UNIVERSITY OF LATVIA

79th International Scientific Conference of the University of Latvia

Clinical and pharmacogenomic implications of xanthine dehydrogenase genetic variation in Latvian tuberculosis patients

Vīksna Anda[1,3], Igumnova Viktorija[1,2], Kivrāne Agnija[1,2], Freimane Lauma[1,2], Pole Ilva[3], Bandere Dace[1], Ozere Iveta[1,3], Ranka Renāte[1,2]

[1]*Riga Stradiņš University, Riga, Latvia*
[2]*Latvian Biomedical Research and Study Centre, Riga, Latvia*
[3]*Riga East University Hospital, Centre of Tuberculosis and Lung Diseases, Upeslejas, Latvia*

Background of the study

- Xanthine dehydrogenase (XDH) is involved in the oxidative metabolism of purines and is encoded by the *XDH* gene. XDH can be converted to xanthine oxidase (XO) by reversible sulfhydryl oxidation or by irreversible proteolytic modification. XO is involved in the oxidative metabolism of clinically significant drugs, including pyrazinamide.
- *XDH* gene is highly polymorphic; several polymorphisms are related to the variability in enzyme activity and also enzyme deficiency, which leads to xanthinuria. Genetic polymorphisms of *XDH* gene have been studied as modifiers of drug toxicity and/or efficacy.
- Recently, a single common tag SNP (rs17011368) located in Mo-pt domain of *XDH* has been shown to accurately predict high enzyme activity of an individual.

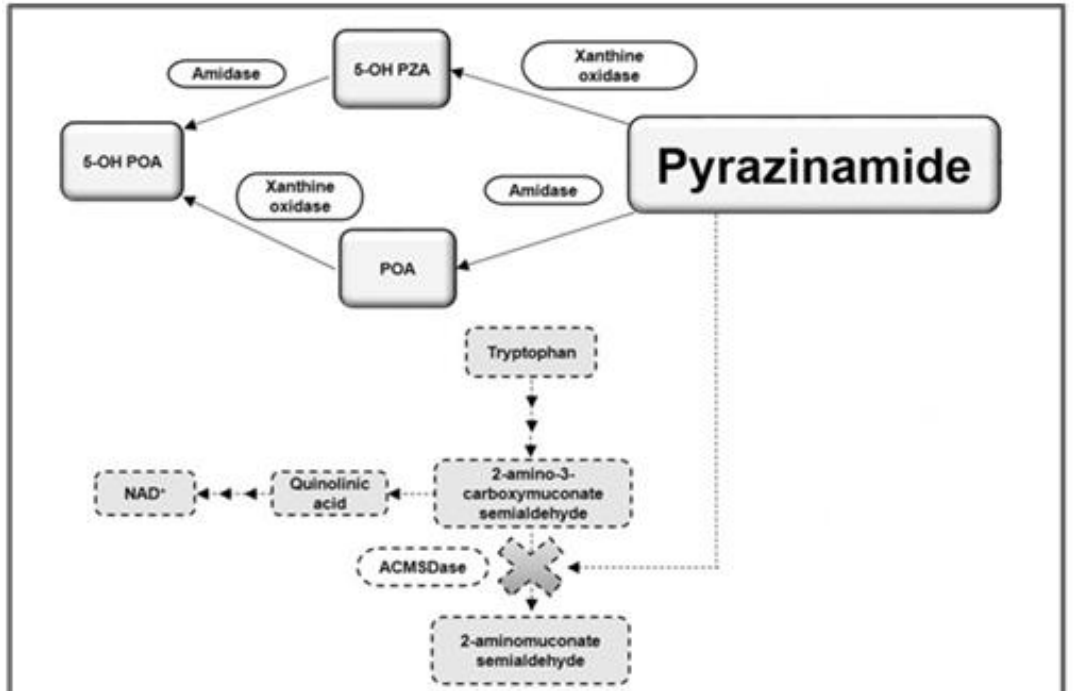


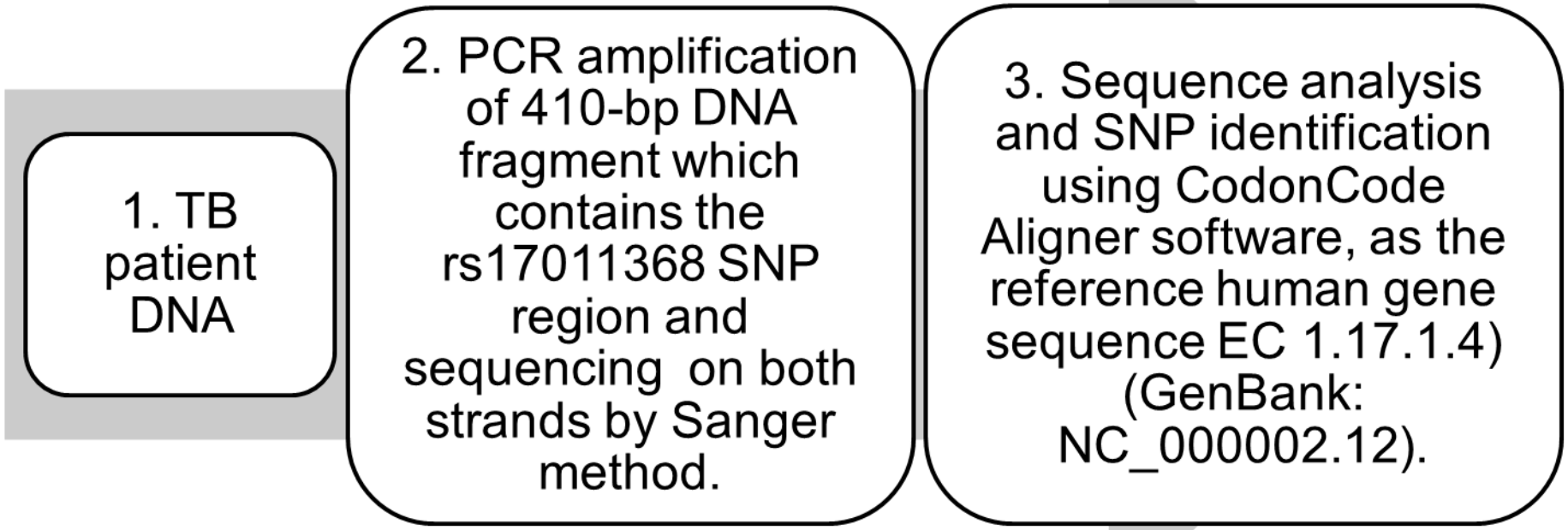
Figure 1. Schematic representation of the candidate genes involved in the metabolism of pyrazinamide (Ilse Du Preez & Du Toit Loots, 2018).

Figure 2. Location of rs17011368 in the *XDH* gene.

The aim of the study, materials and methods

- **The aim** of this study was to identify genetic polymorphisms of metabolic enzyme XDH in Latvian tuberculosis patients receiving pyrazinamide.

- Clinical information were obtained from the Centre of Tuberculosis and Lung Diseases, Riga East University Hospital, Latvia. The study protocol was approved by the Central Medical Committee of Ethics in Latvia.



Results

- Data comprises 33 TB patients: 10 (30.3%) women and 23 (69.7%) men, age range 19 - 82 years.
- Table 1 contains information about the patients biochemical indicators before and after the TB therapy.
- Sequencing results:
  - 32/33 patients carried the major rs17011368 T allele and were classified as a **wild type**.
  - The second allele (rs17011368 C, p.Ile703Val) was present in **one** heterozygous patient.
- No significant associations of the genotypes with clinical characteristics were observed.

Characterisation of the study participants		
Body mass index	kg/m2 (SD)	21,87 (±5,17)
Anti-tuberculosis drug concentration		
Pyrazinamide	mg/kg (SD)	30,9 (±5,81)
Biomedical indicators before therapy		
ALAT	U/L (SD)	20,41 (±14,9)
ASAT	U/L (SD)	23 (±22,93)
Biomedical indicators after therapy		
ALAT	U/L (SD)	**58,65 (±94,61)**
ASAT	U/L (SD)	**59,10 (±98,8)**
Hyperfermentemia after therapy		
ALAT	No of patients	**7/33 (21,21%)**
ASAT	No of patients	**6/33 (18,18%)**

Table 1. Characterisation of study participants biochemical indicators (ALAT rederent values for women <31 U/L, men <41 U/L; ASAT referent values for women <31 U/L, men <37 U/L).

***XDH* gene rs17011368**	
No of patients carried the minor allele (C, p.Ile703Val)	**1/33 heterozygous patient carried the minor allele with frequency (0,015)**
No of patients carried the major alleles (T/T=wild type)	**32/33 homozygous patients carried major alleles with frequency (0,984)**

Table 2. Distribution of *XDH* gene rs17011368 among Latvian TB patients.

Conclusions

- The observed frequency of missense T>C allele, which was associated with high XDH activity, was similar to other northern European populations (Figure 3).
- In order to assess the merits of pyrazinamide pharmacogenomics in the treatment of tuberculosis additional research is needed in a larger cohort.

Databases	Allele frequency
Global minor allele frequency (GMAF)	0.05192 (C)
1000 Genomes Project	0.05192
The Genome Aggregation Database (gnomAD)	0.05257
Exome Aggregation Consortium (ExAC)	0.03506
NHLBI Exome Sequencing Project (ESP) Exome Variant Server	0.06166
Trans-Omics for Precision Medicine (TOPMed)	0.05496

Figure 3. *XDH* gene rs17011368 allele frequency

Acknowledments.This study was supported by RSU grant/agreement No. 23030103.