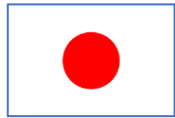


Integrated application of human and pathogen genomic information for improvement of treatment outcome and control of drug-resistance in Asian tuberculosis patients



Principal Investigator:
Katsushi Tokunaga
(Director, Genome Medical Science Project, National Center for Global Health and Medicine)



Thai-side Principal Investigator:
Surakameth Mahasirimongkol
(Senior Physician, Department of Medical Sciences, Ministry of Public Health)



Indonesian-side Principal Investigator:
Rika Yuliwukandari
(Dean, Faculty of Medicine, UPN Veteran Jawa Timur)



1. Collection of bioresources and establishment of "Integrative Asian TB Genome Database"

2. Identification of genomic biomarkers

2.1. Host factors

2.2. Pathogen factors (*under submission*)

2.3. Host-pathogen interaction

3. Drug response and predictive algorithm

3.1. Drug response gene

3.2. Development of predictive algorithm

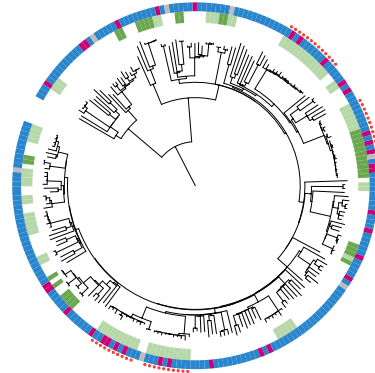
4. HLA in COVID-19 patients and related studies (*in preparation*)

1. TB Control Strategy Utilizing WGS (whole genome sequencing) of *Mycobacterium tuberculosis* (MTB)



MTB whole genome sequencing

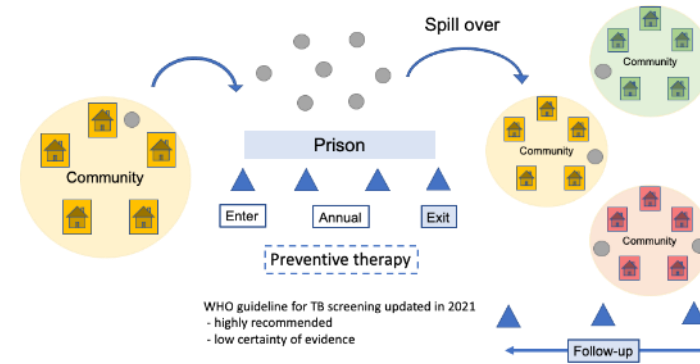
Lineage identification



Strain and subspecies typing

- Clustered case (cut-off 5)
- Clustered case (cut-off 12)
- Formerly incarcerated
- No history of incarceration
- Large cluster (cut-off 12)

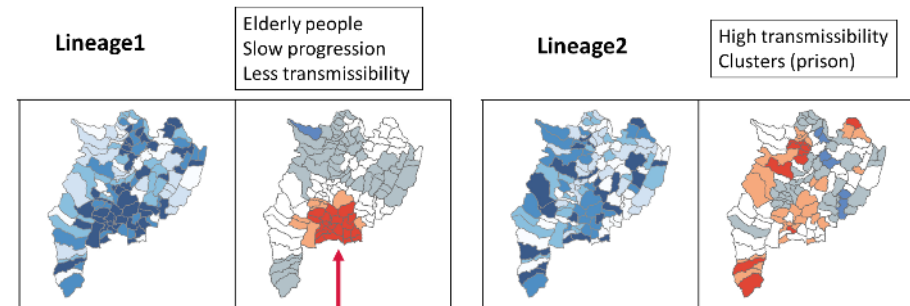
Clustering and Outbreak



We published Lineage 2 and prison are risk factors for clustering (Miyahara R, *et al. Tuberculosis* 2020), and TB screening positivity among contacts (Miyahara R, *et al. EID* 2022)

Surveillance

Lineage-dependent spatially targeting screening?



Screening targeting elderly people (especially who had risk of TB) in the areas of TB lineage1 hotspots

Screening household contacts
 Screening in prison

Drug resistance genotype

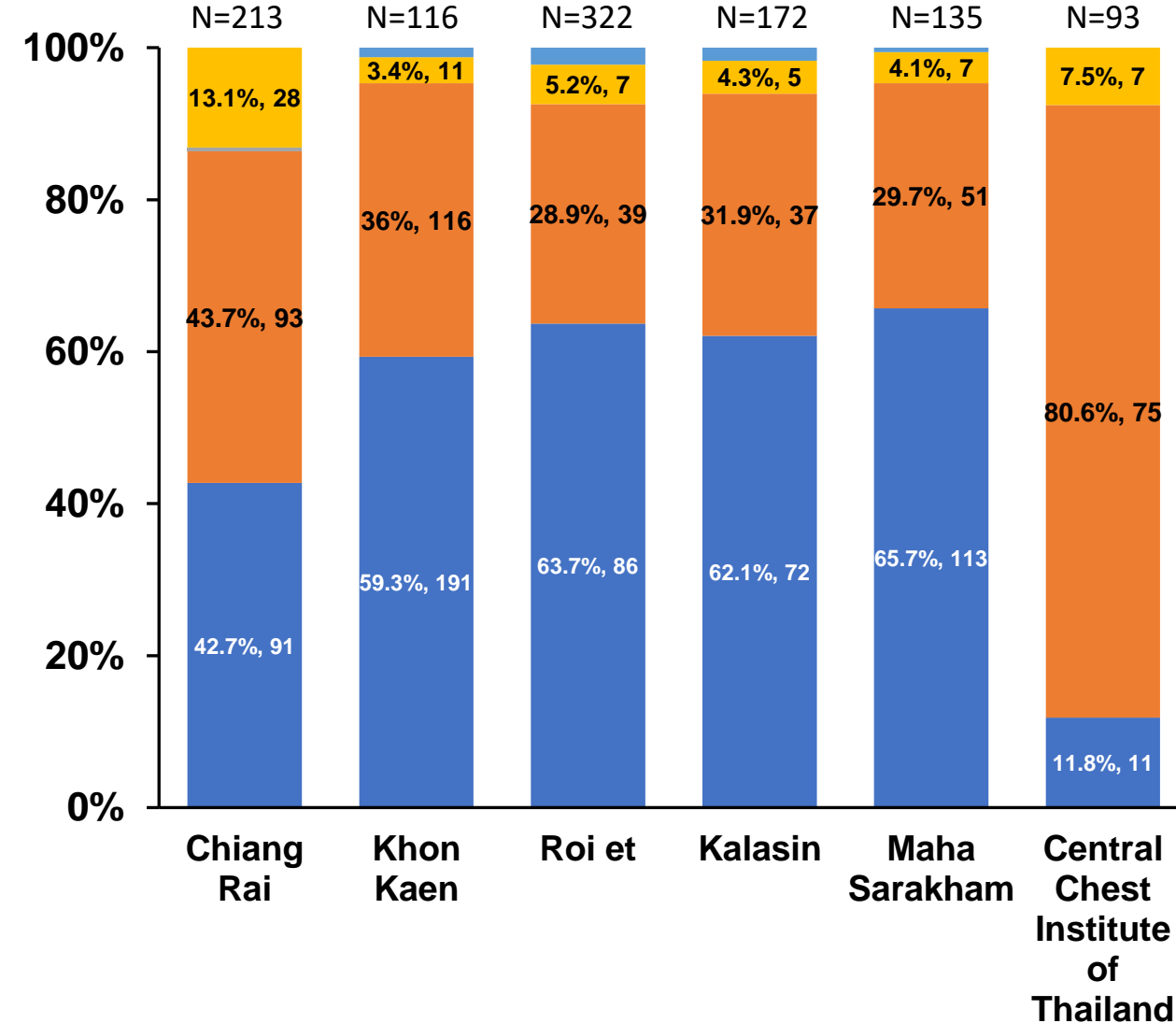
Mutation associated with Drug resistance in MTB

Drug susceptibility	
Drug	Phenotype
RIF	Resistant
INH	Resistant
ETH	Susceptible
PZA	Susceptible

2 publications based on WGS of MTBC (Thawornwattana Y, *et al. Microb Genom* 2021; Netikul T, *et al. Sci Rep* 2022)

MTB lineages

■ lineage1 ■ lineage2 ■ lineage3 ■ lineage4 ■ MIXED



**HAP3 Cohorts:
- WGS of MTB
- human genomic DNAs**

**Received DNAs = 1,152
QC pass = 1,070
WGS pass = 1,051**

	lineage1	lineage2	lineage3	lineage4	MIXED
Chiang Rai	91 (42.7%)	93 (43.7%)	1 (0.5%)	28 (13.1%)	0
Khon Kaen	191 (59.3%)	116 (36%)	0	11 (3.4%)	4 (1.2%)
Roi et	86 (63.7%)	39 (28.9%)	0	7 (5.2%)	3 (2.2%)
Kalasin	72 (62.1%)	37 (31.9%)	0	5 (4.3%)	2 (1.7%)
Maha Sarakham	113 (65.7%)	51 (29.7%)	0	7 (4.1%)	1 (0.6%)
Central Chest Institute of Thailand	11 (11.8%)	75 (80.6%)	0	7 (7.5%)	0
Total	564	411	1	65	10

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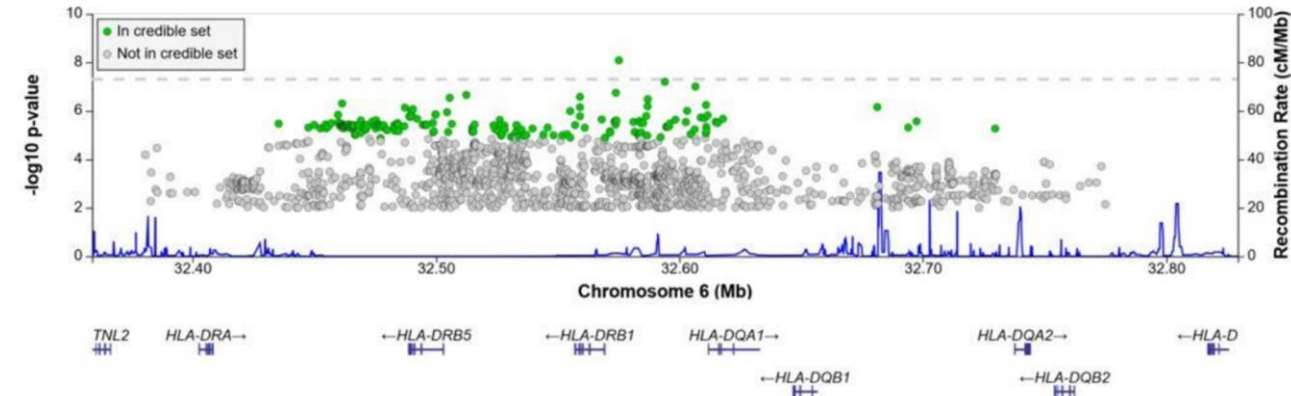
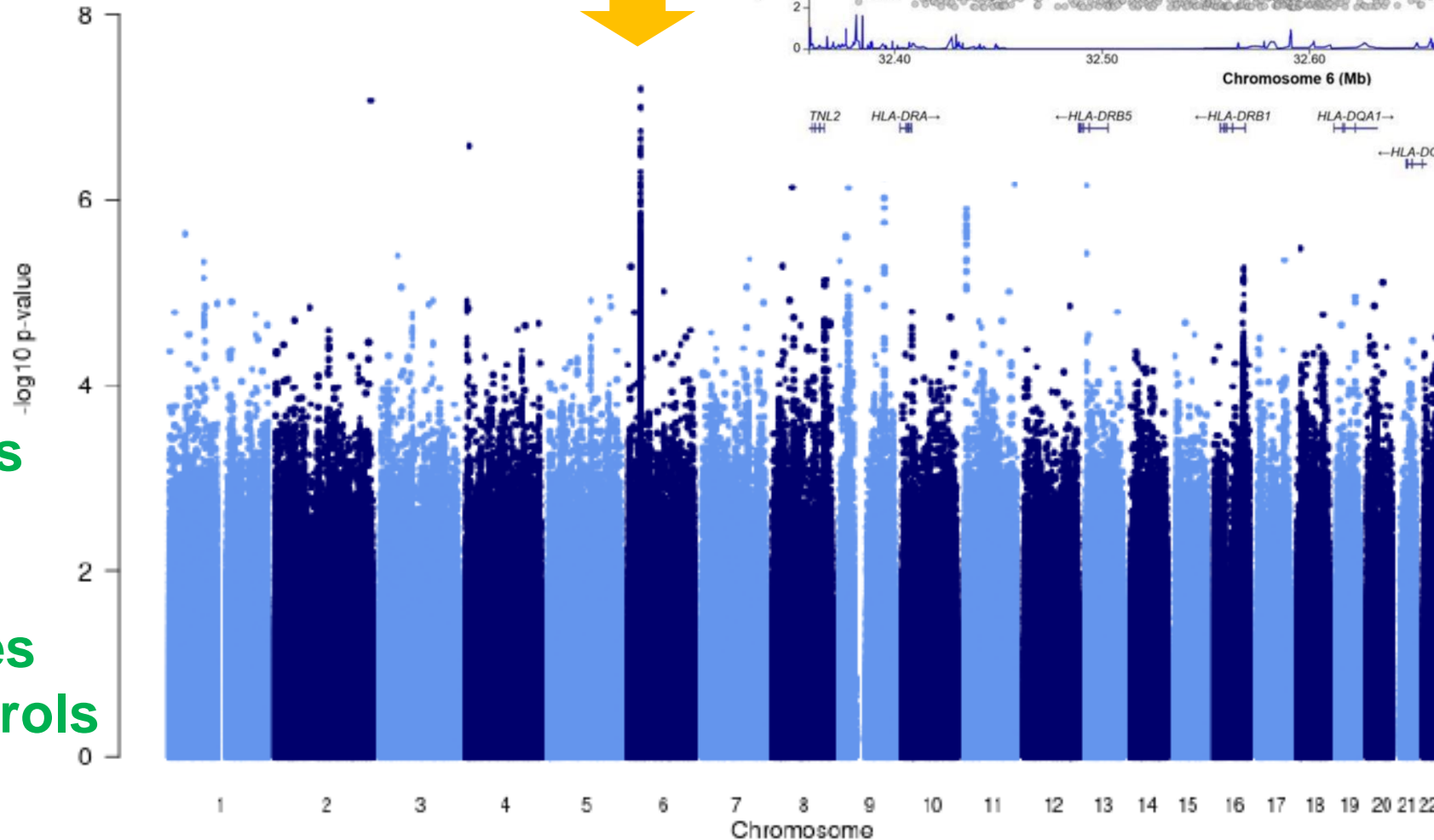
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2.1 International Meta-GWAS (host genetics) for Tuberculosis

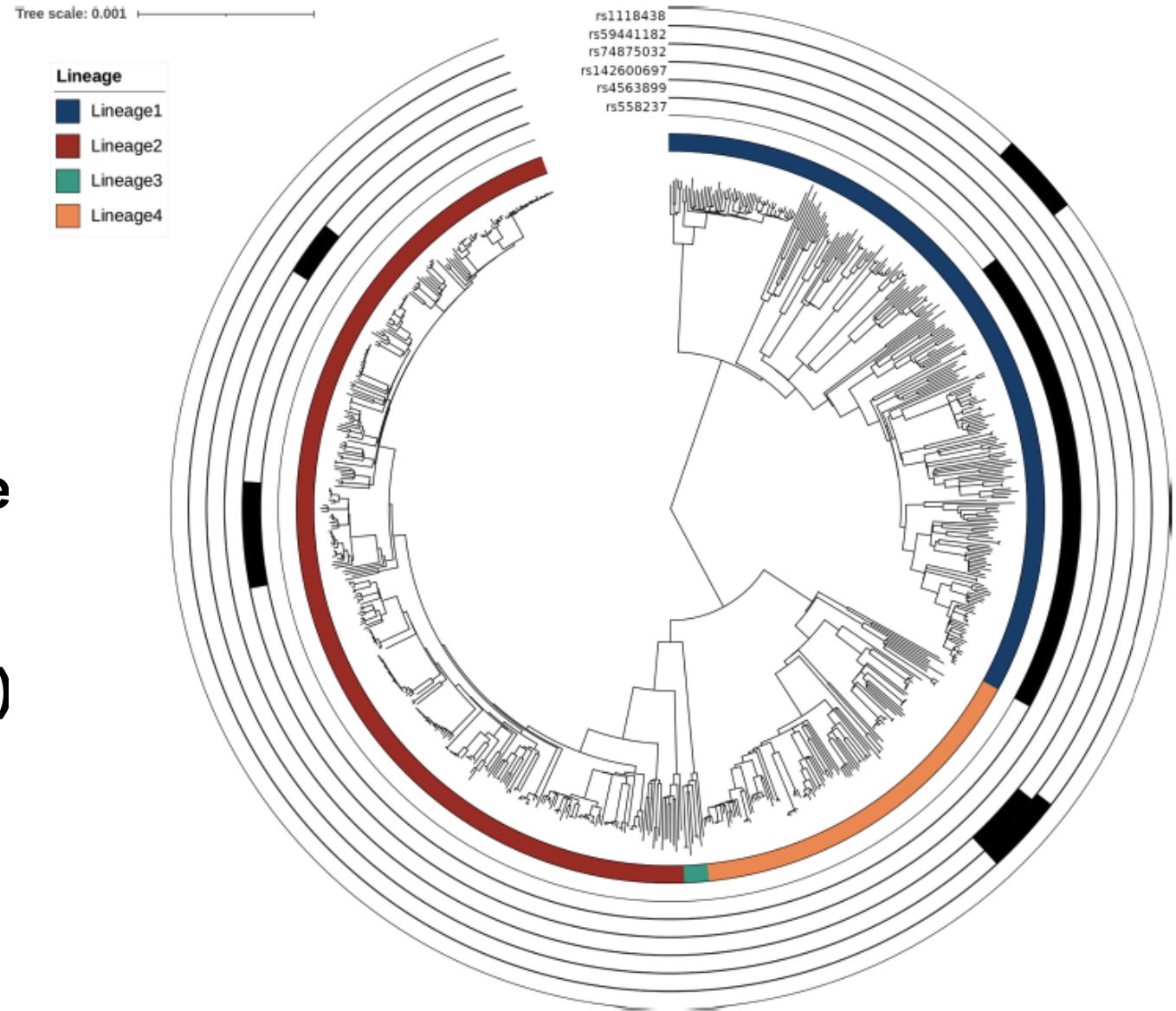
10 countries
>20 labs

14,153 cases
19,536 controls



2.3 Host-Pathogen GxG Analysis for Tuberculosis

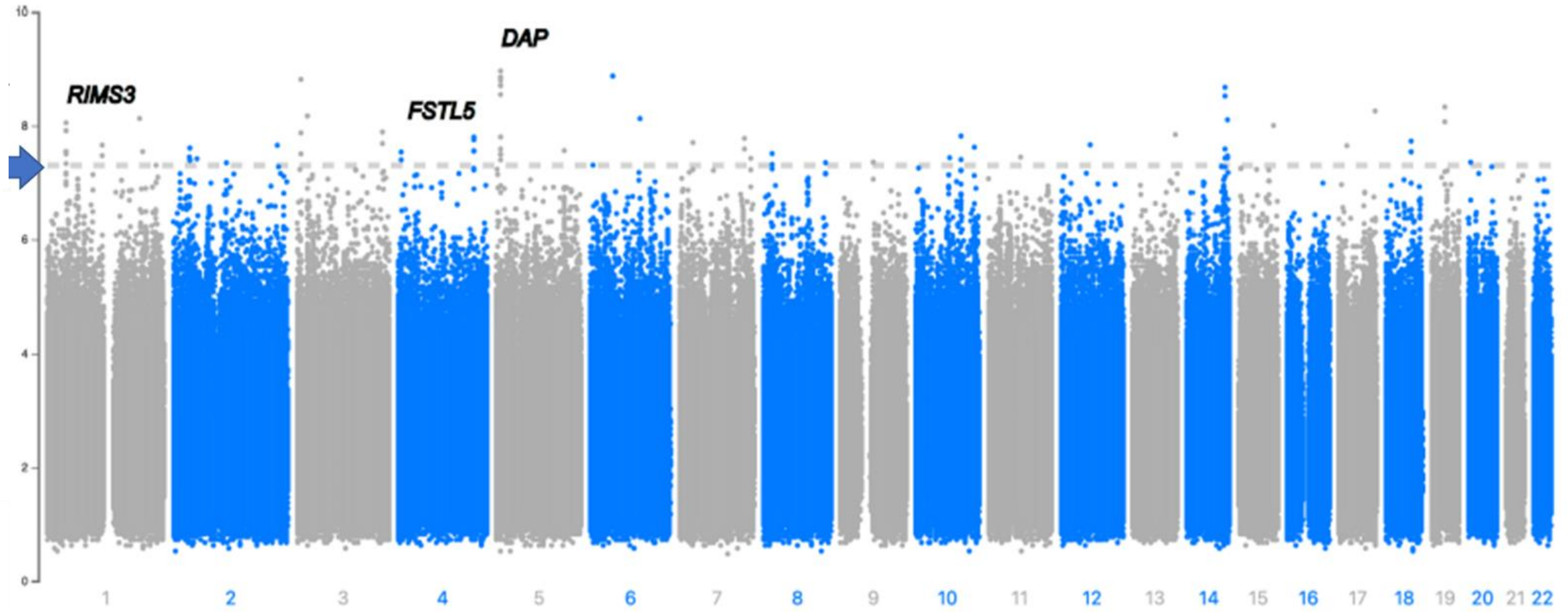
A phylogenetic tree for the Thailand *M. tuberculosis* with the top host genome-to-genome association hits (human rs numbers) and the associated nodes highlighted (black bands)



2.3 GxG Association Analysis for Tuberculosis

8 gene regions including *FSTL5* were detected ($p < 5 \times 10^{-8}$)

DAP and *RIMS3* link to the IFN γ cytokine and host immune system



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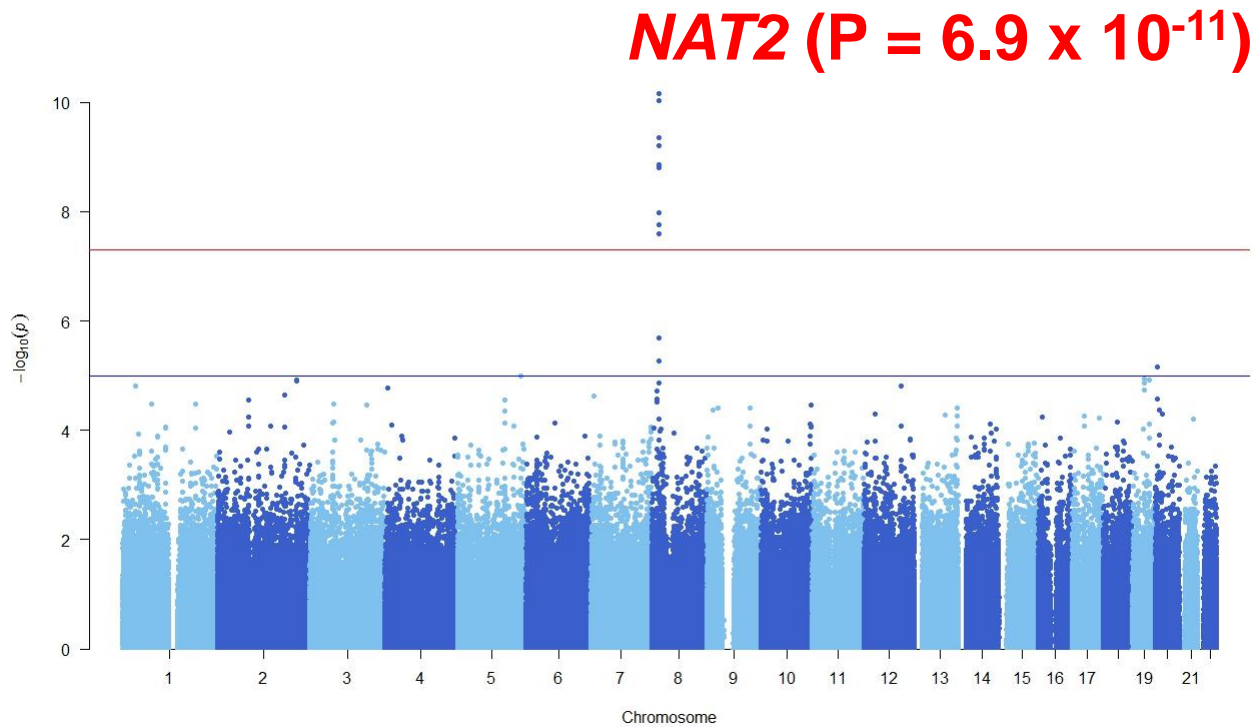
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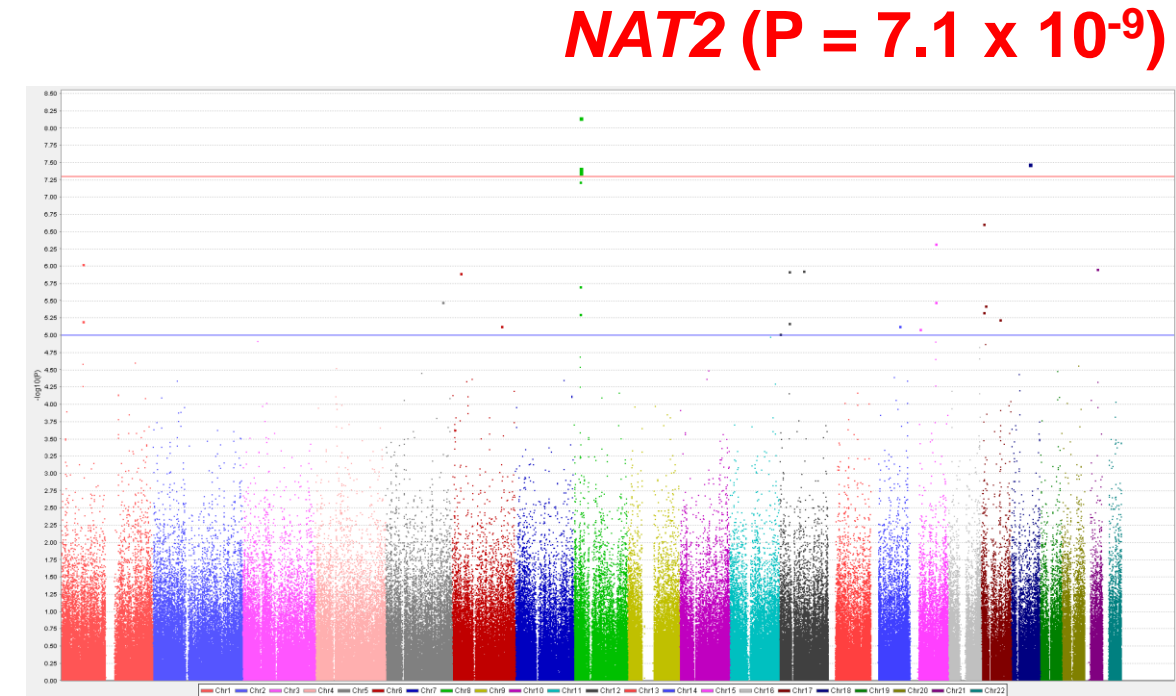
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3.1 GWAS for Adverse Drug Reactions and Pharmacokinetics in TB Patients

Liver injury induced by anti-TB drugs
(SATREPS, 79 cases vs 239 controls)

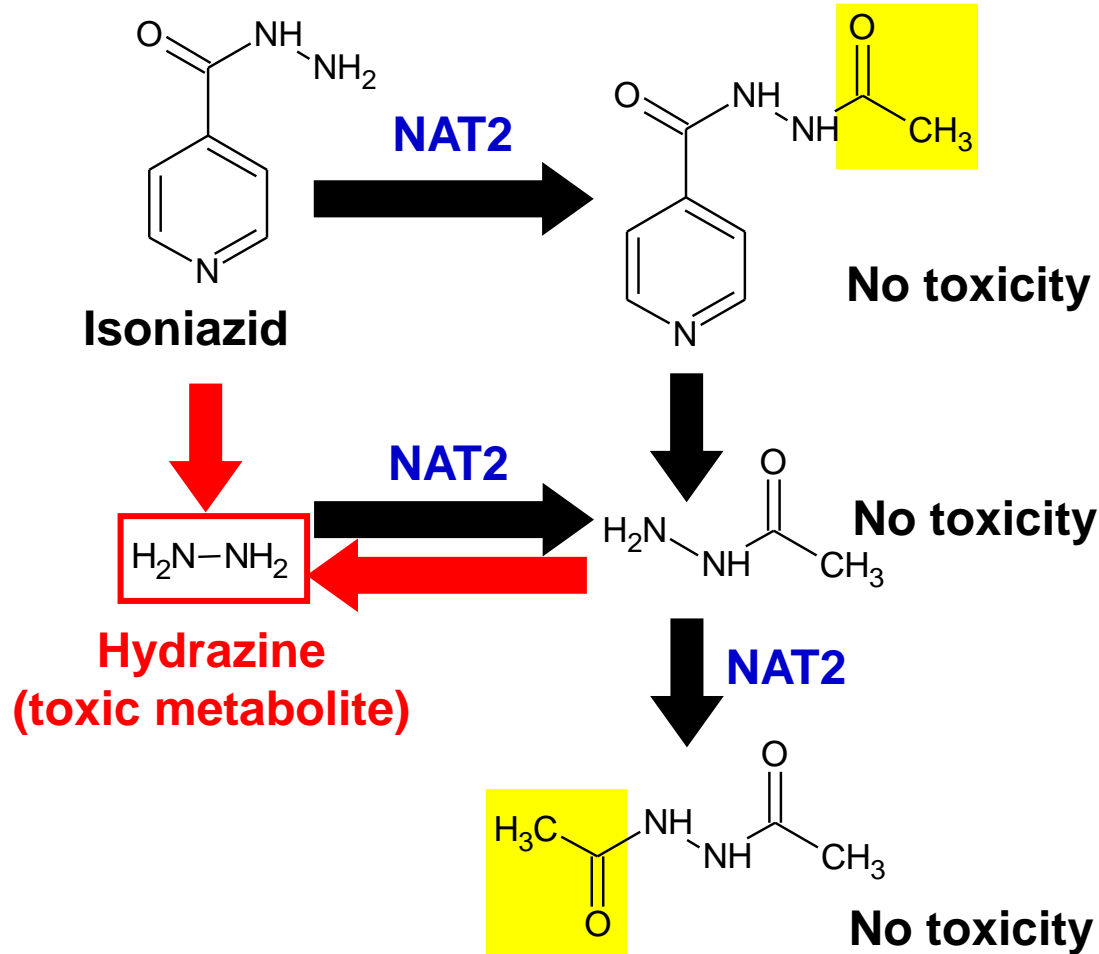


Isoniazid levels in blood
(e-ASIA JRP, 66 cases)

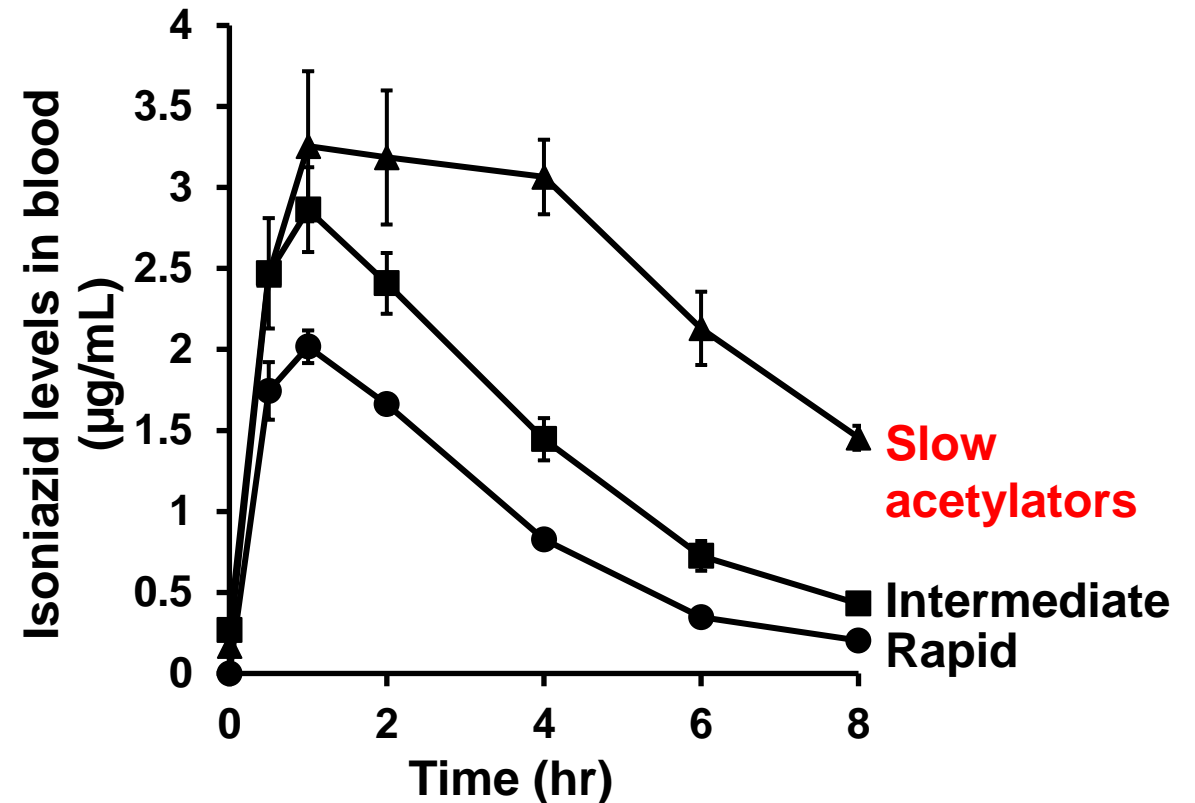


Suvichapanich *et al. Antimicrob Agents Chemother.* 63(8): e02692-18 (2019)

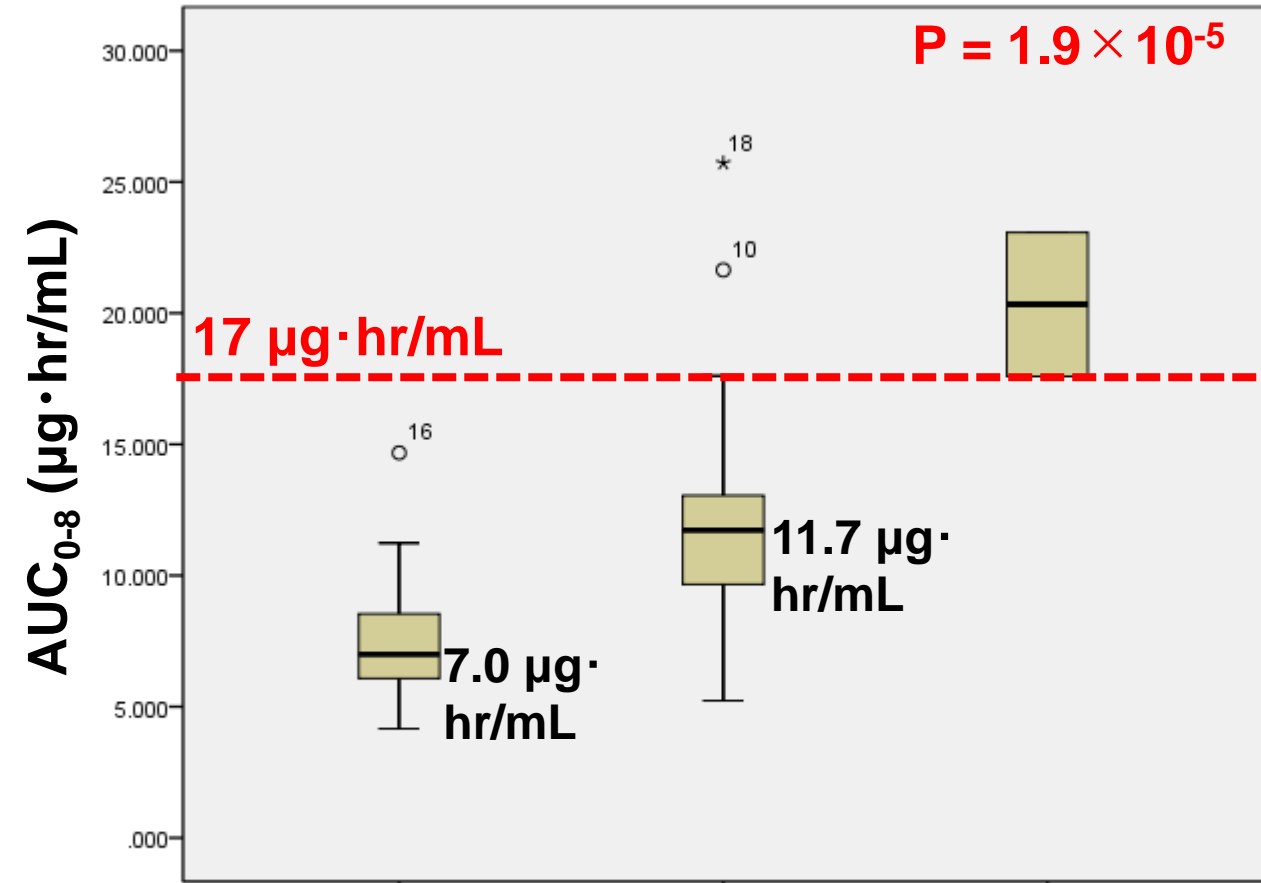
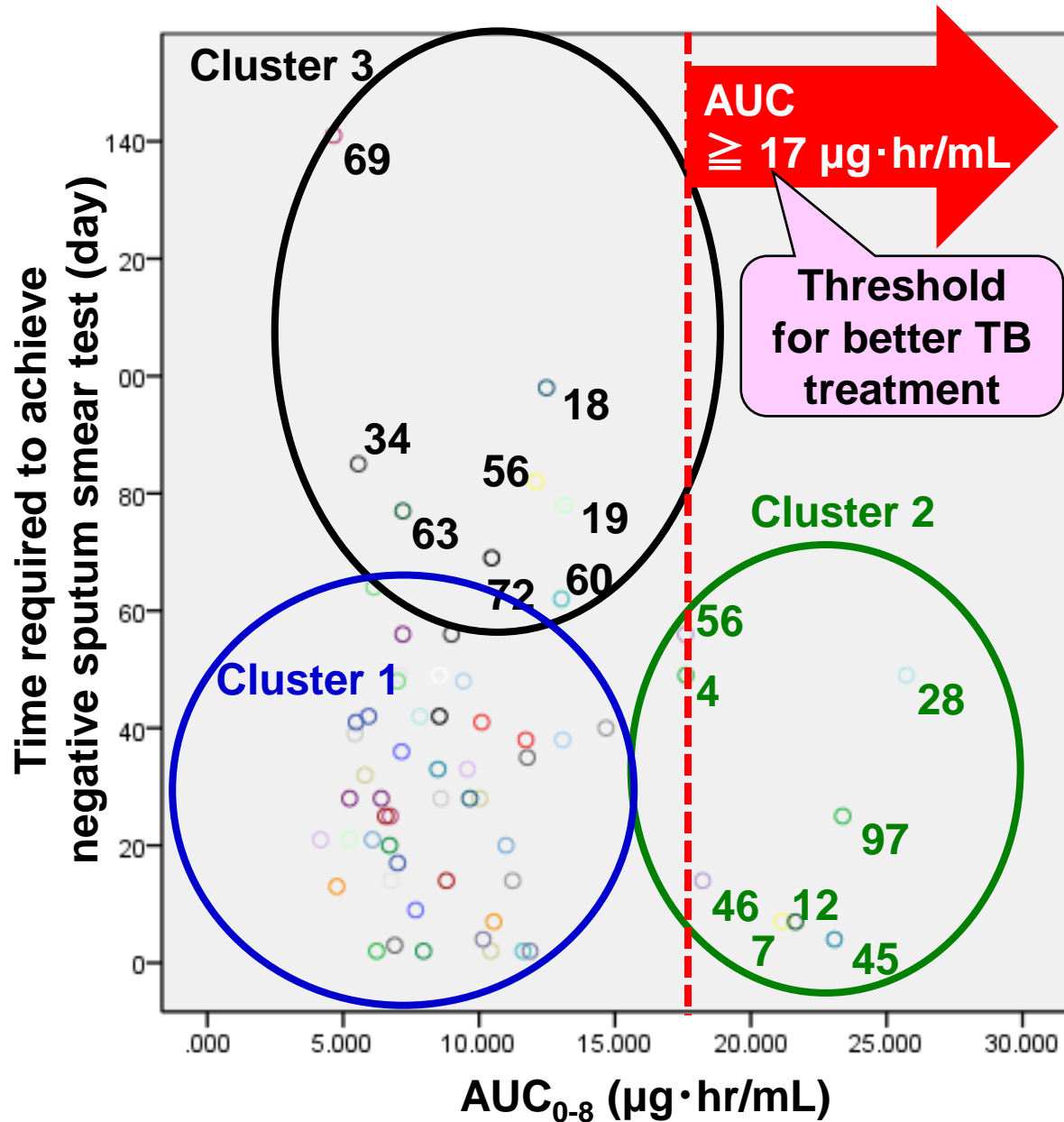
3.1 NAT2 is Associated with Isoniazid Levels, Affecting Both Efficacy and Toxicity



No variant allele → Rapid acetylator
One variant allele → Intermediate acetylator
Two variant alleles → **Slow acetylator**



3.2 Prediction for Appropriate Administration of Isoniazid



NAT2 Status Rapid (n=33) Intermediate (n=25) Slow (n=2)

The achievement to AUC ≥ 17 µg·hr/mL by 2 to 3-times increase of isoniazid dosage will lead to better TB treatment outcomes.

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4. High Resolution HLA Analysis of Thai COVID-19 Patients

3 weeks Training of NGS and Data Analysis in August 2022

NGS based HLA Sequencing

Trainer: Yosuke Omae, Chales Khor, Katsushi Tokunaga

Trainee:

1. Naphatcha Thawong, Ministry of Public Health, Thailand
2. Thoranin Intarajak, Chulabhorn Royal Academy, Thailand

Analysis of NGS-HLA Data

Trainer: Charles Khor

1. Naphatcha Thawong
2. Thoranin Intarajak

