in the liver are transported by the blood to the skin
- several common precipitating factors: excess iron in the liver, moderate or heavy alcohol use, smoking, taking estrogens, and infection with hepatitis C virus
- unlike other porphyrias, most cases of PCT are acquired (referred to as sporadic or Type I PCT), and not inherited → this is secondary to a UROD inhibitor, uroporphomethene, which is generated within the liver
- iron overload of mild to moderate degree is present in all PCT cases and is required for the generation of this UROD

PCT (porphyria cutanea tarda)



http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

- sensitivity to the sun and sometimes artificial light, causing burning pain and sudden painful skin blistering, redness (erythema) and swelling (edema)

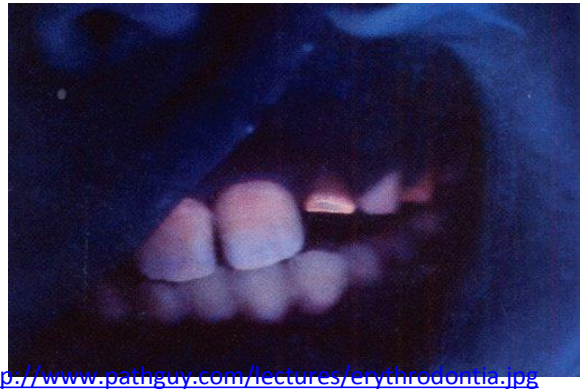
- **diagnosis** is based on the measurement of concentrations of porphyrins in urine, stools and blood - with a predominance of uro-porphyrinogen and heptacarboxylporphyrin
- fluorescence of plasma porphyrins at 619-620 nm

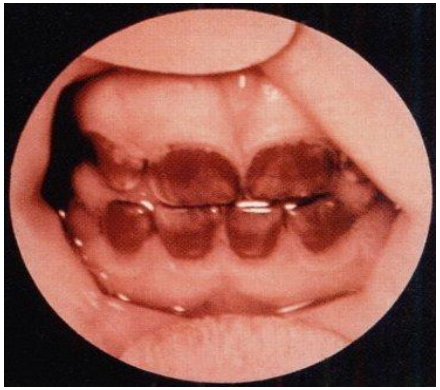
- the evidence of a deficiency of URO-D in red blood cells and the identification of a causal mutation of the URO-D gene allow a confirmed diagnosis

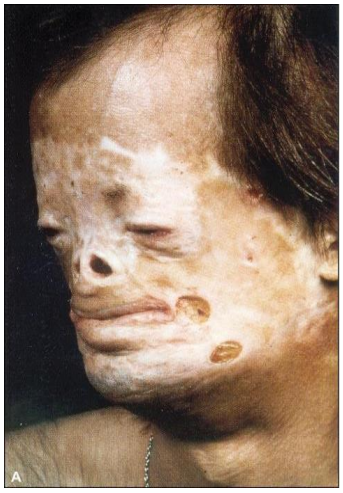
- PCT is the most readily treated porphyria
- **phlebotomy**
- low doses of **chloroquine** or **hydroxychloroquine**
- **avoid sun exposure** as much as possible

Congenital Erythropoietic Porphyria (CEP)

- AR, extremely rare, Günther disease, uroporphyrinogen III synthase
- severe cutaneous photosensitivity at birth or in early infancy with blistering and increased friability of the skin over light-exposed areas, hemolytic anemia
- pink to dark red discoloration of the urine
- the **diagnosis:** markedly ↓d uroporphyrinogen-synthase activity in erythrocytes and/or markedly ↑ urinary uroporphyrin/coproporphyrin
- **bone marrow transplant**
- ß-carotene





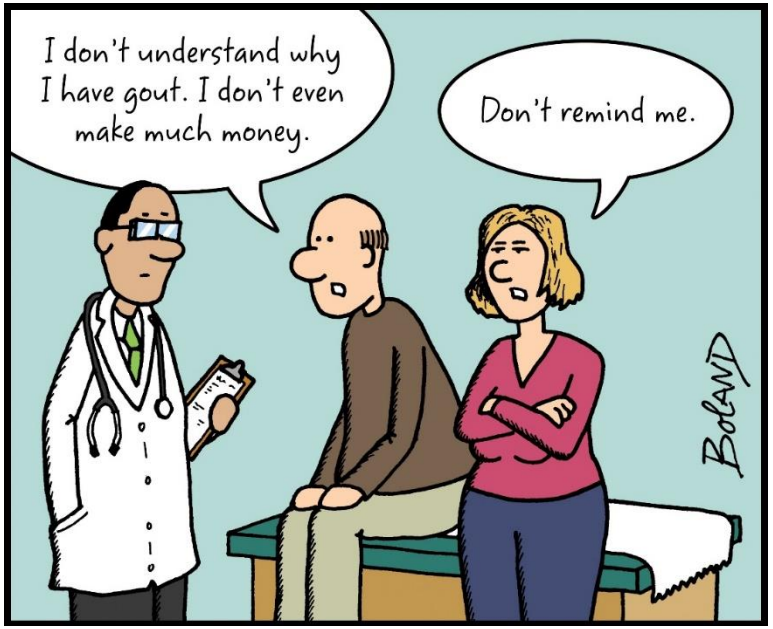


http://www.pathguy.com/lectures/erythrodontia.jpg
http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

Erythropoietic protoporphyria (EPP)

- AD (OMIM*612386), AR (OMIM#177000), defect of ferrochelatase
- X-linked, delta-aminolevulinic acid synthase-2 gene, OMIM #300752

- protoporphyrin accumulates first in the bone marrow, and then in red blood cells, plasma and sometimes the liver
- early onset in childhood
- **diagnosed**: ↑ protoporphyrin IX in erythrocytes and plasma
- photosensitivity and erythrodontia → swelling, burning, itching, and redness of the skin
- hemolysis and liver abnormalities- ca hepatis
- neurological abnormalities rarely
- **therapy**: transfusion, beta-caroten, transplant
- EPP patients should also not use any drug or anesthetic which causes cholestasis



- disorders of uric acid metabolism
- disorders of purines/pyrimidines metabolism
- porphyrias

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