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Pharmacogenetic Aspects of Anti-Tuberculosis Therapy in Latvian Population

Summary of the Doctoral Thesis for obtaining the scientific degree “Doctor of Science (*PhD*)”

Sector Group – Medical and Health Sciences
Sector – Basic Medicine
Sub-Sector – Clinical Pharmacy

Riga, 2025

RĪGA STRADIŅŠ UNIVERSITY

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Abbreviations used in the Thesis

AcHz	acetylhydrazine
AcINH	acetylisoniazid
ADRs	adverse drug reactions
AGs	aminoglycosides
AIHL	aminoglycoside-induced hearing loss
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
AUC	area under the curve
$AUC_{0–6h}$	area under the curve 0–6 hours
BMI	body mass index
bp	base pair
C_{max}	maximum concentration
CYP	cytochrome P450
CYP2E1	cytochrome P450 family 2 subfamily E member 1
DIH	drug-induced hepatotoxicity
DNA	deoxyribonucleic acid
DS-TB	drug-susceptible tuberculosis
GST	glutathione S-transferase
GSTM1	glutathione S-transferase M1 class
GSTT1	glutathione S-transferase T1 class
hgs	haplogroup
Hz	hydrazine
IA	intermediate acetylator
INA	isonicotinic acid
INH	isoniazid
MDR-TB	multidrug-resistant tuberculosis

MIC	minimal inhibitory concentration
MR	metabolic ratio
mRNA	messenger ribonucleic acid
Mtb	*Mycobacterium tuberculosis*
mtDNA	mitochondrial deoxyribonucleic acid
NAT2	N-acetyltransferase 2
NGS	next-generation sequencing
PGx	pharmacogenetics
PK	pharmacokinetic
RA	rapid acetylator
RIF	rifampicin
ROS	reactive oxygen species
rRNA	ribosomal ribonucleic acid
SA	slow acetylator
TB	tuberculosis
TDM	therapeutic drug monitoring
tRNA	transfer ribonucleic acid
tSCC	time to sputum culture conversion
UTR	untranslated region

Introduction

Personalised medicine postulates treatment adjustment to the individual characteristics of each patient such as genetics, environment, anthropometric information, and also lifestyle, and it includes pharmacogenetics (PGx) and therapeutic drug monitoring (TDM) as key components.

PGx is the study of how a patient`s genetic variations impact drug exposure and effects. With studies indicating that 91–99 % of individuals carry at least one clinically actionable PGx variant, the field of PGx presents substantial opportunities for optimising treatment, preventing adverse drug reactions (ADRs), and minimising avoidable healthcare costs through personalised clinical interventions (van Driest et al., 2014; van der Wouden et al., 2017; Tafazoli et al., 2021; Kabbani et al., 2023).

At the same time, TDM involves real-time sampling practice of measuring drug concentrations in biological samples at specific time points to ensure effective and safe dosing (Fang et al., 2024; Thu et al., 2024). TDM is generally indicated for drugs with a narrow therapeutic index, substantial ADRs, extended dosing regimens, and significant individual variability in treatment response (Tuzimski and Petruczynic et al., 2020; Fang et al., 2024). In addition, effective TDM should take into account patient-specific factors such as age, body composition, metabolic status, hepatic and renal function, and concurrent medication use (Lea-Henry et al., 2018; Fang et al., 2024). Accurate and advanced analytical methods are essential for the reliable implementation of TDM.

Thus, PGx and TDM provide clinically relevant information on identified associations between genetic variations in genes encoding drug-metabolising enzymes, genes encoding drug transporters or drug targets, and individual variability in drug response (Hlaváč et al., 2020).

Tuberculosis (TB) is a communicable disease that was the leading cause of death from a single infectious agent worldwide until the emergence of

the 2019 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (WHO, 2023). The most visible impact of the pandemic was a decline in the number of reported diagnosed TB cases, from 7.1 million in 2019 to 5.8 million in 2020, with a rebounded recovery to 7.5 million in 2022 (WHO, 2023). In Latvia, the TB incidence rate (per 100,000 population) decreased from 24 cases in 2019 to 16 cases in 2021 (ECDC and WHO, 2022). However, a sharp increase to 19 cases per 100,000 population was observed in 2022, reflecting the detrimental effects of major disruptions caused by the pandemic affecting on key processes related to TB diagnosis, treatment, and prevention services (ECDC and WHO, 2022; WHO, 2023). Although the overall incidence of TB is declining, both drug-susceptible tuberculosis (DS-TB) and multidrug-resistant tuberculosis (MDR-TB) remain to be a current global health threat (WHO, 2023).

In treating DS-TB strains, a high cure rate of up to 85 % has been achieved with 2-month chemotherapy regimen of isoniazid (INH), rifampicin (RIF), ethambutol, and pyrazinamide, followed by a further 4 months of INH and RIF; this treatment regimen is widely recognised as cost-effective and affordable (WHO, 2022b). The prodrug INH, chemically characterised as isonicotinic acid hydrazide, is the centrepiece of the currently recommended treatment regimen; however, it is assumed that variants in genes coding specific drug-metabolising enzymes, including N-acetyltransferase 2 (NAT2), cytochrome P450 family 2 subfamily E member 1 (CYP2E1), and glutathione S-transferase M1 class (GSTM1), could be related to the pharmacokinetic (PK) and pharmacodynamic alterations of the INH metabolism and accumulation of toxic substances, which, subsequently, can affect the treatment response and lead to development of drug-induced hepatotoxicity (DIH) (Ellard and Gammon, 1976; Yang et al., 2019; Ignatius and Dooley, 2023). Specifically, the predominant metabolic pathway of INH in humans is acetylation by NAT2 isoforms, encoded by a variety of NAT2 alleles to its principal metabolite, acetylisoniazid (AcINH),

which lacks antimycobacterial activity (Becker et al., 2007; Klein et al., 2016; Namdar and Peloquin, 2023). Other INH metabolites, such as hydrazine (Hz), isonicotinic acid (INA), acetylhydrazine (AcHz), and diacetylhydrazine are generated by amidase-induced hydrolysis, glycine conjugation, hydrazone formation, and further acetylation (Becker et al., 2007).

In addition, MDR-TB treatment with second-line antimicrobials is characterised by high rates of adverse events and a prolonged duration of 18–20 months for most patients on longer regimens (WHO, 2022c). Moreover, there is an increased probability of treatment failure and death: in 2019, the treatment success rate for people treated for MDR-TB with second-line regimens was only 63 % (WHO, 2023). Following the introduction of recently endorsed shorter, bedaquiline-based all-oral regimens, aminoglycosides (AGs), such as amikacin and streptomycin, have been categorized as Group C agents, which includes both TB-specific and repurposed medicines, and are now considered as lower priority anti-TB drugs (WHO, 2022c). Furthermore, the use of kanamycin and the polypeptide capreomycin is no longer recommended (WHO, 2022c). Although the use of second-line injectable drugs has decreased in recent years, they remain crucial for anti-MDR-TB therapy and can be included in longer-term treatment scenarios. Additionally, for patients on extended regimens containing amikacin or streptomycin, an intensive phase of 6–7 months is recommended for most cases (WHO, 2022c). Patients` individual susceptibility to aminoglycoside-induced hearing loss (AIHL), one of the ADRs, is more likely to occur in individuals with multiple AG ototoxicity-related mitochondrial deoxyribonucleic acid (mtDNA) MT-RNR1 gene variants transmitted by maternal inheritance (Freimane et al., 2023).

During the last years, PGx studies have become increasingly important in TB treatment. While PGx can be effectively used as a standalone tool, it can also be combined with TDM to further refine personalised treatment strategies. This

flexibility in approach reflects the diversity of TB populations and the adaptability of personalised medicine, enhancing therapeutic efficacy while minimising the risk of ADRs (Hobbie et al., 2008a; Ignatius and Dooley, 2023; Hong et al., 2020; WHO, 2022a). Consequently, exploring novel precision-medicine-guided biomarkers to monitor the efficacy and safety of TB treatment is essential to further reduce the likelihood of acquired drug resistance due to ineffectiveness or noncompliance with therapy, and to minimise the costs associated with prolonged TB treatment (Alsultan and Peloquin, 2014; Reid et al., 2019; Perumal et al., 2020; Sturkenboom et al., 2021).

Aim of the Thesis

To explore the PGx aspects, separately and in combination with PK factors, of anti-TB therapy in the Latvian population with a focus on INH and AGs.

Objectives of the Thesis

The following objectives are set to reach the aim of the Doctoral Thesis:

1. To determine the *NAT2* and *GSTM1* genotype frequencies in patients with DS-TB in Latvia.
2. To develop next-generation sequencing- and bioinformatics-based protocol for the full-length *CYP2E1* gene analysis.
3. To examine the association between the genetic determinants of key INH-metabolising enzymes (NAT2, CYP2E1, and GSTM1) with the PK parameters of INH and its two metabolites (AcINH, INA) in patients with DS-TB in Latvia**.**
4. To examine the association between the genetic determinants of key INH-metabolising enzymes (NAT2, CYP2E1, and GSTM1) and PK parameters of INH and its two metabolites (AcINH, INA) as potential predictors of treatment response and treatment outcome in patients with DS-TB in Latvia.

5. To examine the association between the genetic determinants of key INH-metabolising enzymes (NAT2, CYP2E1, and GSTM1) and the PK parameters of INH and its two metabolites (AcINH, INA) as potential predictors of DIH development in patients with DS-TB in Latvia.
6. To explore the frequency of AIHL-related *MT-RNR1* gene variants in the Baltic-speaking ethnic Latvian population and estimate their prevalence within population-specific mitochondrial haplogroups.

Hypotheses of the Thesis

1. In the Latvian population, gene variants of three key INH-metabolising enzymes (NAT2, CYP2E1, and GSTM1) and six PK parameters of INH and its two metabolites (AcINH, INA) are relevant for treatment response, outcome, and development of DIH in patients with DS-TB.
2. The prevalence of *MT-RNR1* gene variants and mitochondrial haplogroups previously associated with AIHL in the Baltic-speaking ethnic Latvian population is similar to that in global populations of European ancestry.

Novelty of the Thesis

Overall, this Thesis widens our knowledge of the application of precision medicine concepts in the context of anti-TB therapy, which, in turn, contributes to the progress of this research area and its application in clinical practice. This work is highly relevant for the determination and evaluation of PGx biomarkers of three key INH metabolising enzymes (NAT2, CYP2E1 and GSTM1), and for developing monitoring assays to address interindividual differences in the effectiveness and toxicity of INH, considering the underlying genetic composition, and is urgently relevant for patients with DS-TB. It is important to

note that our study considered six key PK parameters of INH and its two major metabolites (AcINH, INA) to ensure a more accurate assessment of clinical and genetic data. Additionally, the obtained genotyping results of the *MT-RNR1* gene in Baltic-speaking ethnic Latvians provided sufficient baseline knowledge, which may be extrapolated to patients with MDR-TB and underscores the importance of this approach. Overall, this Thesis widens our understanding of the application of precision medicine concepts in the context of anti-TB therapy, which, in turn, contributes to the advancement of this field of research and its application in clinical practice.

Discussion

INH PK properties can be influenced by various external factors, such as the patient's genetic make-up, age, gender, specific diet, comorbidities, and consequently, concomitant medications (Requena-Méndez et al., 2014). Specific gene variants of *NAT2* in the host, particularly in the presence of rapid metabolism, could promote the development of additional variants, leading to high-level resistance in *Mycobacterium tuberculosis* (Mtb) and progression to multi-drug resistance (Nagel et al., 2017). Therefore, the synergism of PGx and TDM could provide more accurate information on the bioavailability of the antimicrobial agents used, hence optimising the drug regimen; in turn, several studies have suggested that optimised dosing could improve drug exposure, reduce the possibility of acquired drug resistance, lower the costs associated with prolonged TB treatment, and reduce the incidence of ADRs (Ramachandran and Swaminathan, 2012; Pasipanodya et al., 2013; Alsultan and Peloquin, 2014; Reid et al., 2019; Perumal et al., 2020; Sturkenboom et al., 2021).

Characteristics of the NAT enzyme family

N-acetyltransferases (NATs) belong to phase II reaction drug- metabolising enzymes and are present in most eukaryotic species, as well as in prokaryotes (Wu et al., 2007). Cytosolic NAT enzymes catalyse the transfer of acetyl groups via the active site cysteine residue in the N-terminal region from endogenous acetyl-CoA to xenobiotics that favour aromatic amines, arylhydroxylamines, and hydrazine derivatives, as substrates, as well as the O-acetylation of their N-hydroxylated metabolites, thereby playing an important role in drug biotransformation and excretion (Wu et al., 2007; Sim et al., 2008). The two NAT enzymes present in humans, NAT1 and NAT2, exhibit different but overlapping substrate specificities (Klaassen, 2008).

Genetic diversity of *NAT2* acetylator statuses among patients with drug-susceptible tuberculosis in Latvia and comparative populations

It is important to note that in early genetic studies, *NAT2* variants were referred to as alleles; however, it is now understood that *NAT2* haplotypes represent specific combinations of multiple alleles within the gene (Gutiérrez-Virgen et al., 2023). In the Thesis, the term "alleles" is used, although technically they are haplotypes, based on the use of the term in databases and literature. This approach is a widely accepted and practical, particularly in the PGx context, as the term refers to an inheritable unit that may encompass multiple gene variants and influence pharmacological responses. In both the first and third studies, sequencing data analysis was performed using the human arylamine N-acetyltransferase gene sequence (X14672.1) as a reference. However, significant changes were made to the *NAT2* nomenclature in March 2024, coinciding with the transition to new allele definitions in the PharmVar database (NG_012246.1), which were also updated on the PharmGKB database. The legacy *NAT2*4* reference allele, commonly used in genetic studies, has now been classified as a gene variant and listed in PharmVar as *NAT2*4.001*. Despite this change, it remains suitable for comparisons involving the enzymatic or structural properties of polymorphic NAT2 proteins.

Interindividual variability in INH metabolism results from the high variability of the *NAT2* gene, and more than 65 variants within the 870-base pair (bp) long coding region of *NAT2* (Hein and Doll, 2012). The catalytic activity of *NAT2* depends on combinations of "rapid" alleles (*NAT2*4.001* (retired *NAT2*4*), *NAT2*4.002* (retired *NAT2*11A)*, *NAT2*1* (retired *NAT2*12A*), and *NAT2*4.003* (retired *NAT2*13*)) and "slow" alleles (*NAT2*5*, *NAT2*6*, and *NAT2*7*), which have been described as either slow acetylator (SA), intermediate acetylator (IA), or rapid acetylator (RA) status (Gross et al., 1999; Hein and Doll, 2012; Gutiérrez-Virgen et al., 2023). The acetylator status of the *NAT2* varies

considerably across geographical regions and is one of the most critical covariates in explaining the PK variability of INH and its implications for efficacy and toxicity (Thomas et al., 2022; Ignatius and Dooley, 2023). A study by Upton et al. (2001) revealed inter-ethnic differences in the prevalence and frequency of *NAT2* alleles, highlighting that the proportion of individuals with SA and RA statuses varies between ethnic groups. This is the first study to investigate the distribution of *NAT2* acetylator status in patients with DS-TB in Latvia. All individuals were of European ancestry; however, notable ethnic heterogeneity was observed. Specifically, 49 patients were Latvians, 30 were Russians, and 6 were of other ethnicity (1 Belarusian, 2 Ukrainians, 2 Poles, and 1 Lithuanian) reflecting the multi-ethnic composition of the country's population.

Of the 85 TB patients analysed for the *NAT2* acetylator status, 44 (51.8 %) were SA status carriers, 37 (43.5 %) were IA status carriers, and only four (4.7 %) individuals were classified as RA status carriers.

The results obtained for the SA phenotype were similar to those reported in individuals of European ancestry (Caucasian) and African Americans (40–60 %); in turn, SA status carriers were most prevalent among Northern Africans (90 %) and Scandinavians (75–80 %) and lowest in Canadian Eskimos and Japanese (5 %); in Chinese population, the proportion of SA status carriers is approximately 20 %, whereas in Africans, including Egyptians it exceeds 50 % (Hein et al., 2000; Sabbagh et al., 2011; Wang et al., 2016; Gutiérrez-Virgen et al., 2023). In this study, the proportion of SA status carriers did not differ significantly between Latvians and Russians (55.1 vs 46.7, respectively).

In addition, results from the third study on *NAT2* acetylator status diversity revealed that all patients were of European ancestry. During the genotyping analysis, *NAT2* SA status carriers was detected in 68% (23/34) of the patients, while *NAT2* IA status was identified in 32% (11/34).

Distribution of *NAT2* genotypes among patients with drug-susceptible tuberculosis in Latvia

A possible *NAT2* genotype was assigned based on the obtained genotyping data of the conventional 7-gene variant signature, as the presence or absence of signature variants linked to the resultant protein activity (Sim et al., 2014). For *NAT2* gene analysis of heterozygous samples, the amplified DNA fragment was cloned into a vector following standard procedures. Plasmids with confirmed *NAT2* gene inserts were purified from bacterial cultures, and the inserts were sequenced. The presence of different *NAT2* genotypes in patients with DS-TB in Latvia was investigated in both the first and third studies of this Thesis.

In total, 18 *NAT2* genotypes were observed in the first study, reflecting the high genetic variability in the study cohort. Individuals classified as SA status carriers belonged to the following most common genotypes: *NAT2*5/*5*, *NAT2*5/*6*, and *NAT2*6/*6*, observed in 15.3 %, 15.3 %, and 17.6 % of patients with TB in Latvia, respectively; IA status carriers belonged to the most common genotypes: *NAT2*4.001/*5*, *NAT2*4.001/*6*, observed in 10.6 %, 17.6 % of patients, respectively. No patients in the study cohort were classified as having a RA status. In the third study, 9 *NAT2* genotypes were observed. SA status carriers belonged to the following genotypes: *NAT2*5*/**5*, *NAT2*5*/**6*, *NAT2*6*/**6, NAT2*5*/**7*, and *NAT2*7*/**7*, observed in 0.324%, 0.176%, 0.118%, and both 0.029%, respectively; IA status carriers were linked to the following genotypes: *NAT2*4.001/*5*, *NAT2*4.001*/**6, NAT2*4.001*/**7* and *NAT2*1*/**5*, observed in 0.147%, 0.118%, and both 0.029%, respectively. While the results of these two studies differ, the relatively small number of patients in the third study (34 in total) should be taken into account. In the study by Hein (2009), the expression of NAT2 allozymes in a heterologous manner provided indirect evidence, implying a differential effect of *NAT2* variant alleles, and consequently

revealing heterogeneity within the SA status. Furthermore, recent findings have shown that individuals classified as *NAT2*6/6* genotype carriers exhibit a "very slow" acetylator status, and homozygous carriers show a higher risk of DIH (Huang et al., 2002; Leiro-Fernandez et al., 2011; Ruiz et al., 2012). However, due to the low number of the patients, statistically significant *NAT2*6/6* genotype-related differences were not observed in our studies.

Diversity of *NAT2* alleles among patients with drug-susceptible tuberculosis in Latvia and comparative populations

The first study on the allele distribution of *NAT2* revealed the presence of seven *NAT2* alleles in patients with DS-TB in Latvia: three SA status alleles (**5*, **6*, **7*), and four RA status alleles (**4.001*, **4.002*, **1*, **4.003*). The most frequent allele in the study cohort was *NAT2*6* with an observed frequency 0.388, followed by the SA *NAT2*5* and the RA *NAT2*4.001* alleles (absolute frequencies 0.306 and 0.194, respectively). These findings are consistent with previous studies in populations of European ancestry (Sabbagh et al., 2011). In the study conducted by Tiis et al. (2020), the average frequency of *NAT2*6* was approximately 30 %, while the *NAT2*5* allele typically prevailed in 50 % among individuals of European ancestry; in our study, the *NAT2*6* allele occurred slightly more frequently in both Latvian and Russian patients with TB. In contrast, in a study by Gra et al. (2010), the *NAT2*5* allele was the most prevalent in native Russians (frequency 0.416); the frequencies of the *NAT2*4.001* and *NAT2*6* alleles in Russians were reported to be 0.253 and 0.288, respectively. A possible explanation for these discordances could be the relatively small sample size (85 in total). Furthermore, the observed frequencies of the *NAT2*5* and *NAT2*6* alleles were not statistically significantly different in our cohort. It is important to note that the mixed ethnicity of the cohort, based primarily on the criteria of a specific infectious disease, could

complicate the scientific evaluation, and therefore it would be highly relevant to determine the frequency of *NAT2* alleles in historical groups of native Baltic-speaking ethnic Latvians. Similarly, the results of the third study on the allele distribution of *NAT2* revealed the presence of five *NAT2* alleles: three SA status alleles (**5*, **6*, **7*) mirroring the first study, and two RA status alleles (**4.001*, and **1*). The results of the two studies are not significantly different.

Characteristics of the GST enzyme family

The involvement of glutathione S-transferase (GST) enzymes in drug metabolism and their role in cell signalling pathways and apoptosis, is being studied extensively (Townsend and Tew, 2003). GSTs are eukaryotic and prokaryotic phase II detoxification enzymes that belong to a large multigene family of isoenzymes and are widely expressed across most living organisms (Townsend and Tew, 2003; Cummins et al., 2011). It has been suggested that GST quenches reactive molecules by binding glutathione to the enzyme hydrophilic G-bond with subsequent activation of the glutathione thiol group, thereby initiating conjugation to a xenobiotic substrate in the adjacent hydrophobic H-part of the enzyme, rendering the cell-dangerous compound more water-soluble and preventing it from binding to cellular proteins or nucleic acids, as reported by Eaton and Bammler (1999).

Genetic characteristics of the enzyme encoded by the *GSTM1* gene

In the research conducted by Pearson et al. (1993), human cytosolic mu-class GSTs were divided into five subgroups based on substrate differences and arranged in the following gene coding order: 5'-*GSTM4*-*GSTM2*-*GSTM1*-*GSTM5*-*GSTM3*-3'. The *GSTM1* gene was determined to have high variability with four different alleles (*GSTM1* null/null, *GSTM1* plus/plus, *GSTM1* plus/null, and *GSTM1*-duplex) (Board, 1981; Wu et al., 2012). The study by Xu

et al. (1998) suggested that the *GSTM1* null genotype of interest arose from recombination between two regions of high sequence homology flanking the locus of this gene, resulting in a deletion of a 20 kb long deoxyribonucleic acid (DNA) fragment that prevents the transcription and translation. This deletion, frequently observed in HeLa cells, may stem from an unequal crossing with *GSTM2* due to their high sequence homology, where overexpression of *GSTM2* compensates for the lack of *GSTM1* (Bhattacharjee et al., 2013). Notably, the *GSTM1* null genotype-environment interaction, as highlighted in a recent study by Nakanishi et al. (2022), increases the risk of various medical conditions, including oncology, neuropsychiatric disorders, gastroenterological diseases, pulmonary/respiratory issues, gynaecological/obstetric conditions, infectious diseases, and cardiovascular events. Additionally, in the context of DS-TB, studies have investigated another GST class enzyme, glutathione S-transferase T1 (GSTT1), encoded by the *GSTT1* gene. However, several studies have concluded that neither the *GSTT1* deletion genotype nor the *GSTM1*/*GSTT1* double deletion genotype is significantly associated with DIH (Li et al., 2013; Yang et al., 2019; Chanhom et al., 2020). For this reason, further investigation of *GSTT1* genotypes was not pursued in our studies.

Distribution of *GSTM1* genotypes among patients with drug-susceptible tuberculosis in Latvia and comparative populations

The findings by Nakanishi et al. (2022) revealed that this gene has a widespread null genotype or homozygous gene deletion, present in approximately 50% of individuals of East Asian and European ethnicities, however, the prevalence varies among populations and regions of continental origin, with important implications for achieving the goal of personalised medicine in clinical practice. The prevalence of the *GSTM1* null genotype in patients with DS-TB in Latvia was explored in both the first and third studies of

this Thesis. In the first study, the homozygous null mutation in *GSTM1* was detected in 48.2% (41/85) of the patients. Furthermore, the distribution of *GSTM1* null genotype in the cohort falls within the frequency range observed in populations of European ancestry (0.474–0.529), as reported by Kurose et al. (2012). More specifically, ethnicity-based subgroup analysis showed that the frequency of *GSTM1* null genotype did not differ significantly between Latvian and Russian patients with TB in the study cohort: in 53.1% (26/49) and 46.7% (14/30), respectively ($p = 0.647$), and were consistent with a previous study conducted in the Russian population (Gra et al., 2010). In the third study, the *GSTM1* null genotype was present in 58.8% (20/34) of the patients, while the *GSTM1* plus genotype was observed in 41.2% (14/34) of the patients. In particular, all the patients in the cohort were of European ancestry and despite the small number of participants, this finding was quite similar to the first study. Furthermore, a study by Kreile et al. (2016) revealed that the *GSTM1* null variant was present in 55.8% of childhood acute lymphoblastic leukaemia cases and in 47.9% of controls within the Latvian population, both of which fall within the frequency range observed in populations of European ancestry. These findings are consistent with the data presented in the first and third publications.

Characteristics of the cytochrome P450 enzyme family

Cytochromes P450 (CYPs) are a superfamily of haemoproteins found across all kingdoms of life, primarily functioning as monooxygenases (Danielson, 2002). In humans, these enzymes, which are predominantly membrane-associated, are located either in the inner mitochondrial membrane or in microsomes of hepatocytes and other cell types contributing to the oxidative, peroxidative and reductive metabolism of endogenous substrates such as steroids, fatty acids, bilirubin, and exogenous chemicals. Additionally, CYPs play a crucial role in hormone synthesis and breakdown, cholesterol synthesis,

vitamin D metabolism, and most hepatic drug metabolism (Nebert and Dalton, 2006; Zhao et al., 2021).

The human genome encodes at least 57 CYPs, classified into 18 families with at least 40% amino acid identity and 43 subfamilies sharing at least 55% amino acid identity, as reported by Zhao et al. (2021). Notably, the CYP1, CYP2, and CYP3 families are responsible for almost 80% of oxidative drug metabolism and approximately 50% of the total elimination of commonly used clinical drugs (Zhao et al., 2021). The particular interest in CYP-mediated drug metabolism is the variable response of individual patients to administered drugs, affecting the therapeutic action, safety, bioavailability, and drug resistance, thus, determining treatment outcomes (Sathyanarayanan et al., 2020). Genetic variability and epigenetic changes in CYP genes, along with intrinsic and extrinsic factors such as CYP expression levels, functional activity, diet, tobacco and alcohol consumption, and the inhibitory or inducing effects of co-administered drugs, contribute to inter-ethnic and interindividual variability in the therapeutic efficacy of many medications (Danielson, 2002; Liu et al., 2021; Zhao et al., 2021).

Genetic characteristics of enzymes encoded by *CYP2E1* gene

CYP2E1 is a membrane protein highly expressed in the liver and comprises almost 7 % of liver CYPs enzymes (Shimada et al., 1994). CYP2E1 expression and functional activity are inducible by many of its substrates, including isoniazid, ethanol and tobacco, but also by various dietary and pathophysiological conditions, such as fasting, obesity, uncontrolled insulin-dependent diabetes, and non-alcoholic liver disease (Desai et al., 2001; Danielson, 2002; Zhao et al., 2021). It should be emphasised that mitochondrial CYP2E1, as opposed to its microsomal counterpart, is the major source of alcohol- and drug-induced reactive oxygen species (ROS) production, thus,

contributing to oxidative DNA damage and toxicological effects, including DIH (Harjumäki et al., 2021).

In previously discussed INH metabolic pathways, it was proposed that oxidation of Hz and AcHz to reactive metabolites, thus playing an important role in INH-induced liver injury, is mediated by microsomal P450, in particular CYP2E1 (Preziosi, 2007; Tostmann et al., 2008; Ramappa and Aithal, 2013; Metushi et al., 2014). Furthermore, P450 are involved in the direct activation of INH, which binds to microsomal proteins in a nicotinamide adenine dinucleotide phosphate-dependent manner, however, the specific CYP family member responsible for this process remains unclear (Metushi et al., 2012; Wang et al., 2016).

The *CYP2E1* gene is highly variable, but unlike other members of the CYP450 family, there is a limited amount of information on the clinical significance of these variations. Only a few association studies investigating *CYP2E1* genetic variability and its implication for clinically relevant outcomes have provided level 3 conclusive evidence (clinical annotation) supporting a link between the functional role of specific alleles or gene variants in deviations in drug metabolism and/or response to treatment (Vuilleumier et al., 2006; Sun et al., 2008; Singla et al., 2014; Whirl-Carrillo et al., 2021).

The second study, "Next-Generation Sequencing and Bioinformatics-Based Protocol for the Full-Length *CYP2E1* Gene Polymorphism Analysis", demonstrated the successful development of the next-generation sequencing (NGS)-based assay to detect genetic variants dispersed throughout the entire *CYP2E1* gene, targeting all 9 gene exons with interleaving introns, untranslated (UTR), upstream, and intergenic regions. The high-level performance of the assay with sufficient data quality and a high degree of confidence indicated in the ability to detect all possible variants of interest. Importantly, this capability is not limited by the targeted screening of specific gene variants, or sequencing

of separate coding regions only. Compared to whole exome sequencing, which focuses only on protein-coding genes, full-length gene sequencing provides a more detailed analysis by also including regulatory and non-coding regions that are essential for understanding the gene`s function (Burdick et al., 2020). While whole exome sequencing covers a set of genes, it often overlooks these critical regions, which may have clinical significance. The method developed combines the versatility and quality of NGS data with cost-efficiency and technical simplicity, allowing for the simultaneous analysis of multiple regions of interest in the *CYP2E1* gene and facilitating the detection of clinically relevant gene variants.

In the third study the majority of the detected variants in the *CYP2E1* gene observed in 34 patients were intronic, one synonymous exonic, three variants located in a 3`UTR, five intergenic variants, and two – upstream. In the sample set, three allelic variants were identified, i.e. the intronic variants *CY2E1*1B* (rs2070676 G>C), and *CYP2E1*6* (rs6413432 T>A), and the upstream gene variant *CYP2E1*7A* (rs2070673 A>T). Of all identified gene variants, three (rs2515641 (T>C), *CY2E1*1B*, and *CYP2E1*6*) were classified as having clinical significance level 3 according to previous studies (Khrunin et al., 2010; Iacobucci et al., 2013; Richardson et al., 2018; Wu et al., 2019; Yu et al., 2019).

Integrative workflow of pharmacogenetic, pharmacokinetic, and patient-related factor assessment in drug-susceptible tuberculosis care

With regard to the Thesis, it is important to highlight that the efficacy of the PGx study, integrating PK profiling with patient-specific factors related to treatment response and INH-induced liver injury, is evaluated based on the workflow presented in Figure 1. The subsequent discussion sections will cover Figure 1 in a detailed manner.

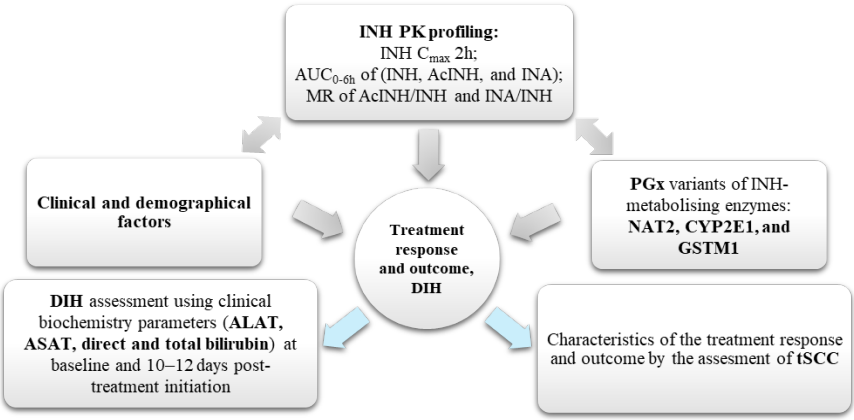

Figure 1 **Schematic representation of the integrative workflow of pharmacogenetic, pharmacokinetic, and patient-related factor assessment in DS-TB care***

* INH – isoniazid; PK – pharmacokinetic; C_{max} – maximum concentration; $AUC_{0–6h}$ – area under the curve 0−6 hours; AcINH – acetylisoniazid; INA – isonicotinic acid; MR – metabolic ratio; PGx – pharmacogenetics; NAT2 – N acetyltransferase 2; CYP2E1 – cytochrome P450 family 2 subfamily E member 1; GSTM1 – glutathione S-transferase M1 class; DIH – drug-induced hepatotoxicity; ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase; tSCC – time to sputum culture conversion.

** Study cohort comprised patients with diagnosed DS-TB (n = 34).

*** The reference ranges for transaminases, direct and total bilirubin were adopted from specific reference ranges of Riga East University Hospital Laboratory Service laboratory "Gaiļezers" to determine the upper limit of normal; DIH case was confirmed based on the increase of ALAT/ASAT values above the upper limit of normal with/without increase of total and conjugated bilirubin levels.

Isoniazid pharmacokinetic data

Using only 2 to 3 samples to predict area under the curve (AUC) values with high accuracy and precision can address the issue of inadequate assessment of drug exposure based solely on maximum concentration (C_{max}) at 2 hours of monitoring (Akkerman et al., 2014). In a study by Ignatius and Dooley (2023), INH demonstrated concentration-dependent bactericidal properties and correlated with AUC 0–24 hours or C_{max}, although the minimum inhibitory

concentrations (MIC) with clinical strains of Mtb vary across countries. NAT2 enzyme activity exhibits genetic variation, resulting in different plasma half-lives of INH: 70 minutes for RA status carriers and 2–5 h for SA status carriers (Brunton et al., 2005). In the third prospective study, plasma concentrations of INH, AcINH, and INA were determined at three time points (pre dose (0h), 2 and 6 hours after drug intake) using liquid chromatography-tandem mass spectrometry method. This approach aimed to evaluate the association of genetic and patient-related factors with six pharmacokinetic parameters: INH C_{max} at 2 hours, INH, AcINH, and INA area under the curve 0–6 hours ($AUC_{0\text{-}6h}$), and the metabolic ratio (MR) values of AcINH/INH and INA/INH, providing a more comprehensive and accurate assessment of the data.

Association of genetic and patient-related factors with isoniazid pharmacokinetic parameters

Our findings in the third study indicate that none of the PK parameters analysed differed significantly between patient groups stratified by biological sex, smoking status, body mass index (BMI), and self-reported daily alcohol intake. Additionally, neither age nor INH dose (mg/kg) correlated with any of INH PK parameters. However, a significant correlation between INH C_{max} at 2 hours and INA ($AUC_{0\text{-}6h}$) was observed in the entire cohort ($p = 0.0099$). Correlations between the PK parameters were significantly stronger when patients were stratified by acetylator status; most observed correlation coefficients were statistically significant, and clear *NAT2* inter-phenotypic differences in INH and metabolite correlation patterns were identified. The mean and median values of PK parameters differed significantly between the *NAT2* SA and IA groups, except for INA $AUC_{0\text{-}6h}$. Specifically, the INH $AUC_{0\text{-}6h}$ and C_{max} at 2 hours values were significantly higher, while the AcINH $AUC_{0\text{-}6h}$ values were significantly lower in the slow *NAT2* acetylators. Additionally, the median values of the AcINH/INH and INA/INH MR were significantly lower in

the *NAT2* SA group. Furthermore, the data confirmed findings from previous studies carried out in adult population with DS-TB, indicating that plasma levels of INH and its metabolites differed significantly between *NAT2* groups (Thomas et al., 2022; Ignatius and Dooley, 2023). Variants in the *NAT2* gene, which play a key role in regulating enzyme activity, have been found to significantly affect the enzyme regulation process (WHO, 2022a). In light of this, the World Health Organization has outlined detailed strategies for adjusting INH doses according to the patient's *NAT2* acetylator status, ensuring a more tailored and effective treatment (WHO, 2022a). Additionally, incorporating *NAT2* genotyping into routine clinical practice could be particularly valuable, especially in populations with high variability in *NAT2* acetylator status, facilitating more precise management of TB treatment.

In contrast, stratifying patients according to their *GSTM1* genotype did not improve the correlation coefficients for PK parameters, nor did it reveal distinct grouping patterns. No significant differences were observed in any of the PK parameters between individuals with *GSTM1* plus and *GSTM1* null genotypes. Experimental approaches to assessing the impact of *GSTM1* null genotypes on absorption, distribution, metabolism, excretion, and toxicity remains very limited (Arakawa, 2013). Most studies have focused on *NAT2* variability as the main factor influencing variations in the rate of INH metabolism. However, the role of *GSTM1* in relation to INH kinetics has not been sufficiently investigated and the information currently available is limited. Further research is needed to determine whether and how *GSTM1* variants might affect INH metabolism and clinical outcomes.

Similarly, PK parameters were compared between groups of patients divided according to the presence or absence of each *CYP2E1* gene variant. Our data indicate that only the *CYP2E1*6* allelic variant (rs6413432) was associated with significantly higher values of INH $AUC_{0\text{-}6h}$, while the median values of both AcINH/INH and INA/INH MRs were significantly lower. None of the additional identified gene

variants, including two allelic variants – *CYP2E1*4* (rs6413419) and *CYP2E1*7A* (rs2070673) – previously associated with potential impacts on enzyme function of CYP2E1, exhibited statistically significant associations. The *CYP2E1*6* allelic variant, located in intron 6 and recognized by the DraI restriction endonuclease (Fang et al., 2017), has been linked to altered *CYP2E1* messenger ribonucleic acid (mRNA) expression (Uematsu et al., 1994). While clinical studies, such as that by O'Shea et al. (1997), have noted inter-phenotypic differences in INH inhibition of CYP2E1 activity among carriers with SA status, in vitro studies have demonstrated no significant CYP2E1 inhibition by INH or its metabolites (Balhara et al., 2021). Treatment of DS-TB involves several drugs, including RIF, a CYP2E1 inducer, raising concerns about potential drug-drug interactions that may affect INH metabolism or lead to ADRs through increased production of reactive metabolites, particularly in carriers of SA status (Shen et al., 2008; Yamada et al., 2009). Further research is needed to explore the functional implications of *CYP2E1* gene variants on drug response and clinical outcomes.

Association of genetic and patient-related factors, and isoniazid pharmacokinetic parameters with tuberculosis treatment outcome and time to sputum culture conversion

In the third study, time to sputum culture conversion (tSCC) was used as a treatment response marker, determined by the number of days to the first negative inoculation on Löwenstein-Jensen medium (including the last day), indicating the treatment outcome. Despite the variability in INH exposure, a high TB treatment success rate of 94.1 % was achieved. Most patients were cured, 82.4 % (28/34), while 11.8 % (4/34) completed the treatment, and 5.9 % (2/34) were lost to follow-up. Overall, tSCC data were available for 28 patients. The median tSCC was 52 days (range: 11–197 days); 57.1% (16/28) became Mtb culture-negative in less than 60 days, while for 12 patients (42.9%) tSCC was

exceeded 60 days. Despite this, no significant associations between patient-related factors and treatment outcomes were noted.

Smoking status has previously been identified as an essential risk factor associated with adverse effects on TB treatment success, including delayed sputum culture conversion and prolonged treatment duration (Silva et al., 2018; WHO, 2022b). In the third study, smoking was significantly associated with positive sputum microscopy, underscoring its negative impact. Nonetheless, both smokers and those with positive sputum microscopy results were more likely to achieve a "cured" treatment outcome compared to the "treatment completed" or "lost to follow-up". This finding could be attributed to the fact that patients with positive sputum microscopy result were treated in the hospital until the sputum microscopy was confirmed negative, rather than being treated as outpatients, thereby achieving better treatment adherence.

Another objective of our study was to determine the possible relationship between INH PK and TB treatment outcomes. In our study, it should be noted that the majority of patients (64.7%) exhibited INH C_{max} at 2-hour levels below the therapeutic reference range at the 2-hour time point. Our findings support the perspective that current therapeutic ranges may be excessively high, given the overall favourable treatment success rates observed (Perumal et al., 2020). Furthermore, our results indicated that patients with tSCC time less than 60 days had significantly higher INA/INH MR ($p = 0.026$). This observation was further supported by the Cox regression model, which considered age, sex, smear microscopy, and standardised AcINH/INH ratios across the entire cohort. The model revealed that a one-unit increase in the standardised AcINH/INH MR was associated with a probability of 58% to achieve SCC first. Somewhat controversially, recent studies have reported that longer tSCC and an increased probability of unsuccessful outcomes or recurrence were more frequently observed among patients with low INH C_{max} at 2 hours and/or AUC

concentrations. However, the results of different studies tend to vary, and the involvement of contributing factors remains understudied (Sekaggya-Wiltshire et al., 2018; Ramachandran et al., 2020). Nevertheless, other research, including our current study, have not observed any correlation between INH concentrations and treatment effectiveness.

Even so, in the third study, no effects of *GSTM1* genotype on TB treatment outcomes or tSCC were observed. Similarly, no significant associations were identified between any analysed *CYP2E1* gene variants, *NAT2* acetylator status, and either tSCC or treatment outcomes.

Conversely, the variability in results may be due to differences in study populations, various influencing factors, and the study`s design. TB treatment outcomes are complex and multifactorial events, influenced by factors such as bacillary load, Mtb strain, MIC values estimated specifically for individuals or local populations based on regional Mtb prevalence and resistance patterns, treatment adherence, drug absorption, drug interactions, drug concentration at the site of TB infection, patient demographics, comorbidities, and immune and nutritional status (Colangeli et al., 2018; Perumal et al., 2020). Recent findings have highlighted a significant difference in INH concentration between lung/airway epithelial lining fluid and blood plasma, suggesting potential drug accumulation at the site of disease, which may explain the efficacy of first-line regimens (McCallum et al., 2021).

Association of genetic and patient-related factors, and isoniazid pharmacokinetic parameters with drug-induced hepatotoxicity

Decades of clinical observations have identified several untoward treatment-related effects associated with INH therapy, including gastrointestinal, neurological, disorders, rheumatological conditions, skin reactions, and idiosyncratic hepatotoxicity, all of which contribute to significant morbidity

leading to reduced treatment effectiveness (Ramappa and Aithal, 2013; Ignatius and Dooley, 2023).

Approximately 2 to 28 % of patients taking INH experience a transient increase in serum alanine aminotransferase (ALAT)/aspartate aminotransferase (ASAT) levels, typically occurring 4 to 8 weeks after the start of INH therapy without the need for discontinuation, and the incidence increases with age; in turn, severe liver injury and even liver failure occur in approximately 0.1 % of all patients (Wang et al., 2016; Yang et al., 2019; Ignatius and Dooley, 2023). In the third study, transaminase levels increased in 4 patients (11.76 %) after 10–12 days of the anti-TB therapy, resulting in mild DIH in one patient and moderate DIH in another. Notably, two of these patients had elevated ALAT/ASAT levels prior to starting therapy, and one patient experienced simultaneous changes in total and conjugated bilirubin levels. Additionally, severe DIH cases developed in two patients. While our findings align theoretically with global incidence reports, it's important to interpret this result cautiously due to potential variations in the definition of DIH across different studies. Consistency in the demographics of the study population was noted, as previously highlighted, when comparing the characteristics of patients in both DIH and non-DIH groups. This raises the question of the potential molecular mechanisms driving hepatotoxicity.

Furthermore, no significant associations were observed between DIH and patient-related factors such as age, BMI group, self-reported alcohol consumption, smoking status, or INH dose (mg/kg). Previously, Molla et al. (2021) have reported that males were significantly less likely to develop DIH than females. In our study biological sex was slightly associated with DIH, with males having 85 % lower odds than females, however, statistical significance was not reached ($p = 0.071$).

Previous studies suggest that INH plasma levels are higher in SA carriers, leading to increased accumulation and altered elimination of toxic metabolites

(Gupta et al., 2013; Lei et al., 2021; Sileshi et al., 2023). These metabolites mainly form covalent adducts to liver macromolecules, manifesting as hepatocellular necrosis and potentially triggering immune responses (Peretti et al., 1987; Lei et al., 2021). Moreover, due to its high affinity, INH could also bind to key enzymes in cytokine pathways such as peroxidase (Metcalfe et al., 2008). All of these factors may contribute to the high incidence of DIH, while patients with RA status are at increased risk of treatment failure (Sileshi et al., 2023). The results of the third study showed that DIH occurred exclusively in patients with *NAT2* SA (n = 4). However, a statistically significant difference was not reached between the *NAT2* SA and IA status groups. Notably, among the INH PK parameters, AcINH $AUC_{0\text{-}6h}$ was significantly lower in patients with DIH ($p = 0.019$).

Previous studies on the PGx variability of *CYP2E1* have been reported to affect *CYP2E1* mRNA and protein expression and susceptibility to DIH, particularly in the context of the synonymous variant rs2515641, while the *CYP2E1*1B* CG genotype (rs2070676) has been shown to be associated with the development of ADRs in patients with latent TB infection (Yu et al., 2019; Chen et al., 2020). However, no direct proofs for any analysed variants of *CYP2E1* gene contribution in DIH were observed in our study. Nevertheless, we did not observe any effect of *GSTM1* genotype on DIH. However, the results remain controversial as different populations show different effects of the *GSTM1* null genotype on genetic susceptibility to DIH; for example, prevalence studies of the *GSTM1* null genotype in patients with Central Asian ethnicity and in Japanese population (Sotsuka et al., 2011; Chanhom et al., 2020) showed an increased risk of DIH, although data from European (Leiro et al., 2008), Indian and Chinese (Wang et al., 2016) populations did not show consistent results. In the INH metabolic pathways discussed above, GSTs play a role in the detoxification of reactive intermediates produced by the oxidation

of Hz and AcHz (Klein et al., 2016). GST also plays an important role in the binding of cytochrome P450 activated compounds to glutathione. At present, the metabolites produced by GST detoxification have not yet been identified (Sotsuka et al., 2011; Wang et al., 2016). The null genotype may result in reduced total catalytic activity of GST enzymes, leading to bioaccumulation of toxic metabolites and their binding to macromolecules in liver cells, which may result in liver cell necrosis (Lei et al., 2021).

Thus, the first hypothesis was only partially confirmed. Gene variants of three key INH-metabolising enzymes (NAT2, GSTM1, and CYP2E1) were not significantly associated with tSCC, anti-TB treatment outcomes, or the development of DIH in patients with DS-TB in Latvia. In contrast, one of the six INH PK parameters (AcINH) was relevant to the development of INH-related liver injury. While none of the INH PK parameters were linked to treatment outcome, decreased INA/INH and AcINH/INH MRs were associated with Mtb culture positivity in sputum at month 2.

Despite these findings, the results presented in this Thesis are significant for the further development of personalised medicine approaches in TB treatment. Although no direct associations between genetic factors and treatment outcomes were found, the variability in study results emphasises the complexity of TB treatment effects. These data suggest that a multiple-dimensional approach integrating genetic, PK, and patient-related factors is essential for the development of personalised treatment strategies. Ultimately, our study confirms the potential of personalised medicine in the treatment of TB, demonstrating that individual patient profiles, including MRs and risk factors such as smoking, can significantly influence treatment success. Future TB eradication programmes should consider all these data to improve treatment adherence and efficacy, thereby paving the way for more personalised and effective TB control strategies.

Characteristics of aminoglycosides

AGs remain crucial pharmacotherapeutics commonly prescribed worldwide that exhibit broad-spectrum antibacterial properties with high effectiveness against both gram-positive and gram-negative bacteria, mycobacteria, and in some cases against amoeboid and protozoa (Kim et al., 2022). AGs demonstrate concentration-dependent bactericidal properties, so the ratio of the plasma C_{max} to the MIC of the microorganism is a key indicator of AG efficacy. Furthermore, AGs have demonstrated persistent suppression of bacterial growth after brief exposure, a phenomenon known as the post-antibiotic effect, which explains high-dose, extended-interval dosing regimens (MacDougall, 2017). AG exerts its therapeutic function by specifically inhibiting protein synthesis in prokaryotic cells through irreversible binding to the 16S ribosomal ribonucleic acid (rRNA) decoding site in the 30S subunit of the bacterial ribosome. Although this binding does not prevent the formation of the translation initiation complex, it stops further translation of the mRNA and interferes with the initiation of protein synthesis. AG also induces mistranslation of mRNA, leading to premature termination of translation with detachment of the ribosomal complex, and incompletely synthesised protein or incorporation of incorrect amino acids, resulting in the production of truncated and non-functional proteins. Consequently, this led to an induced stress response, resulting in cell death, through collapse of the bacterial membrane (MacDougall, 2017; Kim et al., 2022).

Aminoglycoside adverse drug reactions

However, the use of AGs carries significant side effects, primarily affecting the vestibular and auditory organs (ototoxicity), kidneys (nephrotoxicity), and neuromuscular junctions, and synapses (MacDougall, 2017). These ADRs occur over a wide range of frequencies. Neuromuscular

transmission disorders are relatively rare, whereas ototoxicity occurs in 6 to 62% (auditory) and 0 to 19 % (vestibular) of patients, while the incidence of nephrotoxicity varies from 0 to 50 % of patients (Lanvers-Kaminsky and Ciarimboli, 2017). AG-induced ototoxicity can cause irreversible, bilateral, high-frequency hearing loss or vestibular hypofunction (Kim et al., 2022 Specific factors can increase the risk of drug-induced ototoxicity, including prolonged exposure to high levels of ambient noise, the concurrent use of specific therapeutic agents, such as loop diuretics, quinine and salicylate analgesics, platinum-based anticancer drugs, macrolide antibiotics, glycopeptides, and patient genetic background (Cianfrone et al., 2011; Kim et al., 2022). Prolonged treatments, such as those required for MDR-TB, often result in hearing impairment, with various studies identifying hearing loss as a notable ADR in MDR-TB patients (Jiang et al., 2017; Barbarino et al., 2016). Most drug resistance issues arise from the length of treatment, particularly in terms of tolerability and adherence, as the longer duration required to treat MDR-TB increases the risk of poor treatment adherence and treatment failure (Duggal and Sarkar, 2007).

Functional damage and cellular degradation of the inner ear may occur after administration of any AG, which, depending on the structures affected, is distinguished between cochlear ototoxicity, primarily affecting hearing, and vestibular toxicity, including changes in the semicircular canal affecting balance (Jiang et al., 2017; Lanvers-Kaminsky and Ciarimboli, 2017). A contributing factor to AG-induced ototoxicity is their prolonged half-life, estimated to be around 2–3 hours in blood plasma, but five to six times longer in ear fluids. The increased sensitivity of inner ear sensory cells to AGs may be due to this prolonged presence, together with their role in generating ROS (Jiang et al., 2017). Meanwhile, *MT-RNR1* gene encoding the mitochondrial ribosomal 12S

subunit is a hotspot for AIHL variants, but there is a variability in the nature and frequency of genetic changes in different populations (Barbarino et al., 2016).

Genetic diversity of ototoxicity-related mtDNA *MT-RNR1* gene variants in the Baltic-speaking ethnic Latvian population and comparative populations

The human genome contains a circular mtDNA of 16 569 bp, comprising 37 genes (Barshad et al., 2018). These genes are responsible for the production of 13 polypeptides essential for the oxidative phosphorylation system, along with critical ribonucleic acid components for translation, including 12S and 16S rRNAs, 22 transfer ribonucleic acids (tRNAs), and several non-coding RNAs (Dong et al., 2020; Jones et al., 2021; Kim et al., 2022).

The mitochondrial genome has some unique genetic features, including maternal inheritance, heteroplasmy, threshold effects and mitotic segregation, as well as a relatively high error rate due to the scarcity of the error-checking system (Dong et al., 2020; Wei and Chinnery, 2020). The number of mtDNA copies varies with cellular energy requirements, ranging from 500–2000 copies in lung and liver cells to 4000–6000 copies in cardiac and skeletal muscle cells (Jones et al., 2021). Unlike nuclear DNA, the mitochondrial genome is intronless, with approximately 93 % of its sequence coding, meaning that any genetic variant could potentially have significant functional consequences (Lopez Sanchez et al., 2021). While some variants are recurrent across multiple populations, others are unique to specific individuals. The pathogenic role of many of these variants, particularly in hearing loss, remains to be fully validated and characterised.

In the fourth study, 7.3 % of DNA samples (14/191) showed *MT-RNR1* gene variants in ethnic non-related Latvians; 10 samples were from females (9.3 %) and 4 from males (4.8 %) ($p = 0.273$). All detected mtDNA gene variants were homoplasmic and were present in separate DNA samples. The results revealed the presence of six different genetic changes in the *MT-RNR1* gene.

The most common gene variants observed in this study were m.961insC(n) and m.961T>G with a frequency of 2.09 % (4/191). Both variants were significantly more common among ethnic Latvians than in the general USA population (White Americans) ($p = 0.0273$ and $p = 0.0406$, respectively) (Tang et al., 2002). Additionally, their frequencies were higher in Latvians than those reported in the Polish population (0.6 % and 0.8 %, respectively); however, the difference was not statistically significant for this study cohort (Rydzanicz et al., 2009). Several studies have suggested that the insertion of cytosines at position m.961 in the sequence may enhance the phenotypic effects of two variants (1555A>G and 1494C>T) by indirectly affecting the tertiary structure of rRNA and its ability to bind AGs (Li et al., 2004; Li et al., 2005). However, it should be noted that m.961 is localised in cluster C of the mtDNA genome, between rRNA loops 21, and 22 and this region is not evolutionarily conserved (Li et al., 2004).

Further, the m.827A>G and m.951G>A gene variants were each identified in 2 out of the 191 DNA samples (estimated frequency in our cohort = 1.05 %); the frequency of the m.827A>G gene variant in Latvians was consistent with those reported in Poland and the USA (1.05 versus 0.2 and 0.78, respectively) (Rydzanicz et al., 2009; Ealy et al., 2011). This gene variant is localised between species in a highly conserved region of the 12S rRNA encoding the ribosomal A site across species (Barbarino et al., 2016). Furthermore, this genetic alteration has been associated with both non-syndromic hearing loss and AG-induced ototoxicity (Barbarino et al., 2016; Jiang et al., 2016). However, the incomplete penetrance of hearing loss induced by this variant requires the contribution of modulating factors such as nuclear modifier genes, exposure to ototoxic drugs, or the influence of the mtDNA haplotype, which may be required for the clinical phenotypic consequences to manifest (Jiang et al., 2016).

The 1555A>G and 1494C>T mtDNA variants mentioned above are located in the highly conserved coding region of the human 12S rRNA gene, adjacent to each other, but do not form a bp. These variant positions participate in the formation of the aminoacyl-tRNA acceptor site (A site) of the small ribosomal subunit. The presence of the 1555A>G or 1494C>T induces the formation of a bp between 1555A-1494T or 1494C-1555G, resulting in the addition of a terminal bp at the end of the stem loop. This structural change makes the 12S mitoribosomes more similar to prokaryotic ribosomes, where the A site of 16S rRNA is the binding target of AGs (O'Sullivan et al., 2017). The significance of these variants has been experimentally demonstrated by establishing a bacterial ribosomal background incorporating human mitoribosome. In this system, residues of the A site in helix 44 of bacterial 16S rRNA were replaced with homologous fragments of eukaryotic A-site sequences (both wild-type and mutant) (Hobbie et al., 2008b; O'Sullivan et al., 2017). Mitohybrid ribosomes showed reduced protein synthesis in vitro, correlating with increased antibiotic toxicity (Hobbie et al., 2008b; O'Sullivan et al., 2017). Thus, mitochondrial dysfunction may be indicative of both dose-dependent and genetically inherited susceptibility to AG-induced ototoxicity (Hobbie et al., 2008b; O'Sullivan et al., 2017). Thus, mitochondrial dysfunction may be indicative of both dose-dependent and genetically inherited susceptibility to AG-induced ototoxicity. Nevertheless, this pathogenic variant has been rarely detected in the populations of China and White Americans, with carrier frequencies of 0.024 % and 0.05 %, respectively (Ealy et al., 2011; Han et al., 2016). While both m.1555A>G and m.961T>A variants were identified in one carrier each with an estimated frequency of 0.52% in our fourth study cohort. The observed prevalence of the m.1555A>G variant in Latvians (i.e. 0.52) was statistically similar to frequencies reported in studies from Finland, Poland, the USA, New Zealand and the United Kingdom (Scrimshaw et al., 1999;

Rydzanicz et al., 2009; Ealy et al., 2011; Rahman et al., 2012; Soini et al., 2017). In addition, the pathogenic m.1555A>G variant is frequently reported among patients with AIHL in Asian populations, reaching up to 13.3 % and 33% in China and Japan, respectively, while a high frequency of 17 % has been observed in adult patients with non-syndromic hearing loss in the Spanish population, (Li et al., 2005; Lu et al., 2010; Yano et al., 2014).

In contrast, the 1095T>C variant is located in a conserved region of the 12S rRNA located close to the P site of the small subunit of the ribosome, indicating its important role in the initiation of mitochondrial protein synthesis. This nucleotide substitution disrupts an evolutionarily conserved bp in the helix 25 loop of 12S rRNA (Wang et al., 2005). The effect of this variant on the tertiary or quaternary structure of the rRNA can lead to a reduction in mitochondrial protein synthesis, interference with translation, a significant decrease in cytochrome c oxidase activity, and, consequently, mitochondrial dysfunction and hearing impairment (Thyagarajan et al., 2000). In general populations or in normal hearing controls worldwide, the m.1095T>C variant has been exceptionally uncommonly documented. Nevertheless, it has been associated with sensorineural hearing loss in patients from the Russia (Dzhemileva et al., 2009), China and Japan (Li et al., 2005; Lu et al., 2010; Yano et al., 2014). However, three *MT-RNR1* gene variants previously linked to AIHL – m.961delTinsC(n), m.1494C>T, and m.1095T>C – were not detected in our cohort (Tang et al., 2002; Ealy et al., 2011).

Impact of mtDNS haplogroups on aminoglycoside-induced ototoxicity

mtDNA haplogroups (hgs) can be used in modern population genealogy studies and are defined by variants detected in the mitochondrial genome. Affiliation with one of the ancient maternally inherited clans varies across populations (Wei and Chinnery, 2020). While the association between hgs and

inherited diseases or disorders remains ambiguous and lacks strong evidence, some studies have indicated a correlation between hg membership and disease prevalence, such as in Parkinson's disease (Hudson et al., 2013), Alzheimer's disease (Santoro et al., 2010), type II diabetes (Ye et al., 2013), male infertility (Ruiz-Pesini et al., 2000), and multiple sclerosis (Tranah et al., 2015). So far, no clear association between AG-induced ototoxicity, mtDNA variants, and patient hg affiliation has been established. To date, no definitive association has been established between AG-induced ototoxicity, mtDNA variants, and patient hg affiliation. For instance, hg analysis of carriers of the m.961 variant indicates that patients belong to different hgs. This observation suggests that variants at this sequence position have arisen independently multiple times and that different ethnic groups may share this variant (Rydzanicz et al., 2010).

However, in order to evaluate the occurrence of *MT-RNR1* gene variants within specific maternal hgs, the mtDNA hg composition in the samples has been analysed. The six *MT-RNR1* gene variants mentioned above were found in four mtDNA hgs: H, U, T, and J; these hgs were also the most frequent in our sample cohort.

Hg H, which is the most frequent mtDNA hg in all European populations except the Saami, accounted for 38.74% of the samples in this study. Among the hg H samples, three different *MT-RNR1* gene variants were identified: m.961T>G – in four samples, m.951T>A – in two samples, and m.961T>A – in one sample. None of these variants were detected in samples belonging to other mtDNA hgs. All four m.961T>G-positive samples belonged to the subclade H11a of the hg H. Although the m.961T>G variant is also found in different hgs, it is most frequently observed in hg H members (Tang et al., 2002), suggesting its possible neutrality in this hp.

Approximately one-third (32.46%) of the mtDNA variants in this study belonged to the hg U. This observation aligns with earlier studies of the Latvian

gene pool and neighbouring populations (Pliss et al., 2006). All four m.961insC(n)-positive samples in this study were part of hg U, with an estimated frequency of 6.45% for this mtDNA hg. Nevertheless, this genetic alteration has been observed in mtDNA hgs of European ancestry (hp T), Native American/Asian ancestry (hp A), and at least one other mtDNA hp in the USA. These observations suggest that that multiple ethnic groups may be susceptible to carrying this variant (Tang et al., 2002).

To summarise, the second hypothesis was partially confirmed. The two AG ototoxicity-related variants (m.1555A>G and m.827A>G) were identified, both of which are also found in general population. Potentially pathogenic variants (m.961insC(n) and m.961T>G) did not align with the findings in Central European ancestry studies of the general population. In contrast, the m.951G>A variant was consistent with data from the general population of Central European ancestry. Notably, additional variants previously linked to AIHL (m.961delTinsC(n), m.1494C>T, and m.1095T>C) were not detected in our cohort. The majority of observed mtDNA variants were part of hgs commonly found in European populations, supporting the partial confirmation of the hypothesis.

Conclusions

1. The predominance of *NAT2* SA and IA statuses compared to RA status was observed, and the *GSTM1* null genotype frequency was comparable to those documented in global populations.
2. NGS-based full-length sequencing of the *CYP2E1* gene offers high-confidence detection of gene variants with precision and cost-effectiveness, enabling the simultaneous analysis of multiple genomic regions.
3. All but one of the PK parameters of INH and its metabolites were dependent on *NAT2* acetylator status, while *GSTM1* gene variants showed no effect. Additionally, the *CYP2E1*6* (T>A) allelic variant was associated with INH $AUC_{0\text{-}6h}$ and both AcINH/INH and INA/INH MR in patients with DS-TB in Latvia. These findings indicate that combined genotyping approaches are warranted in PGx and TDM studies and highlight the potential clinical implications of such approaches.
4. Genetic factors such as *NAT2* acetylator status, *GSTM1* genotype, and the analysed *CYP2E1* gene variants were not significantly associated with either tSCC or anti-TB treatment outcomes. Several INH PK parameters, however, were significantly associated with anti-TB treatment effects: (a) Decreased values of INA/INH and AcINH/INH MRs were associated with Mtb culture positivity in sputum at month 2; (b) A higher MR of the standard dose of INH was associated with a higher probability of initial cure, while an inefficient MR of INH was unfavourable.
5. These findings may contribute to the future development of personalised medicine strategies in anti-TB treatment.
6. Genetic factors such as *NAT2* acetylator status, *GSTM1* genotype, and the analysed *CYP2E1* gene variants were not significantly associated with DIH development. Among all PK parameters, only a decreased level of

AcINH was associated with DIH. Thus, AcINH plasma levels may serve as a biomarker for INH-related liver injury.

7. The presence of six *MT-RNR1* gene variants, including two AIHL-related (m.1555A>G and m.827A>G) and three potentially pathogenic variations (m.961insC(n), m.961T>G and m.951G>A), in the Baltic-speaking ethnic Latvian population of European ancestry highlights the need to include ototoxicity-related variant analysis in future studies to evaluate the feasibility of mtDNA screening of patients prior to the administration of AG therapy.

Proposals

1. The inclusion of INH and its metabolites in TDM, using three time points to accurately and precisely predict AUC values, together with the determination of the MIC of clinical Mtb strains and the performance of PGx screening, could be beneficial in clinical studies to determine optimal dosing strategies.
2. The results of our study demonstrated that PK parameters of INH and its metabolites were dependent on *NAT2* acetylator status. Furthermore, a decreased levels of AcINH were associated with DIH, highlighting the importance of PGx variations in drug exposure. However, further studies are required to decipher DIH-related mechanisms.
3. The presence of *MT-RNR1* gene variants associated with AIHL in the Baltic-speaking ethnic Latvian population highlights the need to include ototoxicity-related variant analysis in future studies. This inclusion is crucial for assessing the feasibility of DNA screening for patients prior to the initiation of AG therapy.
4. It is essential to emphasise the need for further research to assess whether allelic variants in drug-metabolising enzymes confer a risk of suboptimal response to TB drugs and susceptibility to ADRs in patients with diverse ancestral backgrounds, thereby promoting a PGx knowledge base specific to diverse human populations.

List of publications and reports on the topic of the Thesis

Publications:

1. **Igumnova, V.**, Capligina, V., Krams, A., Cirule, A., Elferts, D., Pole, I., Jansone, I., Bandere, D., Ranka, R. (2016). Genotype and allele frequencies of isoniazid-metabolizing enzymes NAT2 and GSTM1 in Latvian tuberculosis patients. *J Infect Chemother*. 22(7), 472–7. https://doi.org/ 10.1016/j.jiac.2016.04.003

2. **Igumnova, V.**, Kivrane, A., Viksna, A., Norvaisa, I., Ranka, R. Next-Generation Sequencing and Bioinformatics-Based Protocol for the Full-Length CYP2E1 Gene Polymorphism Analysis. (2022). *Pharmgenomics Pers Med*. 15, 959–965. https://doi.org/10.2147/PGPM.S371709

3. **Ulanova, V.**, Kivrane, A., Viksna, A., Pahirko, L., Freimane, L., Sadovska, D., Ozere, I., Cirule, A., Sevostjanovs, E., Grinberga, S., Bandere, D., Ranka, R. (2024). Effect of NAT2, GSTM1 and CYP2E1 genetic polymorphisms on plasma concentration of isoniazid and its metabolites in patients with tuberculosis, and the assessment of exposure-response relationships. *Front Pharmacol*. 15, 1332752. https://doi.org/10.3389/fphar.2024.1332752

4. **Igumnova, V.**, Veidemane, L., Vīksna, A., Capligina, V., Zole, E., Ranka, R. (2019). The prevalence of mitochondrial mutations associated with aminoglycoside-induced deafness in ethnic Latvian population: the appraisal of the evidence. *J Hum Genet*. 64(3), 199–206. https://doi.org/ 10.1038/s10038-018-0544-6

Reports and theses at international congresses and conferences:

1. **Ulanova, V.**, Kivrane, A., Viksna, A., Pahirko, L., Norvaisa, I., Ranka, R. (2023, July 8−12). Exploring the role of single nucleotide variants in CYP2E1 gene: possible implications for tuberculosis pharmacogenetic studies. The Biochemistry Global Summit Tours, The 47th FEBS congress: FEBS Open Bio, Tours, France. Book of Abstracts, 219.

2. **Igumnova, V.**, Kivrane, A., Viksna, A., Pahirko, L., Ozere, I., Bogdanova, I., Krams, A., Cirule, A., Grinberga, S., Sevostjanovs, E., Bandere, D., Ranka, R. (2022, July 14−19). The assessment of first-line anti-tuberculosis drug exposure, inflammatory biomarkers and pulmonary tuberculosis severity association with treatment response. The Biochemistry Global Summit Lisabon, The 46th FEBS congress: FEBS Open Bio, Lisabon, Portugal. Book of Abstracts, 318.

3. **Igumnova, V.**, Kivrane, A., Viksna, A., Freimane, L., Sadovska, D., Capligina, V., Pahirko, L., Ozere, I., Norvaisa, I., Bogdanova, I., Krams, A., Cirule, A., Pugovics, O., Solveiga, G., Sevostjanovs, E., Bandere, D., Ranka, R. (2022, March 25−26). Importance of clinical pharmacogenetic-pharmacokinetic studies in unravelling determinants of tuberculosis treatment outcomes: findings and implications in Latvia. International Scientific Conference on Medicine organized within the frame of the 80th International Scientific Conference of the University of Latvia: Medicina (Kaunas), Riga, Latvia. Book of Abstracts: 58, (Suppl 1), 47.

4. **Igumnova, V.**, Kivrane, A., Freimane, L., Pole, I., Viksna, A., Capligina, V., Sevostjanovs, E., Grinberga, S., Bandere, D., Ranka, R. (2021, March 24−26). Mapping the potential of pharmaco-metabolomics for personalised antituberculosis therapy. Knowledge for Use in Practice, Riga Stradinš University International Research Conference on Medical and Health Care Sciences, Riga, Latvia. Book of Abstracts, 253.

5. **Igumnova, V.**, Veidemane, L., Pole, I., Viksna, A., Kivrane, A., Bandere, D., Ranka, R. (2020, February 5−7). Genotype and allele frequencies of anti-tuberculosis drug metabolizing enzymes NAT2, GSTM1 and XHD in Latvian tuberculosis patients. Expanding the Druggable Proteome with Chemical Biology, EMBL Heidelberg, Germany. Book of Abstracts, 88.

6. **Igumnova, V.**, Veidemane, L., Pole, I., Vīksna, A., Ozere, I., Čapligina, V., Bandere, D., Ranka, R. (2020, January 23−March 20). Exploring pharmacogenetics aspects of anti-tuberculosis treatment in Latvian tuberculosis patients. International Scientific Conference on Medicine organized within the frame of the 78 International Scientific Conference of the University of Latvia: Medicina (Kaunas), Riga, Latvia. Book of Abstracts: 56, (Suppl 1), 15.

7. **Igumnova, V.**, Veidemane, L., Zole, E., Pole, I., Vīksna, A., Bandere, D., Ranka, R. (2017, October 19−20). Screening for mitochondrial DNA mutations associated with antibiotic-induced and non-syndromic deafness in the ethnic Latvian population. 2nd International Conference in Pharmacology: From Cellular Processes to Drug Targets (ICP2017RIGA), Riga, Latvia. Book of Abstracts: Intrinsic Activity. 5 (Suppl. 2): A2.11, doi:10.25006/IA.5.S2-A2.11

8. **Igumnova, V.**, Capligina, V., Bandere, D., Krams, A., Cirule, A., Jansone, I., Ranka, R. (2015, September 29th–3rd October). Distribution of genotypes of NAT2 and GSTM genes in tuberculosis patients in Latvia. 75th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2015, Düsseldorf, Germany. Accessed: https://www.fip.org/abstracts?page=abstracts&action=item&item=12097

Reports and theses at local congresses and conferences:

1. **Igumnova, V.**, Veidemane, L., Pole, I., Vīksna, A., Bandere, D., Ranka, R. (2018, 22.−23. marts). Allele Genotyping of Arylamine N-acetyltransferase 2 Gene in Latvian Population: Comparison of Two Methods. RSU Zinātniskā konference, Sekc. "Infekcijas slimības un imunoloģija", Rīga, Latvija. Tēzes, 10. lpp.

2. **Igumnova, V.**, Pole, I., Čapligina, V., Ozere, I., Bandere, D., Ranka, R. (2017, 6.−7. aprīlis). Prettuberkulozes līdzekļu blakusparādību ietekmējošo ģenētisko faktoru izpēte bērnu tuberkulozes gadījumā. RSU Zinātniskā konference, Sekc. "Infekcijas slimības un imunoloģija", Rīga, Latvija. Tēzes, 10. lpp.

3. **Igumnova, V.**, Čapligina, V., Pole, I., Krams, A., Cīrule, A., Ozere, I., Šķenders, Ģ., Bandere, D., Jansone, I., Ranka, R. (2016, 17.−18. marts). Izoniazīda metabolizējošo enzīmu gēnu analīze Latvijas tuberkulozes slimniekiem. RSU Zinātniskā konference, Sekc. "Latvijas iedzīvotāju veselību apdraudošo eksogēno un endogēno faktoru izpēte", Rīga, Latvija. Tēzes, 49. lpp.

4. **Igumnova, V.**, Bandere, D., Ranka, R. (2015, 26.−27. marts). Prettuberkulozes līdzekļu blakusparādību ietekmējošo faktoru izpēte. RSU Zinātniskā konference, Sekc. "Latvijas iedzīvotāju veselību apdraudošo eksogēno un endogēno faktoru izpēte", Rīga, Latvija. Tēzes, 118. lpp.

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