

# Gout With A Bite

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# Case

- 7 year old male
- Referred from Vredenburg Hospital:
  - previously labeled as cerebral palsy, spastic quadraparesis, severe intellectual deficit and a normal CT brain
  - lost to follow-up in 2003

# Case

- Hx

- developmental delay, abnormal movements (from age 1 year), lower lip biting

- Birth Hx

- NVD at term, unremarkable

- BW 3500g

- APGARS 9 and 10

- no neonatal jaundice

# Case

- Family Hx
  - nothing significant
  - has 5 siblings, others apparently healthy
- O/E
  - disfigured and scarred lower lip
  - CNS: HC 49cm (2 SDs below mean)
    - non-ambulant, wheelchair-bound
    - interactive, smiling
    - appropriate responses
    - cognitive and behavioral involvement
    - choreoathetoid type movements
    - globally increased tone and dystonia
    - contractures at wrists and ankles
  - Other systems: unremarkable

# Summary

- 7 year old boy
- Severe motor disability
- Dystonia and relative cognitive sparing
- Self-mutilatory behavior

# Investigations

- MRI brain: normal
- KUB U/S: bilateral renal medullary calcifications
- Blood:

-urea	2.7	(1.4-5.7mmol/l)
-creatinine	65	(53-80mmol/l)
-uric acid	0.46	(0.12-0.32mmol/l)
- urate/creatinine ratio (urine) 0.57
- Plasma amino acids: normal
- Urine organic acids: normal

# Investigations

- Hypoxanthine-guanine phosphoribosyl transferase activity:
  - patient 0.03nmol/min/mg
  - controls 1.54 and 1.00nmol/min/mg
- Gene mutation analysis:
  - HGPRT1* gene mutation at amino acid 209 (serine to isoleucine)

# Lesch-Nyhan Syndrome: Clinical description

- **Neurological dysfunction**
  - normal prenatal and perinatal course
  - developmental delay with hypotonia and delayed motor skills (3-6mo)
  - fail to reach milestones
- Extrapyrarnidal involvement (6-18mo):
  - action dystonia
  - also choreoathetosis, opisthotonos and ballismus
- Pyramidal involvement: spasticity, hyperreflexia and extensor plantar reflexes
- Initially diagnosed as having cerebral palsy
- Confined to a wheelchair

# Clinical description

- **Cognitive and behavioral disturbances**
  - cognitively impaired
  - persistent self-injurious behavior (2-3yrs)
- **Other compulsive behaviors: aggressiveness, vomiting, spitting and coprolalia**

# Clinical description

- **Overproduction of uric acid**
  - present at birth (not always elevated)
  - deposition of crystals in the kidneys, ureters or bladder
- Stones often not recognized for years
- Gouty arthritis and tophi are uncommon

# Clinical description

## ■ Other

- delayed growth and puberty
- end-stage renal disease despite allopurinol
- megaloblastic anemia

## ■ Life expectancy

- second or third decade
- no disease progression after 3-6 years of age

# Clinical description

- **Lesch-Nyhan syndrome in females**

- X-linked recessive

- female carriers develop gout

- seven reported females with Lesch-Nyhan syndrome

- **Genotype-Phenotype Correlations**

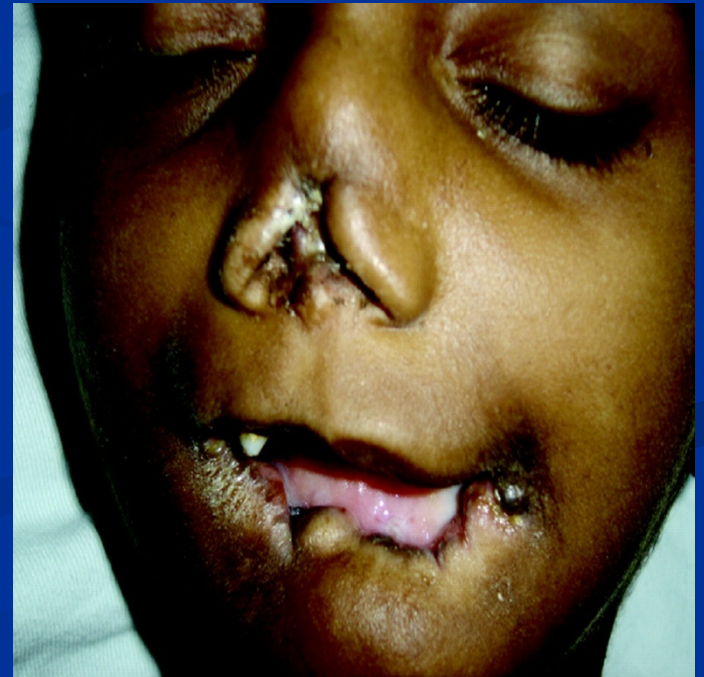
- Lesch-Nyhan syndrome: complete deficiency of HGPRT (<1,5%)

- Kelley-Seegmiller syndrome: partial deficiency (>8%)

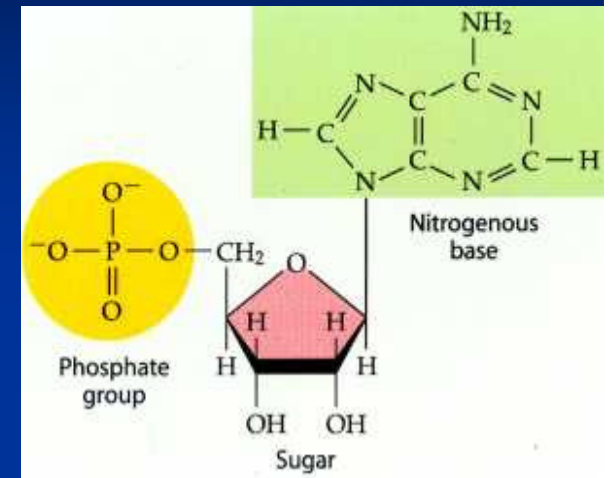
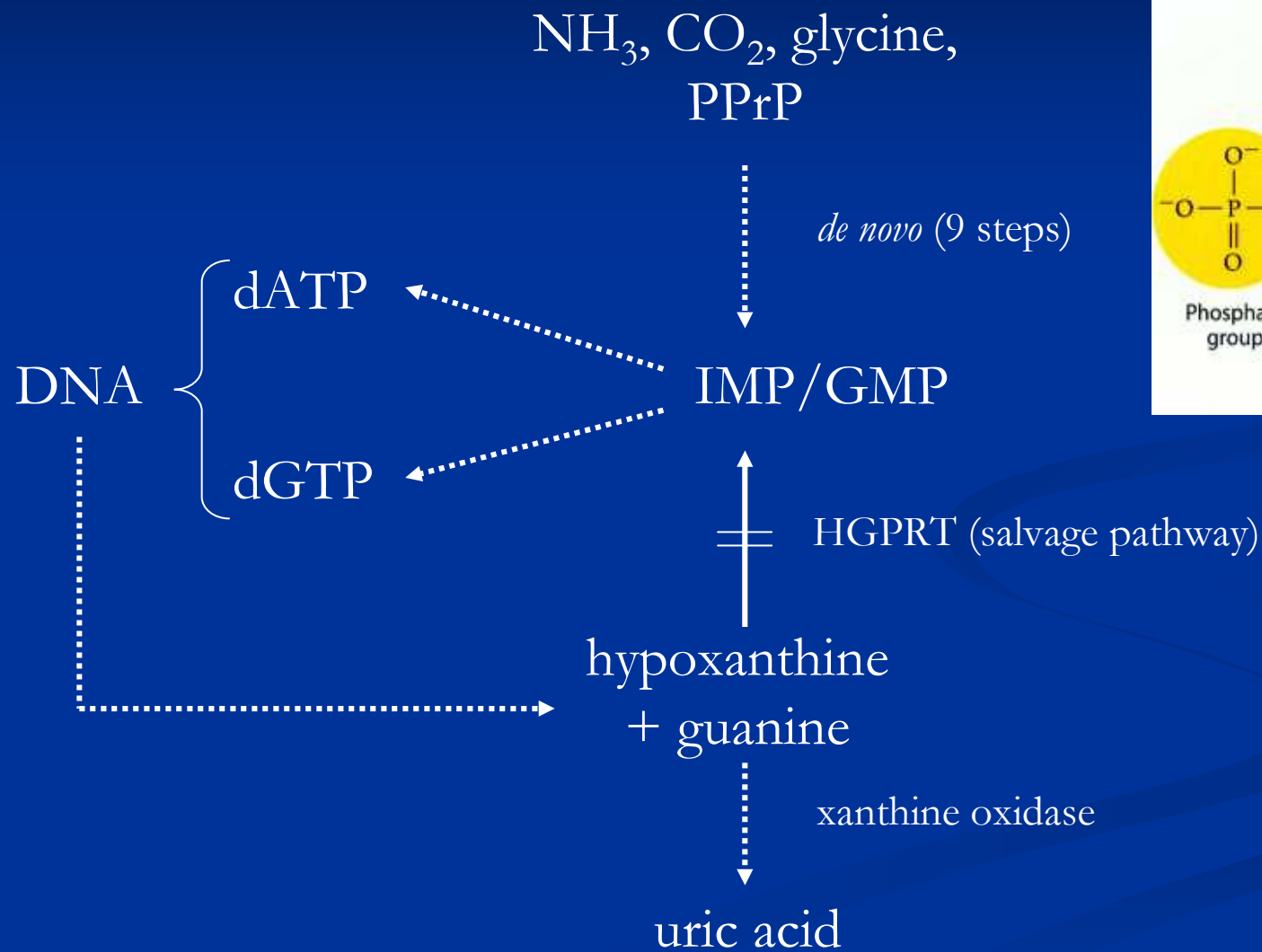
- 1.5% to 8% activity

- **Prevalence**

- approximately 1:380 000



# Biochemistry—purine metabolism



# Biochemistry

- Neurotoxicity: increased uric acid vs depleted purine nucleotides
- Data support the involvement of purines:
  - in GABA and L-glutamate neurotransmission
  - purines may have trophic functions in the brain
- Immaturity and dysfunction of dopaminergic nerve terminals

# Investigations

- **Imaging**

- KUB ultrasound

- CT and MRI brain may show nonspecific changes

- Uric acid: may be normal

- Urate/creatinine ratio (urine):  $>1.4$  is characteristic but not diagnostic

- 24h urate excretion:  $>0.12\text{mmol/kg}$  is characteristic but not diagnostic

# Investigations

## ■ Enzyme activity

rbc lysate (source of HGPRT)

+

$C^{14}$  hypoxanthine

+

PrPP

1) +HGPRT:  $C^{14}$  hypoxanthine +  $C^{14}$  IMP

or

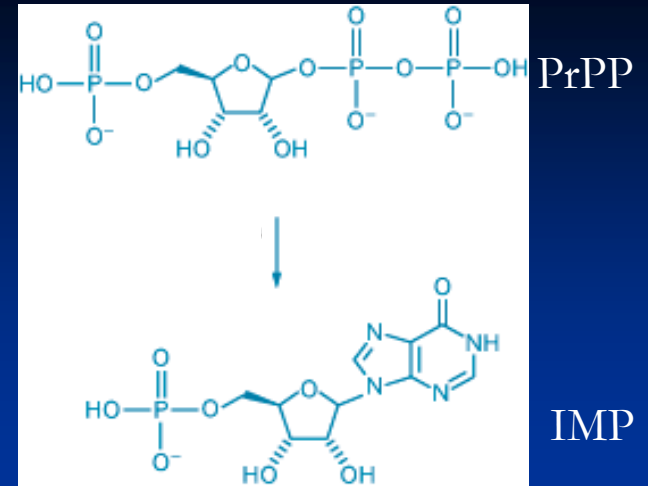
2) -HGPRT:  $C^{14}$  hypoxanthine

remove protein

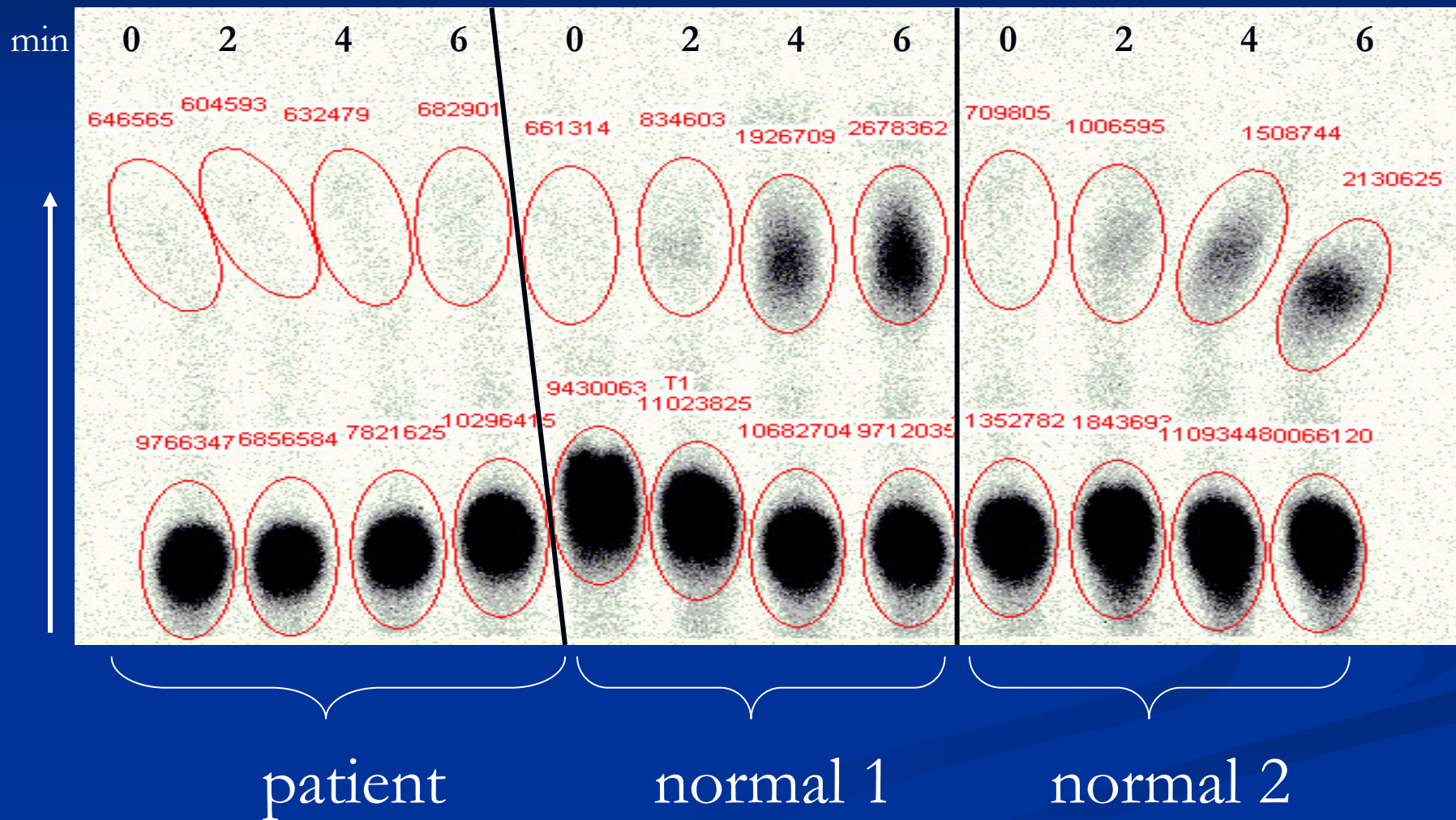
thin-layer chromatography

+

quantify radioactive intensity

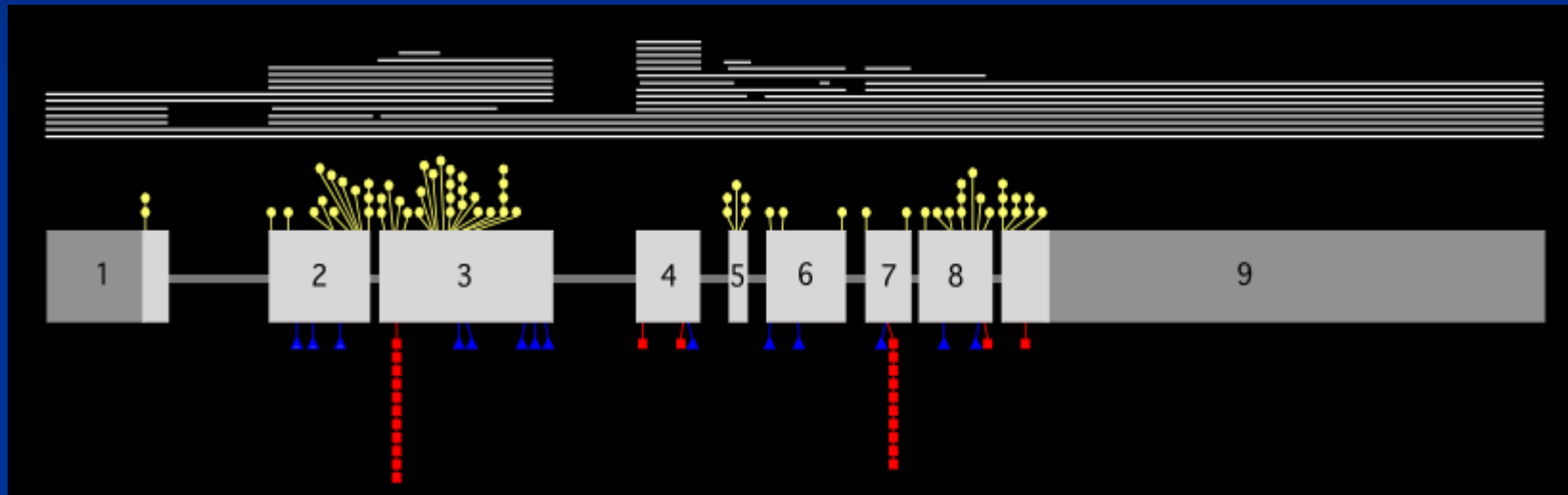


# Investigations



# Investigations

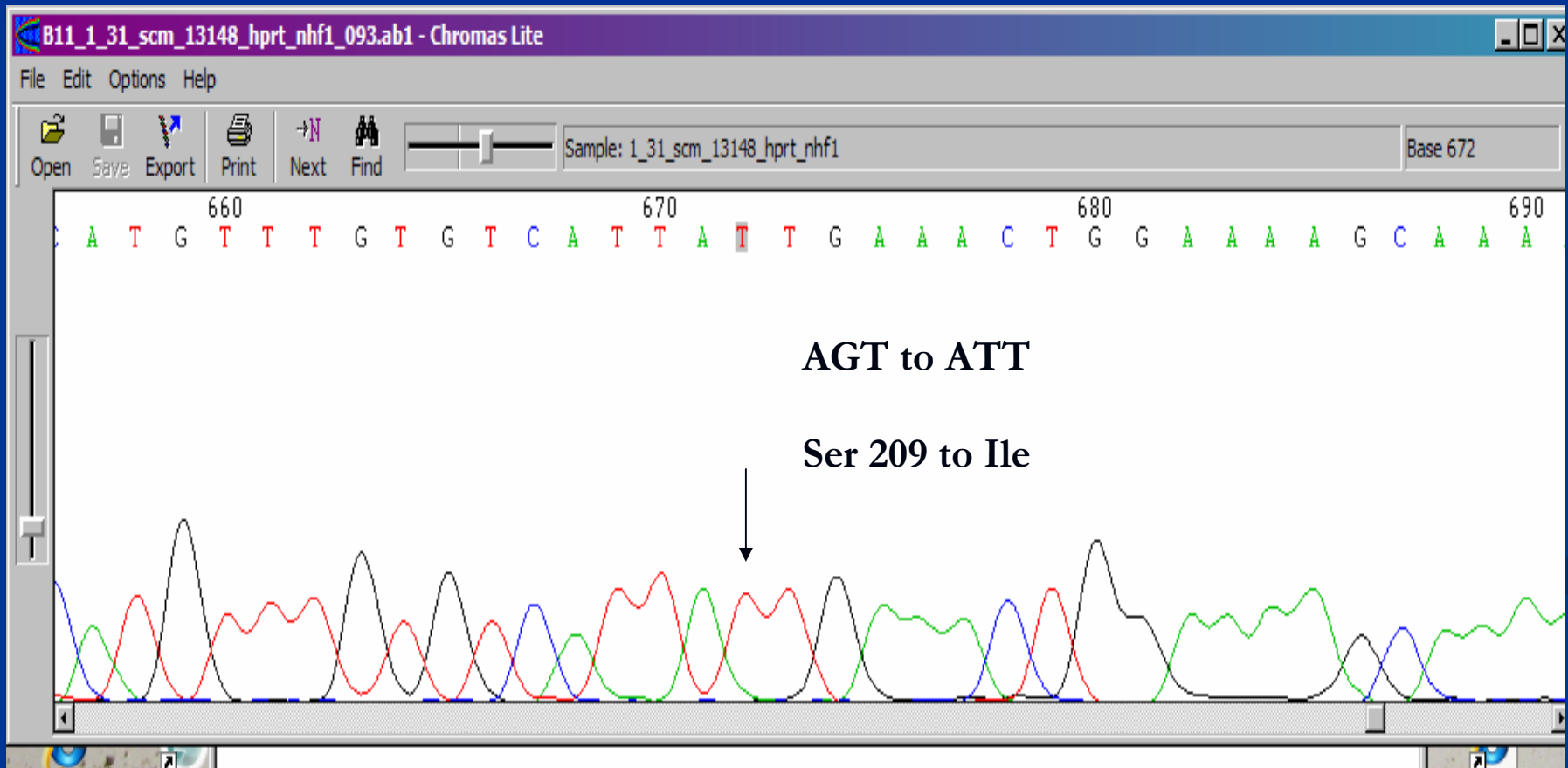
## ■ Gene mutation analysis



- *HGPR1* gene has 9 exons: the coding region depicted as light gray boxes
- Genetic mutations are heterogenous:
  - point mutations leading to amino acid substitution (yellow circles)
  - point mutations leading to premature stop (red squares)
  - insertions (blue triangles)
  - deletions (white lines)

# Investigations

## ■ DNA sequencing



# Management

- Uric acid: maintain in the normal range
- Neurological features:
  - benzodiazepines
  - antispasticity agents
- Behavioral problems/self-injurious behavior:
  - difficult to manage
  - behavioral modification techniques and medication

# Management

- Physical restraints
- Under investigation:
  - deep brain stimulation
  - dopamine replacement therapy
  - S-adenosyl methionine
- Prenatal Testing
  - prenatal testing is available for at-risk pregnancies

# Some Causes of Hyperuricaemia

Underexcretion	Overproduction	Combined
Idiopathic	Idiopathic	Hereditary fructose intolerance
Renal insufficiency	HGPRT deficiency	Glycogenosis I
Familial juvenile gouty nephropathy	PRPP synthetase overactivity	
Acidosis:lactate, ketoacidosis	Tumour lysis syndrome	
Trisomy 21	Glycogenoses III, V and VIII	
Diuretics, salicylates, ethambutol		

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