Diagnostic approach to hereditary renal hypouricemia

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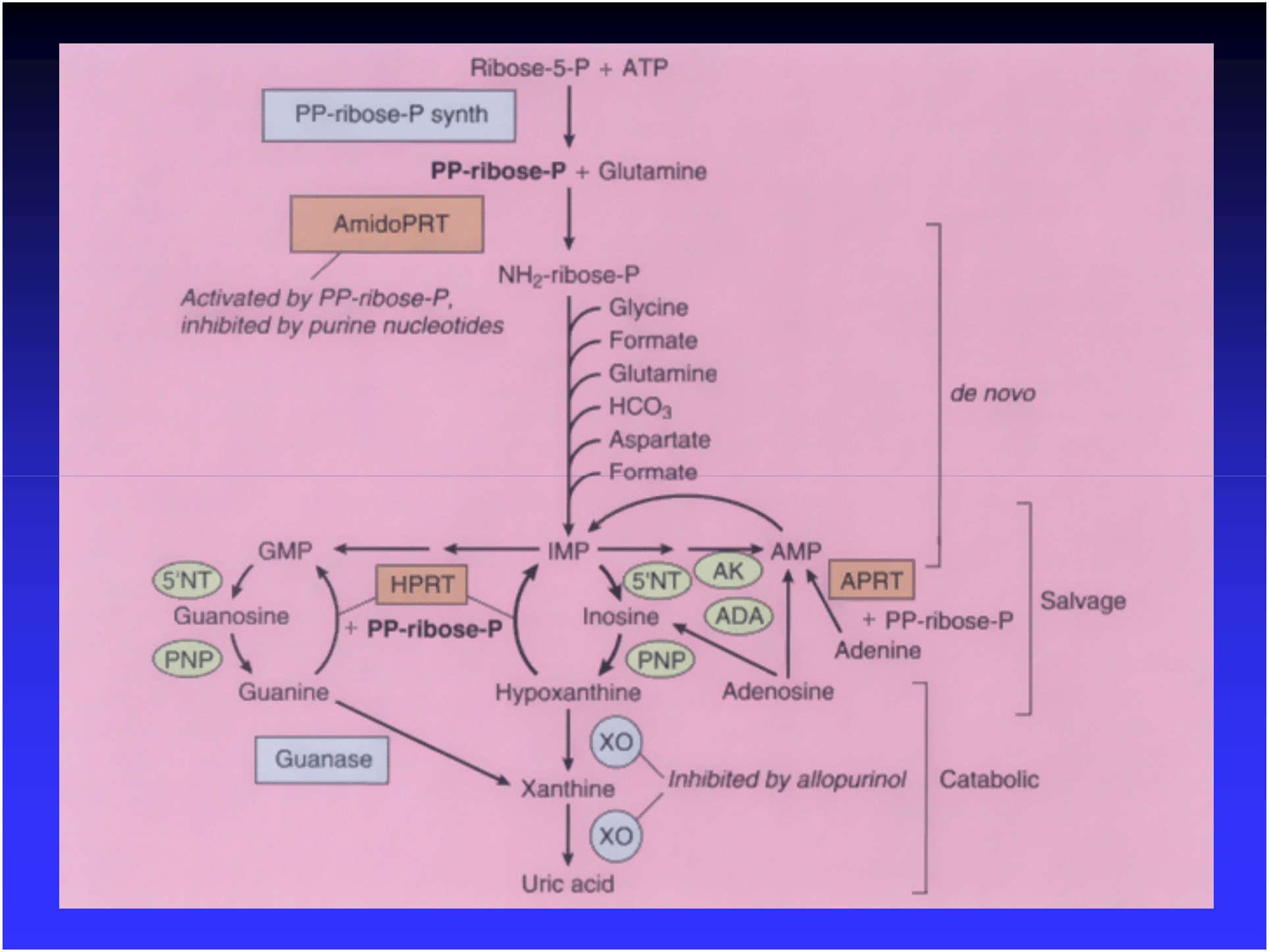

Ribose-5-P + ATP
PP-ribose-P synth
PP-ribose-P + Glutamine
AmidoPRT
Activated by PP-ribose-P, inhibited by purine nucleotides
NH2-ribose-P
Glycine
Formate
Glutamine
HCO3
Aspartate
Formate
de novo
GMP
IMP
AMP
5'NT
HPRT
+ PP-ribose-P
Guanosine
PNP
Guanine
5'NT
AK
ADA
Inosine
PNP
Hypoxanthine
APRT
+ PP-ribose-P
Adenine
Adenosine
Salvage
Guanase
XO
Xanthine
XO
Uric acid
Inhibited by allopurinol
Catabolic

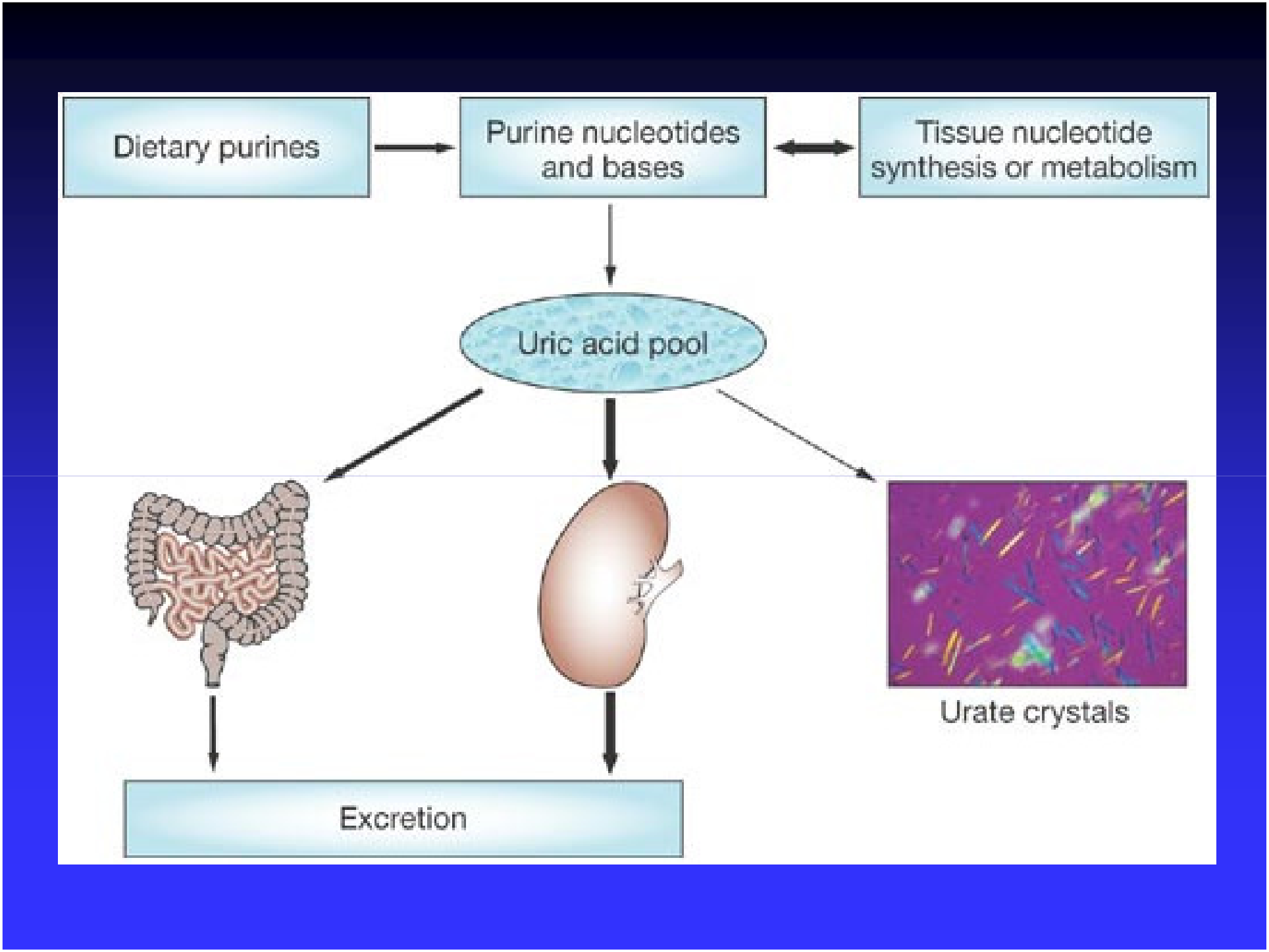
Introduction – hypouricemia

- hereditary renal hypouricemia
  - hereditary xanthinuria

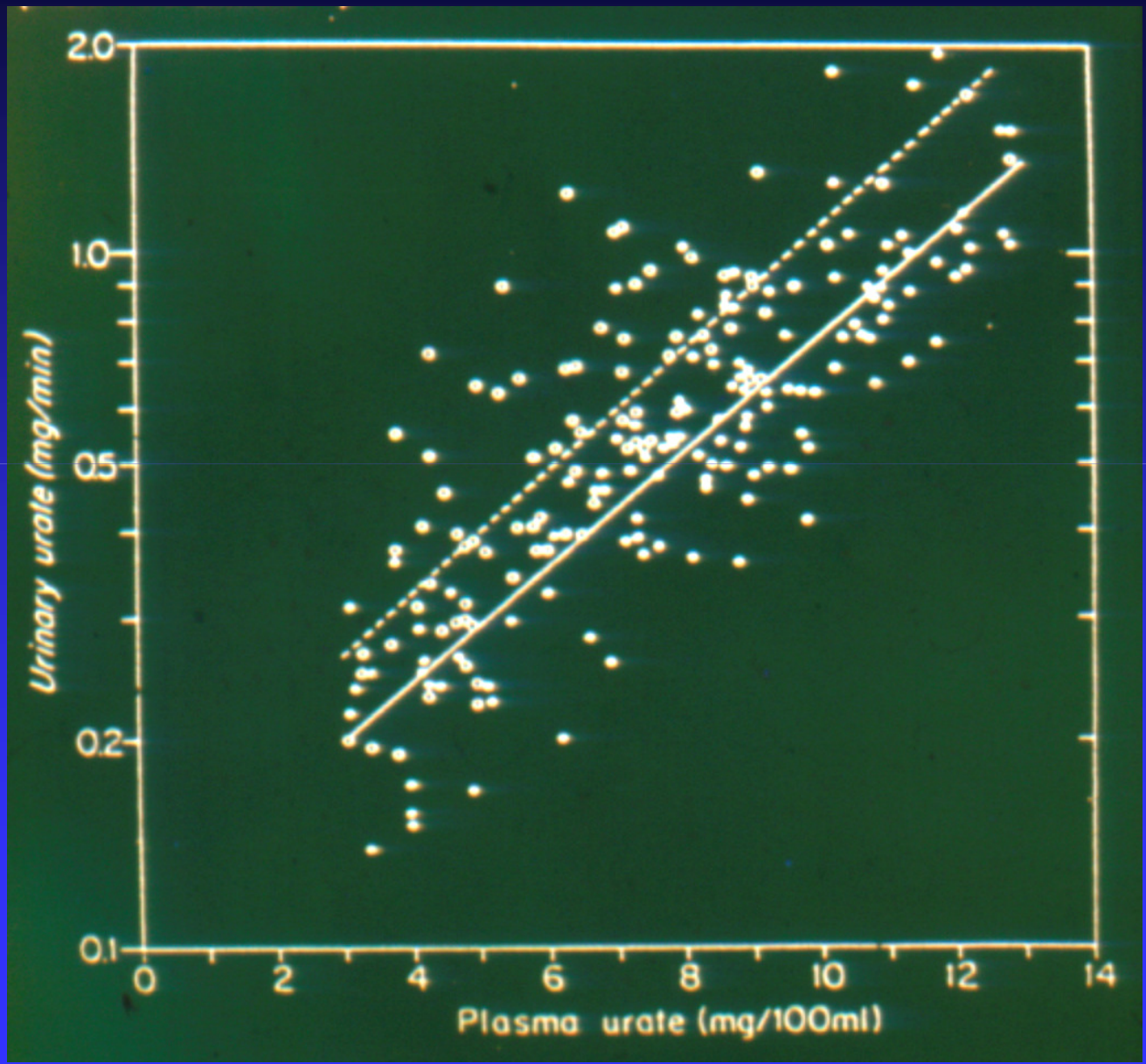
Characteristics of Czech patients

Problems of diagnosis

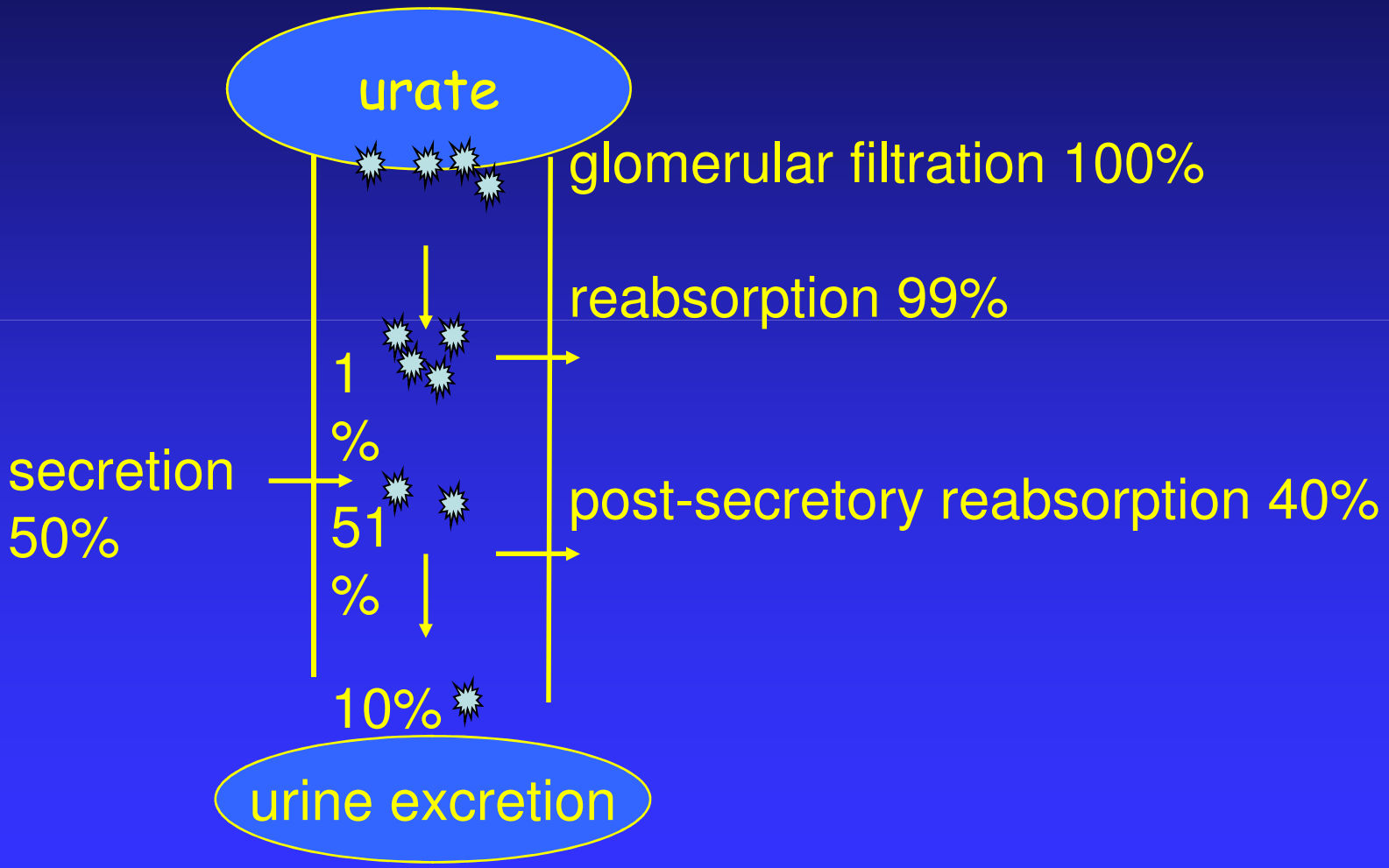
- incidence
- dg. flow charts


Dietary purines
Purine nucleotides and bases
Tissue nucleotide synthesis or metabolism
Uric acid pool
Urate crystals
Excretion

Hypoexcretion of urate



4-component model of urate handling

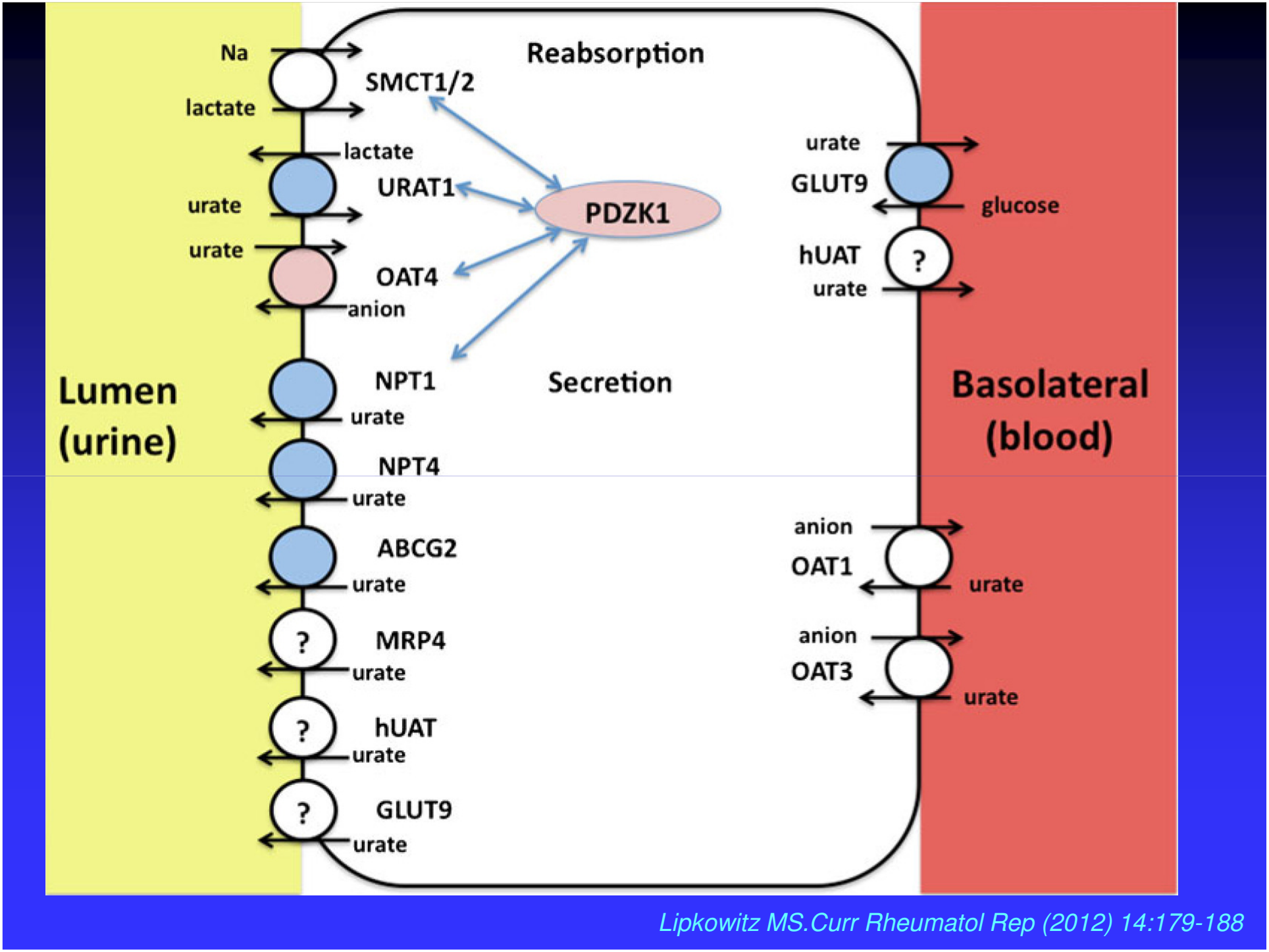


- *Enomoto, A., et al., Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature, 2002. 417(6887): p. 447-52.*

Urate transporter

URAT 1- gene *SLC22A12*

- OMIM 607096, GeneID 116085
- 11q13, 2 transcript variants (3206 and 2940 bp)553 amino acids
- expressed in fetal and adult kidney



Lipkowitz MS.Curr Rheumatol Rep (2012) 14:179-188

Hypouricemia < 119 µmol/l (2 mg/dL)

it is important to distinguish :

primary genetic defect - hereditary xanthinuria

transport defect - primary renal hypouricemia (RHUC1, RHUC2)

secondary increased renal secretion (Fanconi sy.,Wilson´s disease) medication (allopurinol,salicylates)

severe liver disease

thyrotoxicosis, diabetes mellitus, acute respiratory sy.

Hereditary xanthinuria

xanthine oxidoreductase (XO) deficiency type I

XO def. + aldehyde oxidase deficiency type II

molybdenum cofactor def. " " + sulfite oxidase def.

dg.markers: hypouricemia

high urinary concentration of xanthine

symptoms: cca 50% patients - hematuria,renal colic acute renal failure, crystalluria,urolithiasis

th: low purine diet,high fluid intake

(alkalization of urine is of no value)

Hereditary renal hypouricemia

- new transport defect of uric acid

- biochemical markers
  - hypouricemia (S_{KM}<120 µmol/l)
  - increased excretion fraction of uric acid (EF_{KM} >10%)

- clinical features
  - urolithiasis
  - acute renal failure (exercise-induced)

RHUC 1 - URAT1 (*SLC22A12* gene)
RHUC 2 - GLUT 9 (*SLC2A9* gene)

Hereditary renal hypouricemia

mutation - gene SLC22A12
W258X- prevalent mutation

Enomoto, A., et al., Nature, 2002. 417(6887): p. 447-52.
Ichida, K., et al., J Am Soc Nephrol, 2004.15:p.164-73.
Iwai, N., et al., Kidney Int, 2004.66:935-44.
Wakida, N., et al., J Clin Endocrinol Metab, 2005. 90:2169-74.

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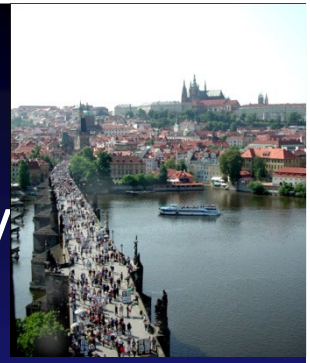


(patients with HPRT def., FJHN, APRT def, ASL def., ADA def.)

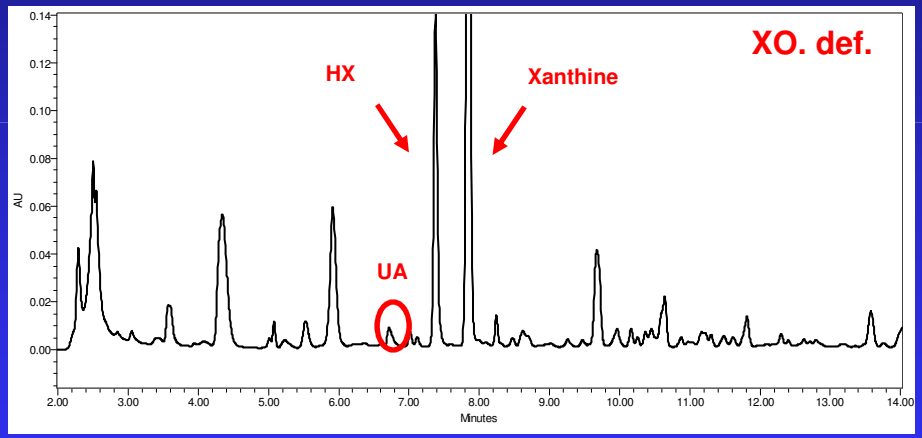
Are disorders with hypouricemia also

in the Czech population ?

Investigation of unexplained hypouricemia

exclusion of secondary causes of hypouricemia !

1.assessment of uric acid - serum , urine



2.urinary purine metabolites

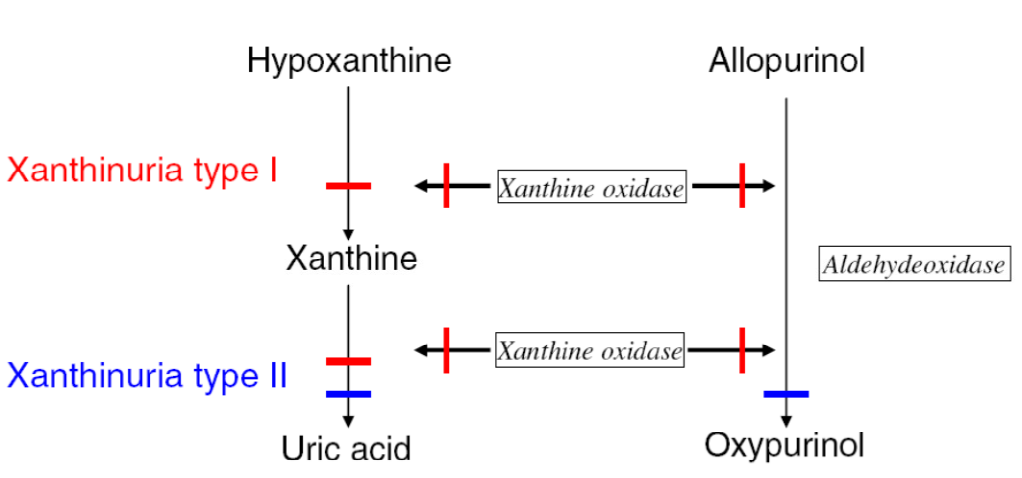
(+ allopur.loading test)

3.molecular genetic analysis

SLC22A12, SLC2A9

(in cooperation with Japan – *SLC17A3, ABCC4, ABCG2*)

Allopurinol loading test



patients with with XO def. type I - able

II - not able to metabolize allopurinol to oxipurinol

1. 300 mg of allopurinol (adults) …… after overnight fasting

2. Oxipurinol determined in plasma … after 1 hour

Ichida K et al (1997) J Clin Invest 99, 2391-97

Clinical and biochemical findings in patients with XDH deficiency

case	age of dg . (years)	first sign	uric acid in serum (µmol/l)	Kaufman index (UA/Cr)	xanthine in urine (mmol/mol Cr)
1.	3	hematuria renal stone	not detectable	0.002	598.0
2.	8	hematuria	53.0	0.04	370.0
3.	9	none	16.0	0.08	327.0
4.	30	none	not detectable		180.0
controls			120- 360	0.7	30.0

Clinical features and mutations (1-7th patients in *SLC22A12* gene) and 8-9th patients in *SLC2A9* gene

case	sex	age yrs	UA µmol/l	FE_{UA} (%)	ARF	uro-lithiasis	mutation
1.	f.	73	124	52.4	+	-	g. 8294-8302del
2.	f.	39	58	53.4	+	-	g. 82948302del/ g.9184C/T
3.	f.	53	78	60.3	-	-	g. 82948302del/ g.9184C/T
4.	m.	35	63	43.0	-	-	g. 8145G/C g.9214G/A
5.	f.	15	35	55.2	-	-	g. 8294-8302del g.9184C/T
6.	m.	5	95	52.6	-	+	1242-1250delGCTGGCAGG
7.	m.	5		50.	-	-	1245-1253delGGCAGGGCT
8	f.	18	11	240.0	-	-	g. 43412_43413insC
9.	m.	23	10	220.0	-	-	g. 43412_43413insC

Clinical features (two UK patients with acute renal failure-ARF) and mutations in *SLC2A9* gene

case	sex	age yrs	UA µmol/l	FE_{UA} (%)	Cr µmol/l	ARF	mutation
1.	m	12	40	93.0	297	+	p.G216R; p.N333S
2.	m	14	58	53.4	202	+	p.G216R

- *further evidence … …..SLC2A9 is a causative gene in RHUC2*

- *supports the prediction….both URAT1 and GLUT9 are essential for UA reabsorption*

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Sebesta I. Adv Chronic Kidney Dis 2012,19(6):398-403
Stiburkova B ,Ichida K,Sebesta I. Mol Genet Metab.2011,102(4):1411-5

Renal hypouricemia -unrecognized disorder ?

absence of *SLC22A12* gene mutations in Greek Caucasian

Tzovaraz V. et.al. Scand J Clin lab Invest.2007;67:589-95

5 patients (Macedonia), 2 (UK) – RHUC1 (URAT 1)

Tesic V. et.al. Plos One. 2011;6(12):e28641

EARLY DIAGNOSIS of INBORN ERRORS OF METABOLISM

1. available methods

2. proper indication

screening

newborn
(PKU, hypothyreosis.etc.)

selective screening
- family history
- suspicious clinical signs

diagnostic guidelines

Dg. flow chart for unexplained hypouricemia (S_{UA}: <120 µmol/l)

Evaluation of case history (urolithiasis, seizures, immunodeficiency)
Exclusion of secondary causes (drugs /allopurinol/, Fanconi sy. etc.)

↓

1. **Estimation of EXCRETION FRACTION OF UA**

↓

if high→ - mol.genet.analysis of URAT1, GLUT9

2. **Urinary concentration of XANTHINE, S-SULFOCYSTEIN, THIOSULFATE**

3. **Urinary concentration of (DEOXY) GUANOSINE, (DEOXY) INOSINE**

↓

if positive - assay of purine nucleoside phoshorylase (PNP) in ery.

Dg.protocol allows to differentiate

a) **XANTHINURIA (def.XO) (lithiasis, 50% of the patients are asymptomatic)**

b) **COMBINED DEFICIENCY OF XO/SULPHITE OXIDASE (seizures in newborns, evaluation od UA could be the first step to diagnosis)**

c) **PURINE NUCLEOSIDE PHOSPHORYLASE (defect of T-cell immunity)**

c) **HEREDITARY RENAL HYPOURICEMIA (lithiasis, high EF-UA)**

d) **Primary hypouricemia can be excluded (? new defect)**

Diagnosis of hereditary renal hypouricemia

1. estimation of uric acid (UA) in serum
- if less then 120 µmo/l

↓

2. estimation of excretion fraction of UA
- if high more than 10%

↓

3. exclusion of other secondary causes of hyperuricosuric hypouricemia
if excluded

↓

4. molecular analysis of *SLC22A* and *SLC2A9* genes

Conclusions

- *hypouricemia → risk factor for kidney injury*

  → indication for detailed purine metabolic investigation

- *hypouricemia can be good diagnostic tool – enables to find asymptomatic patients*

- *available guidelines will help for early diagnosis of purine disorders with hypouricemia*

Conclusions

- *first patients with hereditary renal hypouricemia and xanthinuria were diagnosed in Czech population*
- *findings of a defect in the SLC2A9 gene provides further evidence that SLC2A9 is a causative gene in renal hypouricemia and support the prediction that normal function of both URAT1 and GLUT 9 are essential for normal uric reabsorption*
- *renal hypouricemia is still unrecognized disorder and probably not wide spread in Asia only*