
بسم الله الرحمن الرحيم

Pathophysiology and Genetics of Tyrosinemia Disorders

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Tyrosinemia Disorders

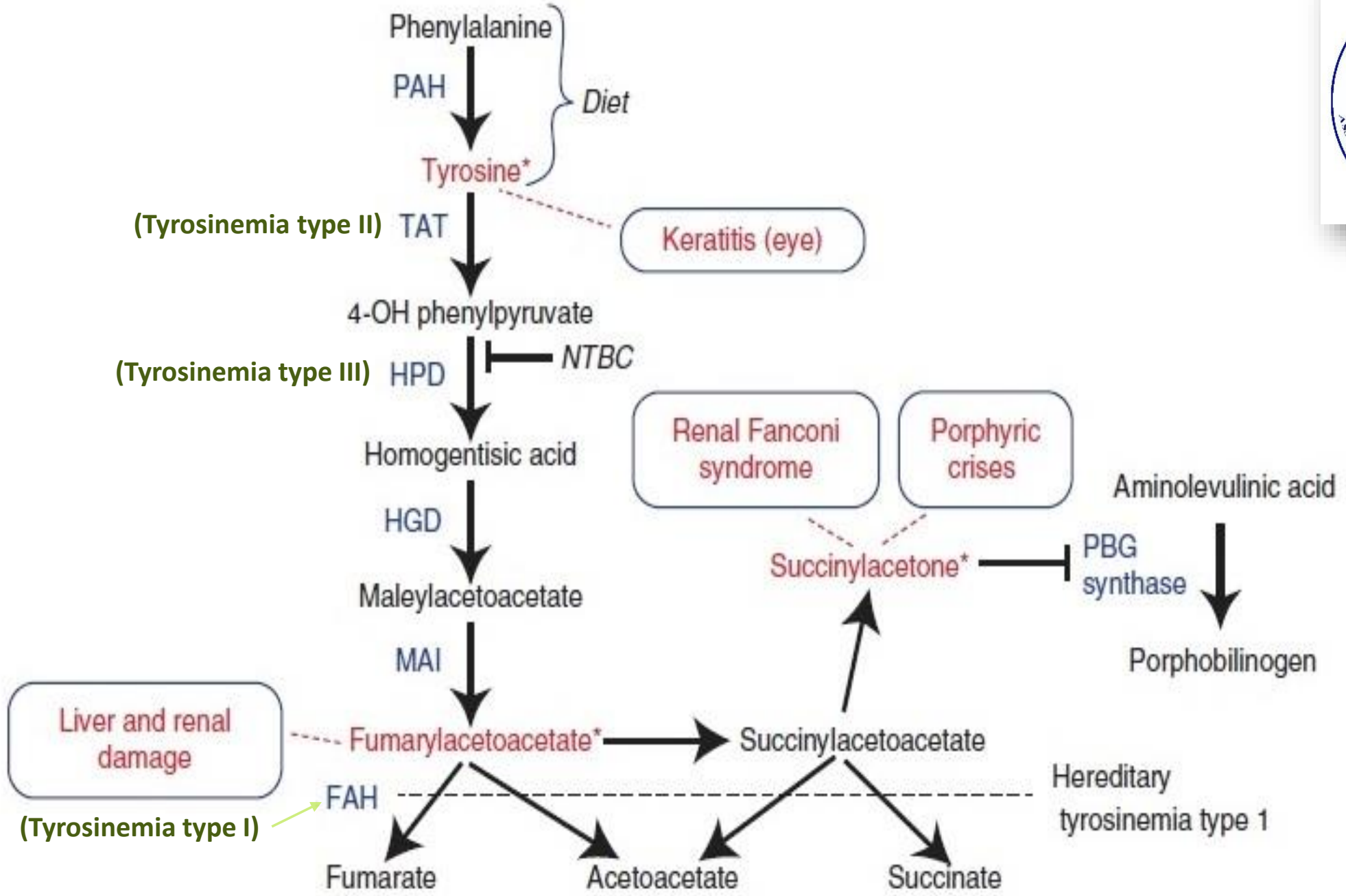
- **Hereditary Tyrosinemia Type I** (HT1) (OMIM276700) is a severe inherited metabolic disease affecting mainly hepatic and renal functions that leads to a fatal outcome if untreated.

- In 1977, fumarylacetoacetate hydrolase (FAH) was identified as the deficient enzyme responsible for HT-1.

Tyrosinemia Disorders

- **Tyrosinemia type II** is caused by a defect in tyrosine aminotransferase (TAT) (EC 2.6.1.5).

- **Tyrosinemia type III,** the rarest of the tyrosine disorders, is caused by a deficiency of *p*-hydroxyphenylpyruvic acid dioxygenase (EC.1.13.11.27)


Phenylalanine
PAH
Diet
Tyrosine*
(Tyrosinemia type II)
TAT
Keratitis (eye)
4-OH phenylpyruvate
(Tyrosinemia type III)
HPD
NTBC
Homogentisic acid
HGD
Maleylacetoacetate
MAI
Renal Fanconi syndrome
Porphyric crises
Aminolevulinic acid
Succinylacetone*
PBG synthase
Porphobilinogen
Liver and renal damage
Fumarylacetoacetate*
Succinylacetoacetate
FAH
Hereditary tyrosinemia type 1
(Tyrosinemia type I)
Fumarate
Acetoacetate
Succinate

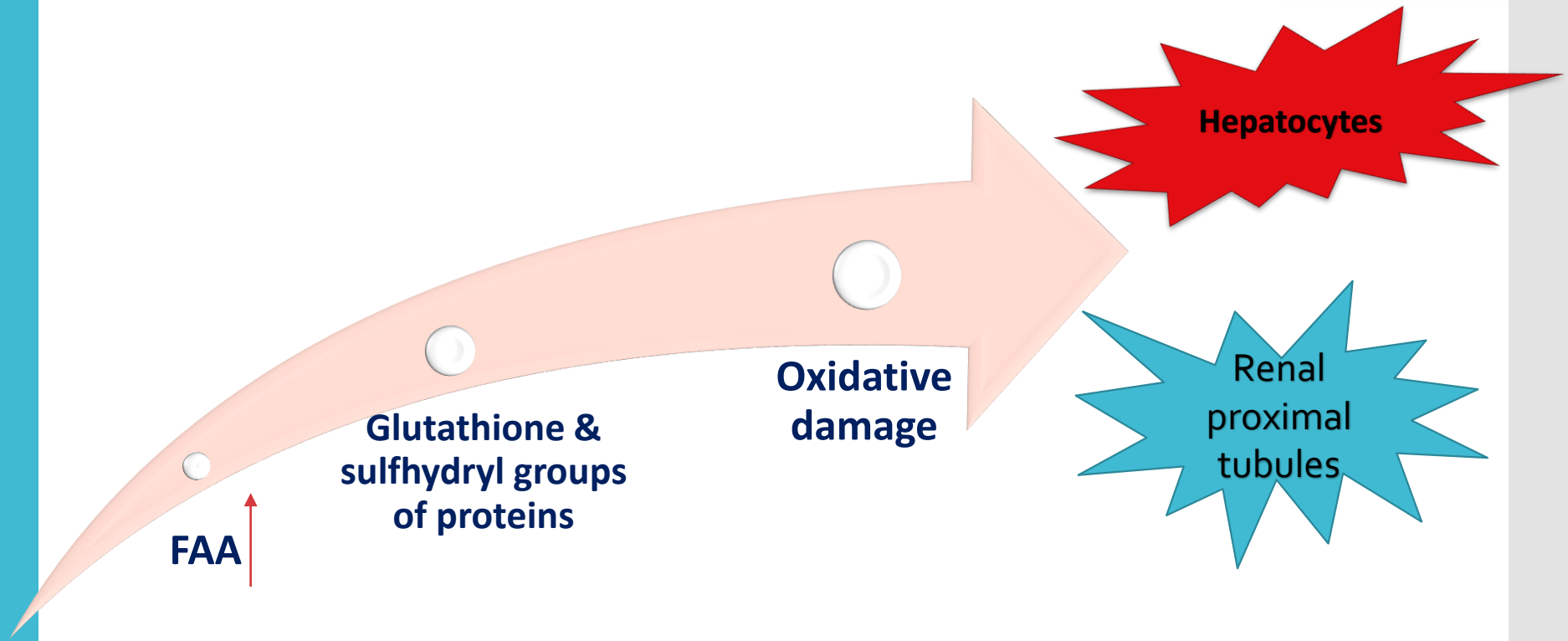
Pathway of Tyrosine Metabolism

- In Fah mutant mice the mRNA for tyrosine amino transferase (Tat), the rate-limiting enzyme in tyrosine degradation, is absent.
- The activity of 4-hydroxyphenylpyruvic dioxygenase (HPD), the second step in the tyrosine degradation pathway, is decreased in human HT-1 liver samples.
- These observations suggest that the clinical effects associated with HT-1 are due to other metabolites resulting from FAH deficiency, not the elevation of tyrosine in the blood.

Tyrosinemia Type I

- In FAH deficiency, fumarylacetoacetate (FAA), the immediate precursor which appears to accumulate in hepatocytes, causing cellular damage and apoptosis.

Tyrosine metabolism pathway



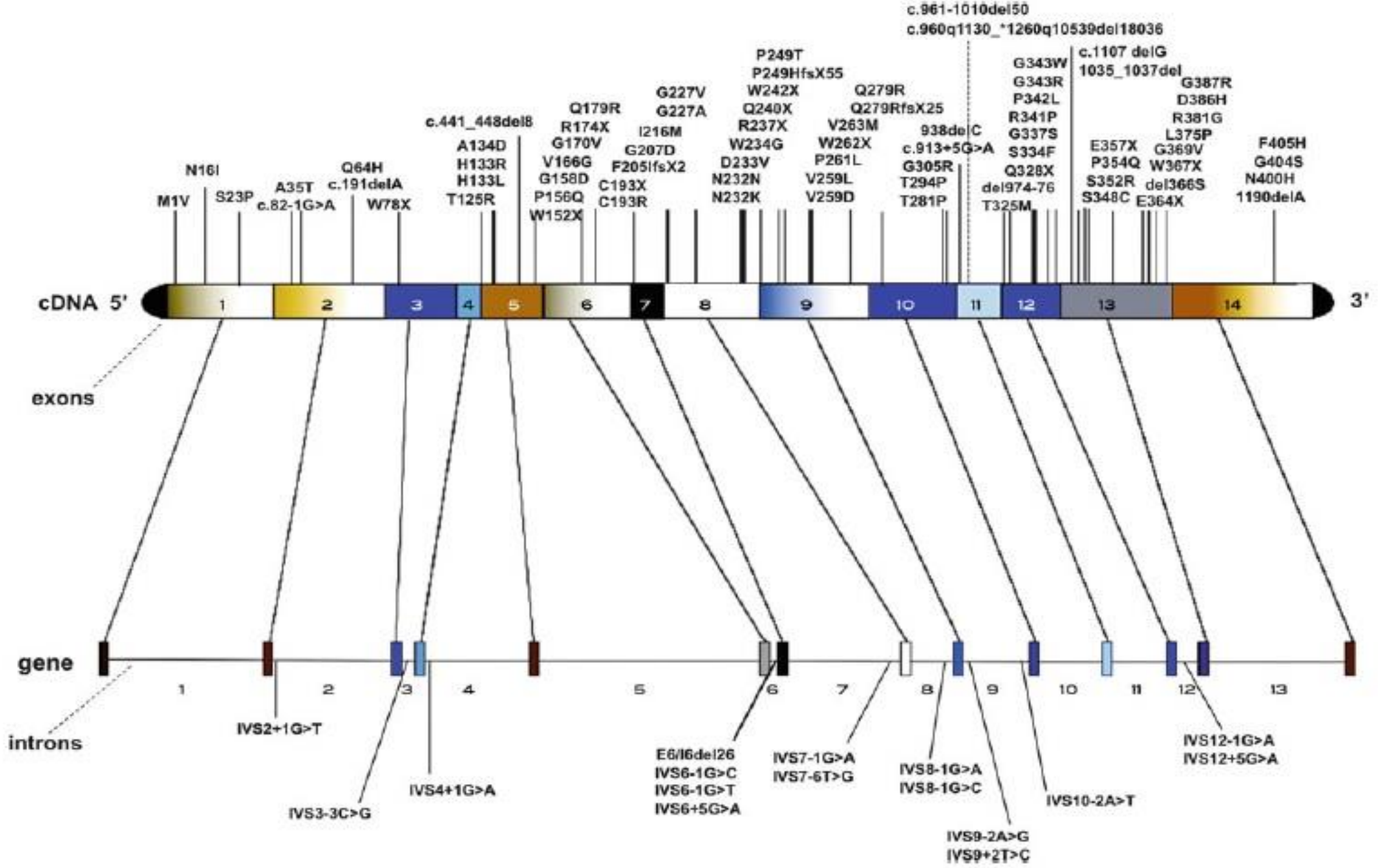
Genetics of Tyrosinemia Type I

- Tyrosinemia type I is inherited in an autosomal recessive manner.

- The human fah gene is located on chromosome 15q23-q25, spans 30–35 kb and consists of 14 exons. The cDNA has an open reading frame of 1,257 bp encoding 419 amino acids

Genetics of Tyrosinemia Type I

- The first mutation reported in the fah gene was the c.47A>T (p.Asn16Ile) in a French Canadian patient and was shown to be causative of FAH deficiency.

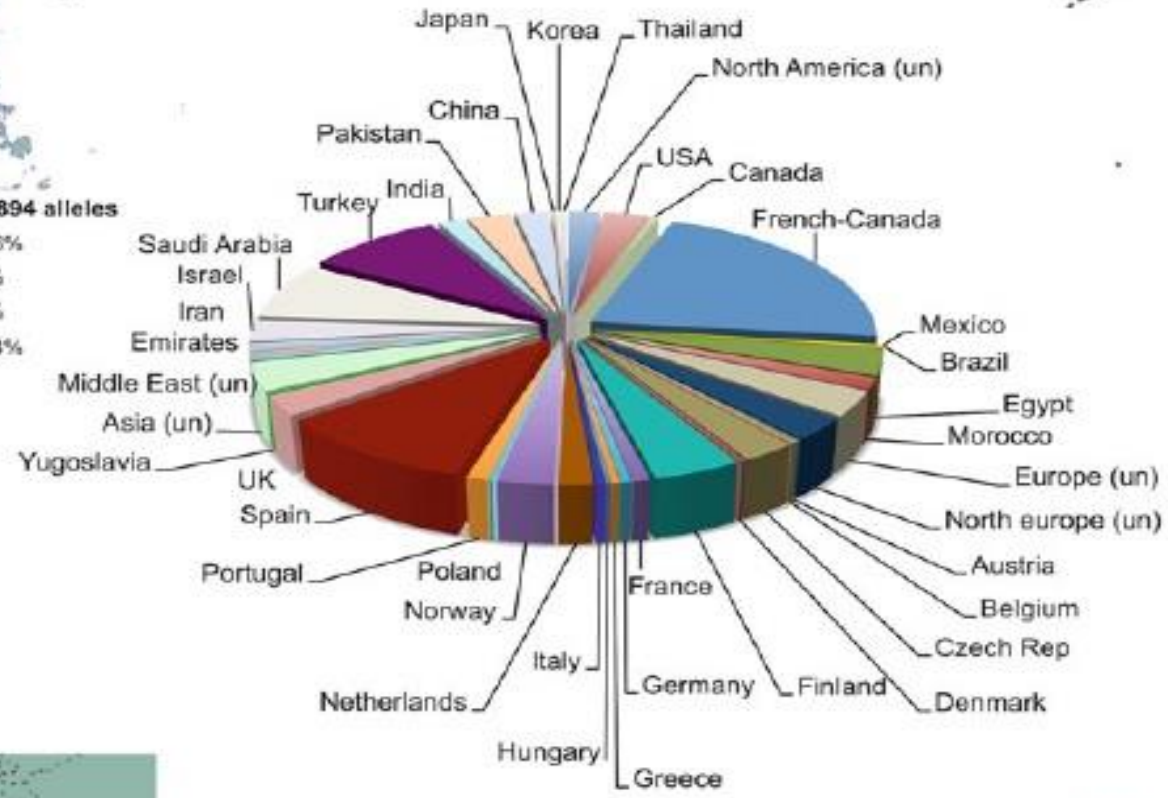

c.961-1010del50
c.960q1130_*1260q10539del18036
P249T
P249HfsX55
W242X
Q240X
R237X
W234G
D233V
N232N
N232K
G227V
G227A
I216M
G207D
F205IfsX2
C193X
C193R
Q179R
R174X
G170V
V166G
G158D
P156Q
W152X
c.441_448del8
A134D
H133R
H133L
T125R
N16I
M1V
S23P
A35T
c.82-1G>A
Q64H
c.191delA
W78X
Q279R
Q279RfsX25
V263M
W262X
P261L
V259L
V259D
938delC
c.913+5G>A
G305R
T294P
T281P
G343W
G343R
P342L
R341P
G337S
S334F
Q328X
del974-76
T325M
c.1107 delG
1035_1037del
E357X
P354Q
S352R
S348C
G387R
D386H
R381G
L375P
G369V
W367X
del366S
E364X
F405H
G404S
N400H
1190delA
cDNA 5'
3'
1
2
3
4
5
6
7
8
9
10
11
12
13
14
exons
gene
introns
IVS2+1G>T
IVS3-3C>G
IVS4+1G>A
E6/I6del26
IVS6-1G>C
IVS6-1G>T
IVS6+5G>A
IVS7-1G>A
IVS7-6T>G
IVS8-1G>A
IVS8-1G>C
IVS9-2A>G
IVS9+2T>C
IVS10-2A>T
IVS12-1G>A
IVS12+5G>A

East Asia **29/894 alleles**

c.974_976delC AinsGC	20.6%
c.960q1130_*1260q10539del18036	14%
p.Arg237X	14%
others	51.4%

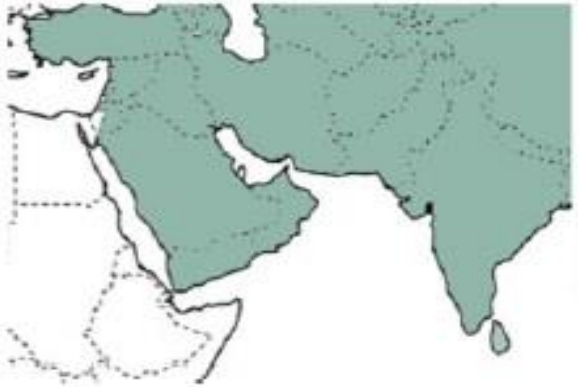
North America **253/894 alleles**

IVS12+5G>A	79%
IVS6-1G>T	6.7%
p.Glu364X	4.3%
others	10%



North Africa **46/894 alleles**

IVS6-1G>T	24 %
IVS4+1G>A	17.4%
p.Thr125Arg	17.4%
others	41.2%



Middle East-South Asia **261/894 alleles**

p.Gln64His	15%
p.Arg237X	14%
IVS12+5G>A	11%
others	60%

Europe **332/894 alleles**

IVS6-1G>T)	29%
IVS12+5G>A	22%
p.Trp262X	14%
others	35%

Mutation distribution of FAH gene

FAH gene mutations in geographic regions

Mutations	Geographic location	Frequency in population
c.1062+5G > A (IVS12+5G> A)*	French Canada	86%
	Northern Europe	46%
p.W262X	Finland	80%
c.554-1G > T (IVS6-1G>T)*	Southern Europe	64%
p.G337S	Norway	58%
p.Q64H	Pakistan	92%
p.D233V	Turkey	94%

Prevalence

- In geographic areas without newborn screening, tyrosinemia type I affects approximately 1 in 100,000 to 120,000 births.

Prevalence

- Two regions of the world have a higher than expected frequency of tyrosinemia type I due to the increased frequency of certain pathogenic variants resulting from a founder effect:

1. In the Scandinavian countries the birth prevalence is estimated at 1:74,000 and 1:60,000 live births, respectively.

2. A founder effect from colonization by French settlers is present in the province of Quebec, Canada. The birth prevalence in the province of Quebec is 1:16,000

Prevalence

- **Tyrosinemia**, **type II** (TYR **II**) affects fewer than one in 250,000 individuals. The condition may be more common in Arab and Mediterranean regions.

- **Tyrosinemia**, **type III** (TYR **III**) is a very rare condition. **Prevalence**: <1 / 1 000 000

Thank You