SATREPS project

Integrated Application of Human and Pathogen Genomic Information for Tuberculosis Control Project

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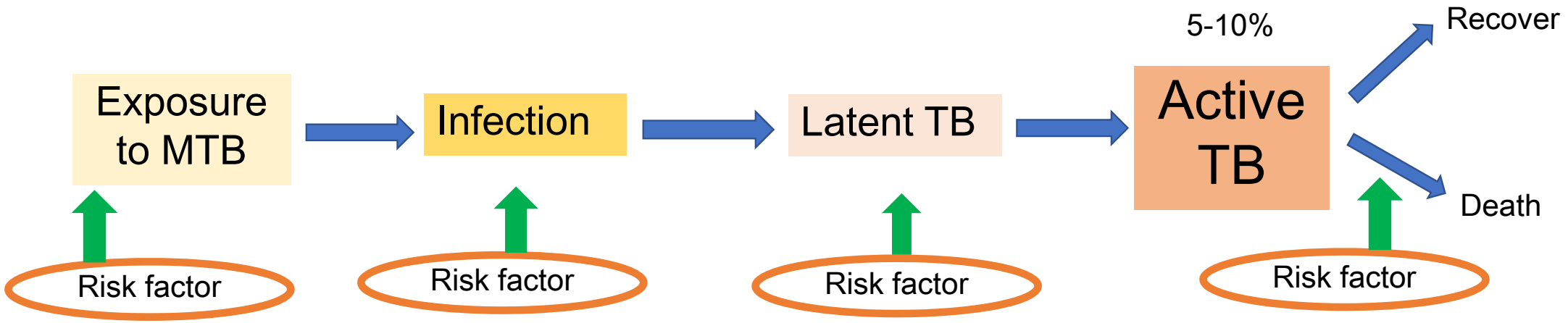
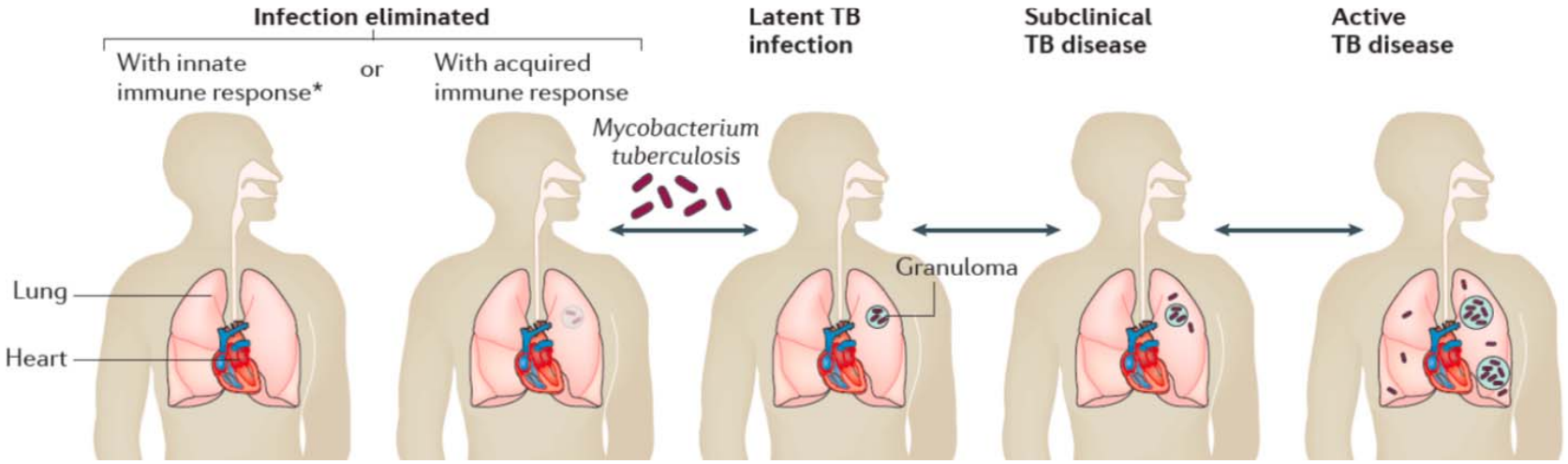
Natural History of TB (*M. tuberculosis* infection to active tuberculosis diseases)





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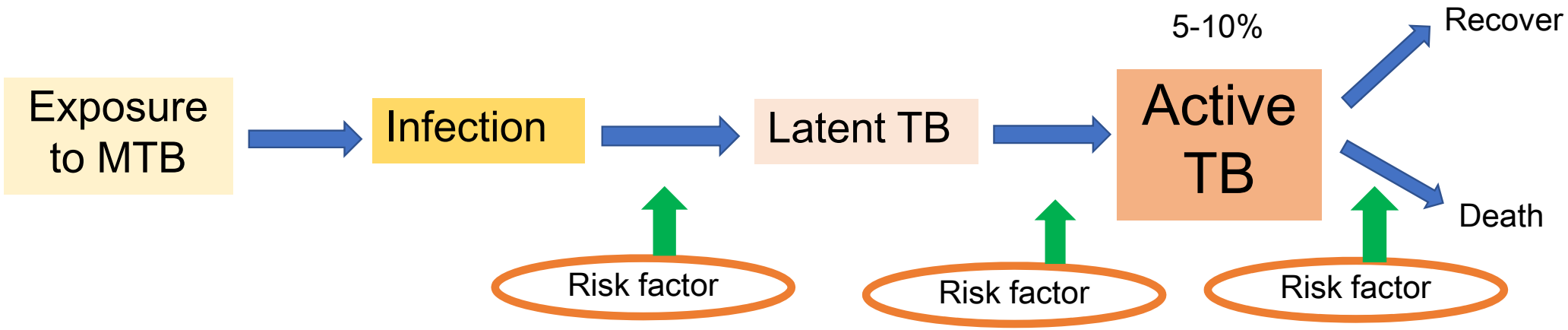
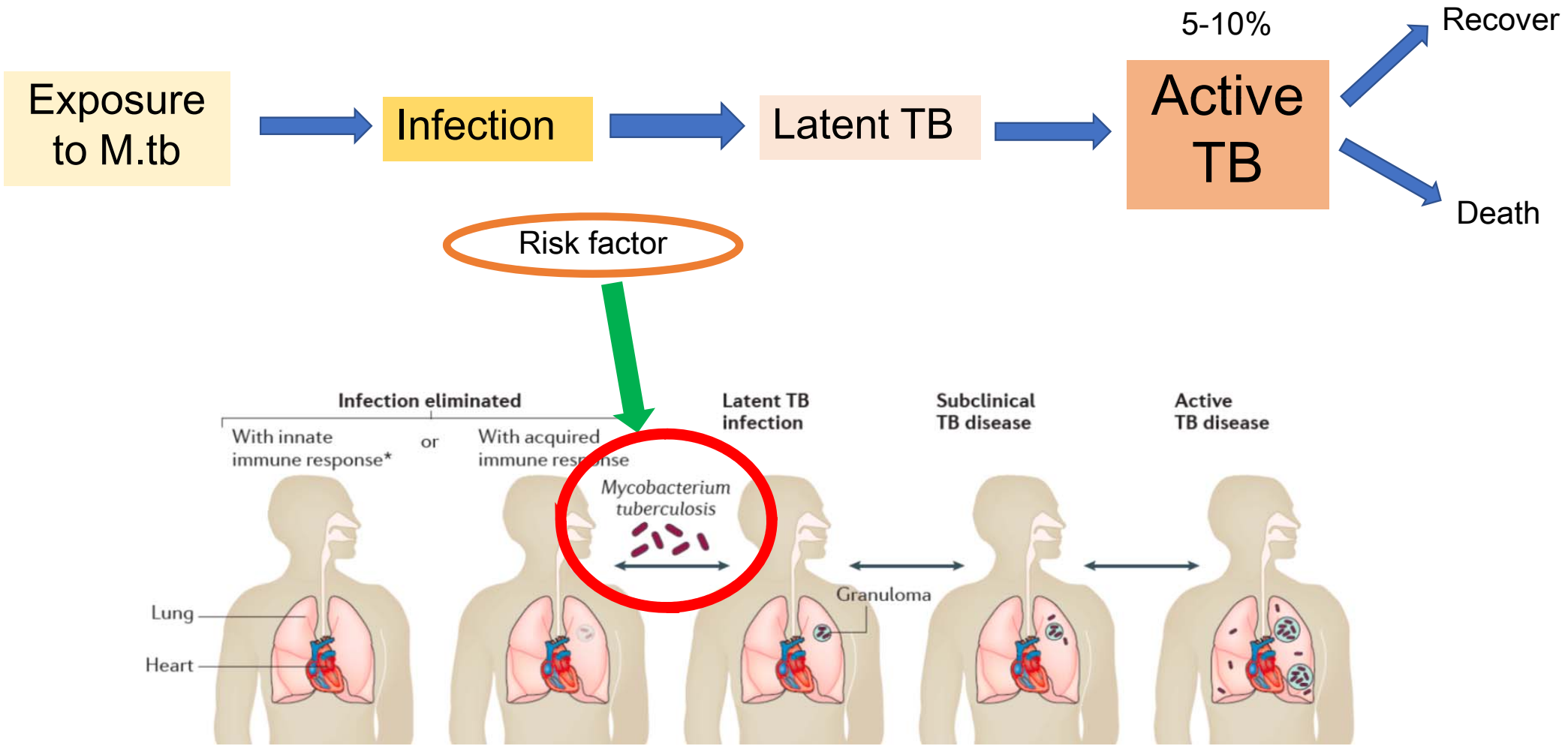


Host susceptibility (Immune system)

- Age (young and old)
- Malnutrition
- Comorbidity (DM, HIV)
- Tobacco smoking
- Host Genetic factors (*TLR2*, *IRGM*, *SLC11A1*, *LAMP1*, *MTOR*, *HLA class Ⅰ*)

Natural History of TB (M. tuberculosis infection to active tuberculosis diseases)

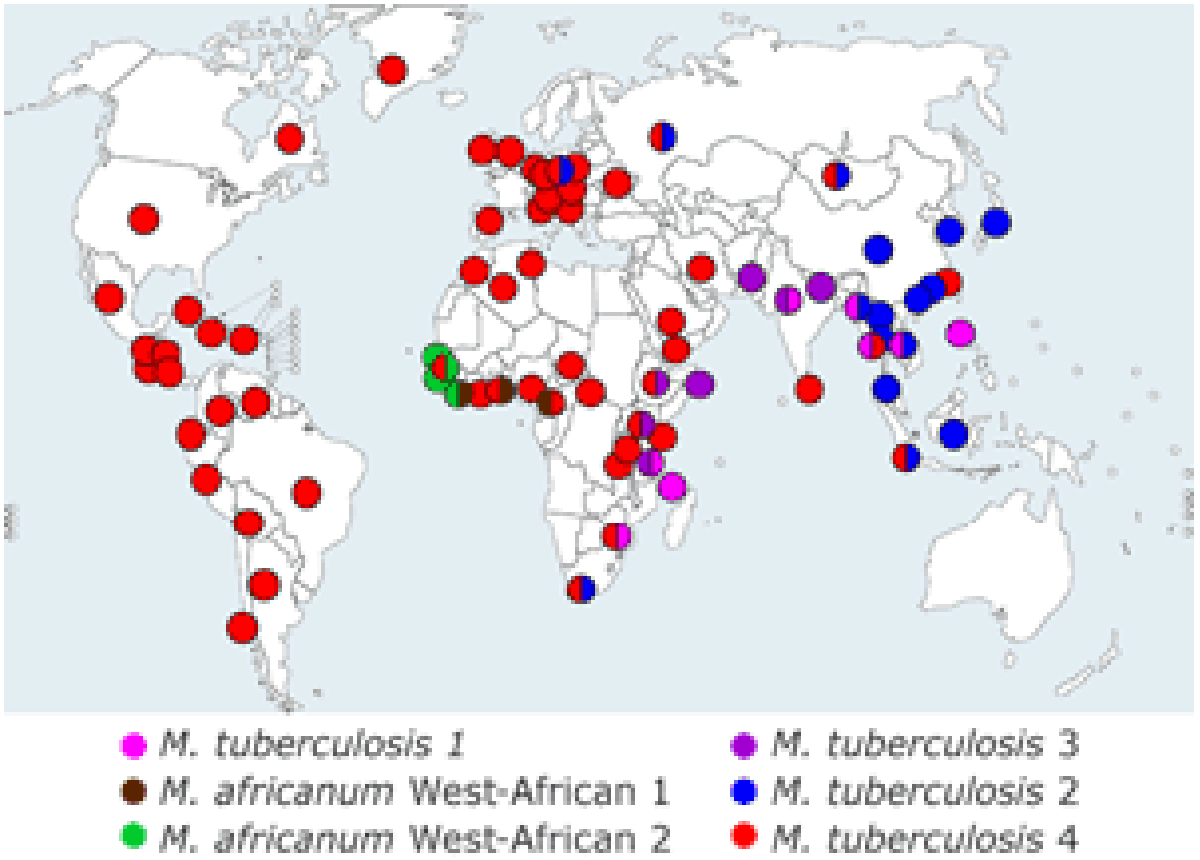


Lineage specific virulence

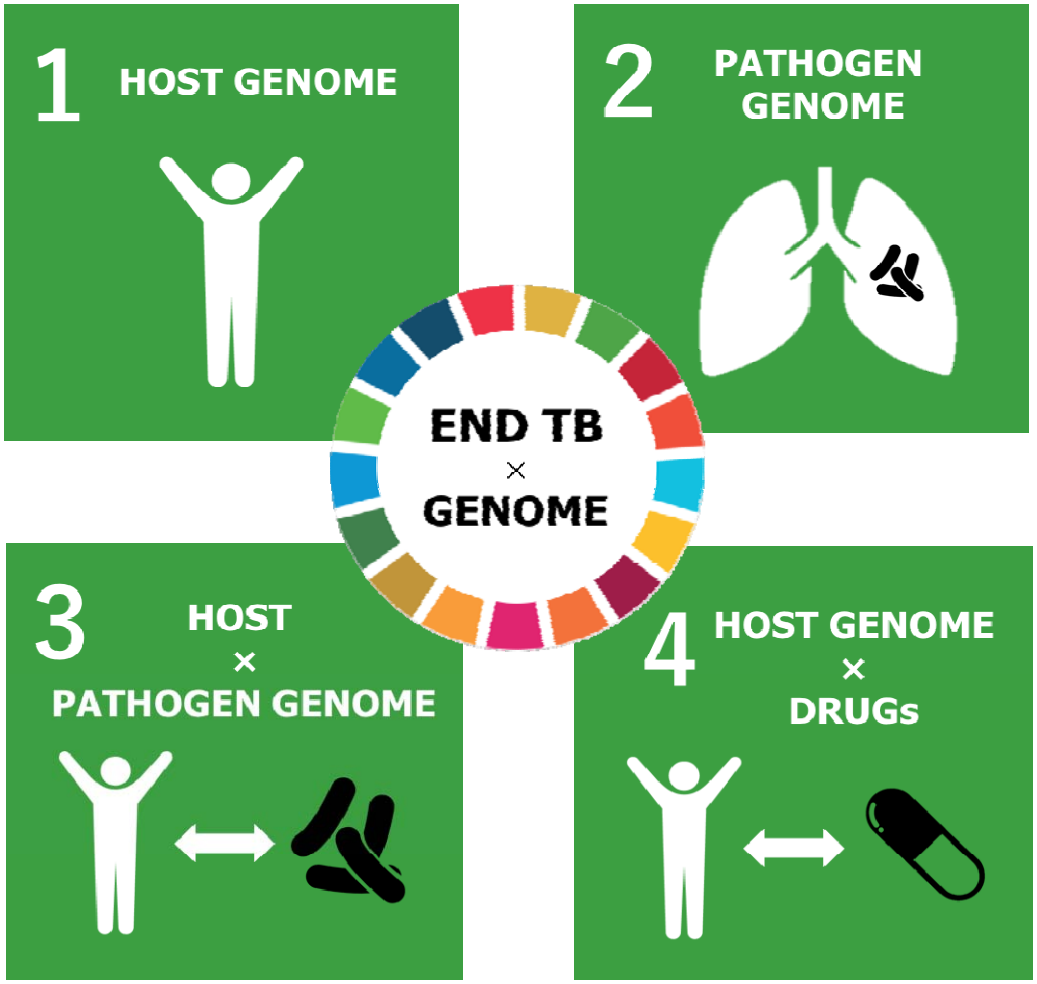
- *M.tb* strains categorize into mainly 6 lineages.
- East-Asian strains (Lineage 2, Beijing strains) in Asian population
  - High virulence
  - High transmissibility
  - High drug resistance rate

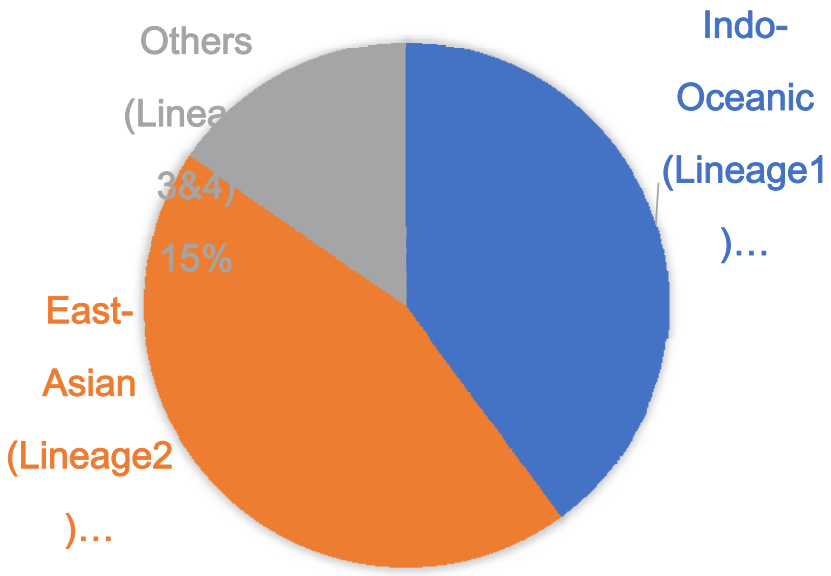
- In Canada or Switzerland, East-Asian strains showed low transmissibility and virulence.

→ **Specific host-pathogen interaction**



Integrated human and pathogen genomic information for tuberculosis





Proportion of TB lineages in Chiang Rai

Methods

In Chiang Rai province

2002-2011

Culture confirmed TB cases

Samples

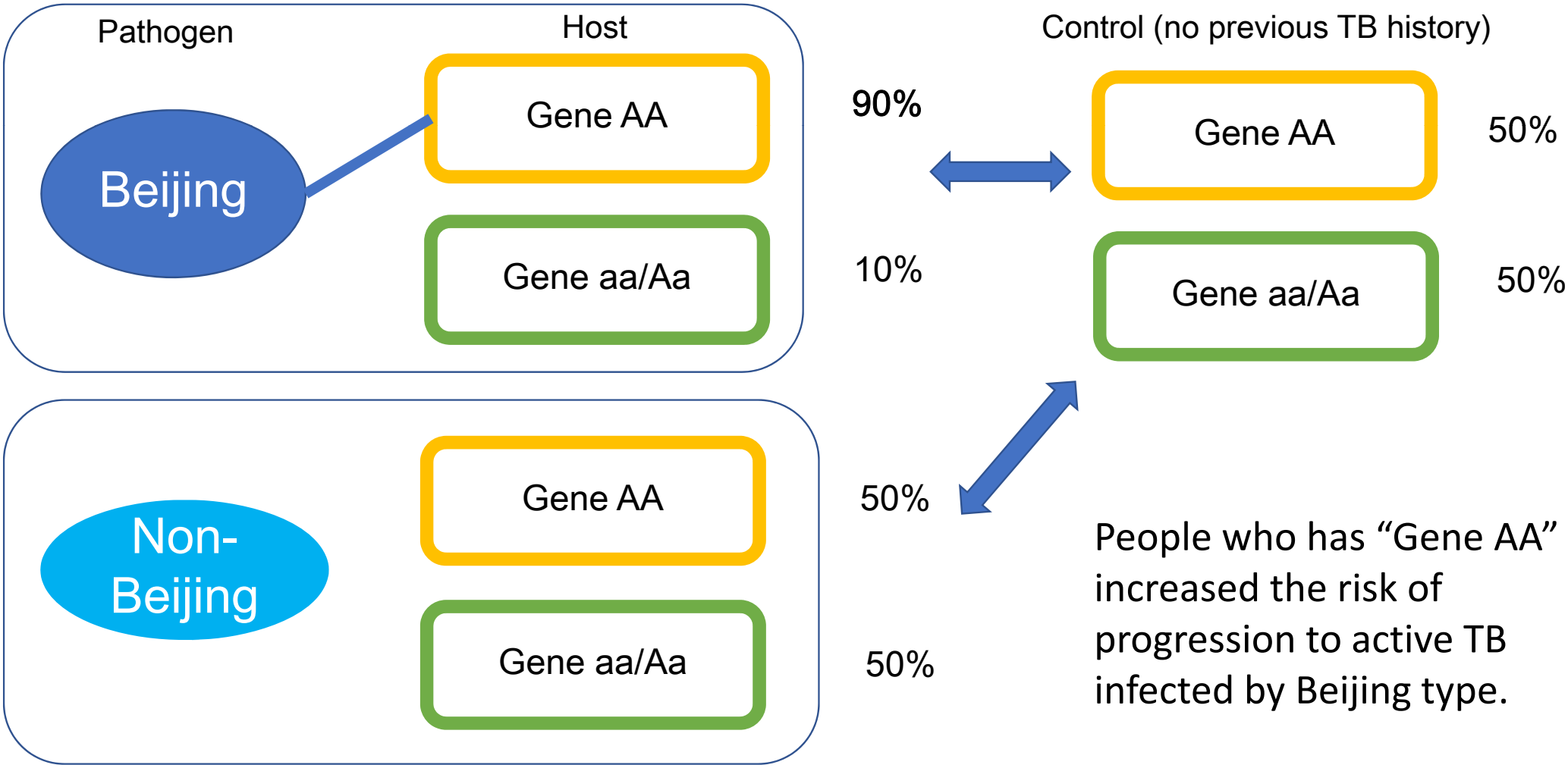
Dataset 1 : TB cases 405, Control 288
Dataset 2 : TB cases 291, Control 558
Dataset 3 : TB cases 854

Whole genome sequencing

GWAS (genome-wide association study)

Total 266 604 SNPs

Host and pathogen interaction analysis (GWAS)

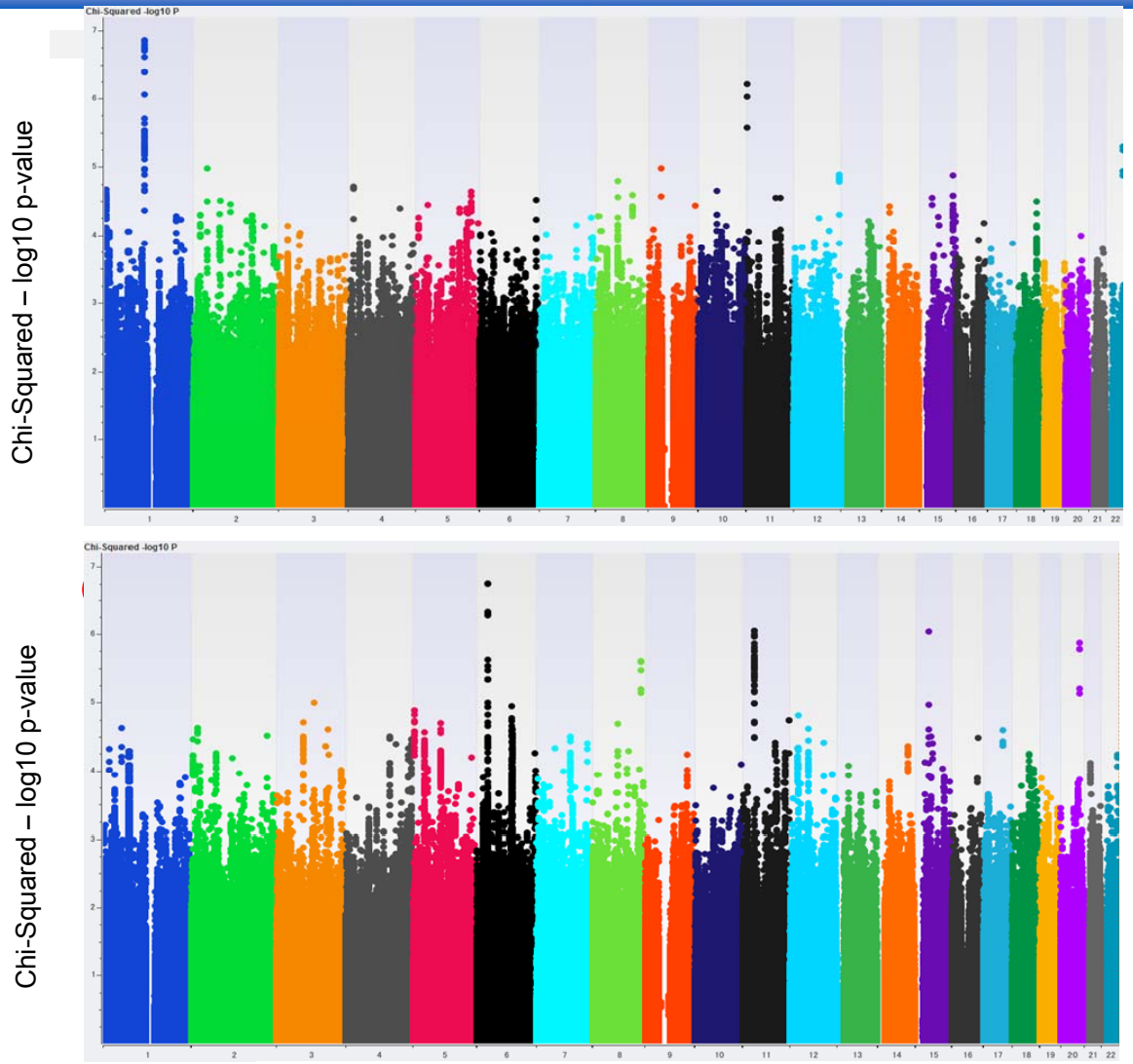


People who has “Gene AA” increased the risk of progression to active TB infected by Beijing type.

Lineage stratified GWAS by focusing on the heterogeneity of TB onset

TB Non-Beijing N=419
Control N=782

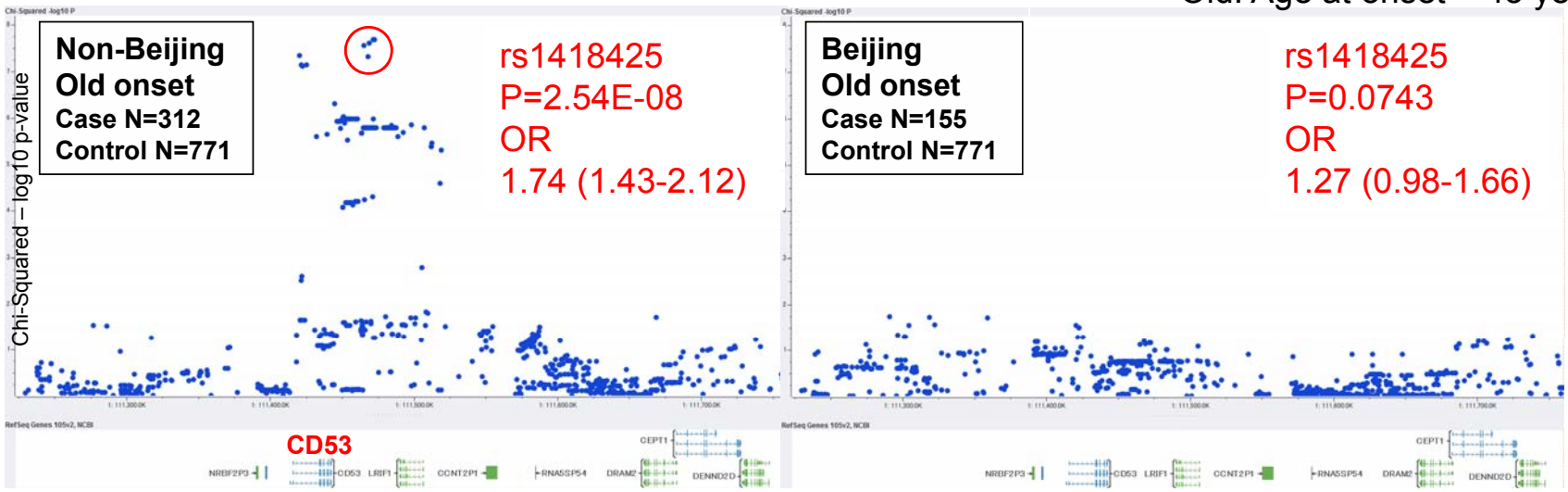
TB Beijing N=267
Control N=782



Updated from Omae Y *et al.* J Hum Genet (2017)

Significant association at *CD53* locus in lineage-based GWAS

Old: Age at onset > 45 years old



rsID	Lineage (Old age onset)	Case		Control		OR (95% CI)	P
		Count	MAF	Count	MAF		
rs1418425	Beijing	155	0.316	771	0.267	1.27 (0.98-1.66)	0.0743
	EAI	266	0.389			1.75 (1.42-2.16)	9.85E-08
	Euro-American	38	0.408			1.90 (1.18-3.04)	6.94E-03
	CAS and Others	8	0.250			0.92 (0.29-2.86)	0.882

Omae Y. et al. Journal of Human Genetics 2017; published online (accepted in July)

Risk of these SNPs is specific to non-Beijing lineage infected cases.

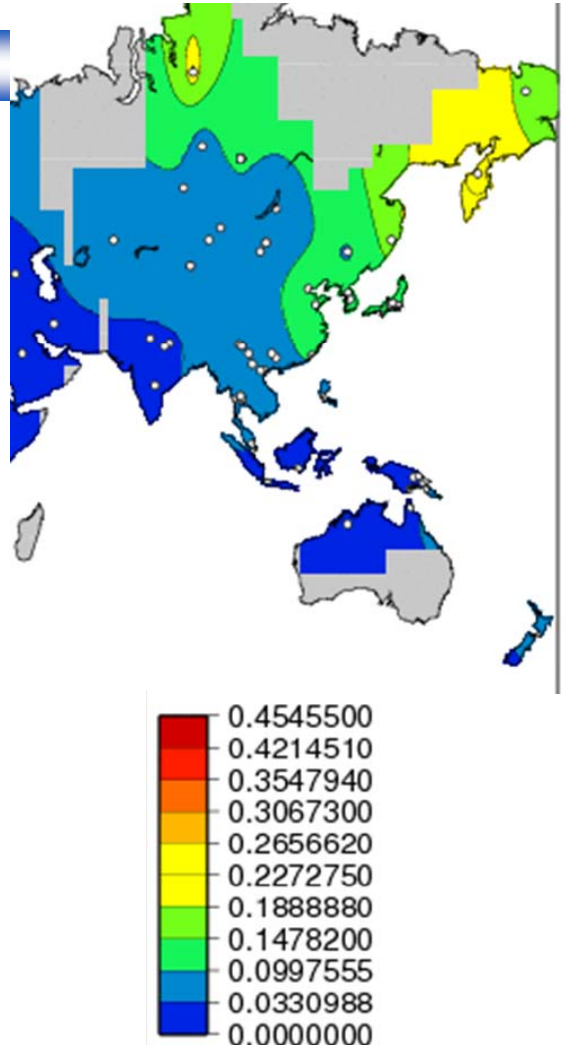
CD53: Leukocyte surface protein known to modulate cytokine production

Association of class II *HLA* with specific MTB lineage

*HLA-DRB1*09:01*							
Linegae stratification	Case count	Case freq.	Control count	Control freq.	p-value	OR	95%CI
ALL	574	0.146	811	0.123	8.82E-02	1.22	(0.97-1.53)
Beijing	140	0.229			8.96E-06	2.11	(1.51-2.91)
EAI	194	0.119			8.63E-01	0.96	(0.66-1.36)
Non-Beijing Non-EAI	45	0.133			7.43E-01	1.09	(0.53-2.07)

*HLA-DQB1*03:03*							
Linegae stratification	Case count	Case freq.	Control count	Control freq.	p-value	OR	95%CI
ALL	574	0.157	811	0.130	5.25E-02	1.24	(1.00-1.55)
Beijing	140	0.229			8.96E-06	2.11	(1.51-2.91)
EAI	194	0.126			9.33E-01	0.97	(0.68-1.36)
Non-Beijing Non-EAI	45	0.156			4.11E-01	1.31	(0.67-2.39)

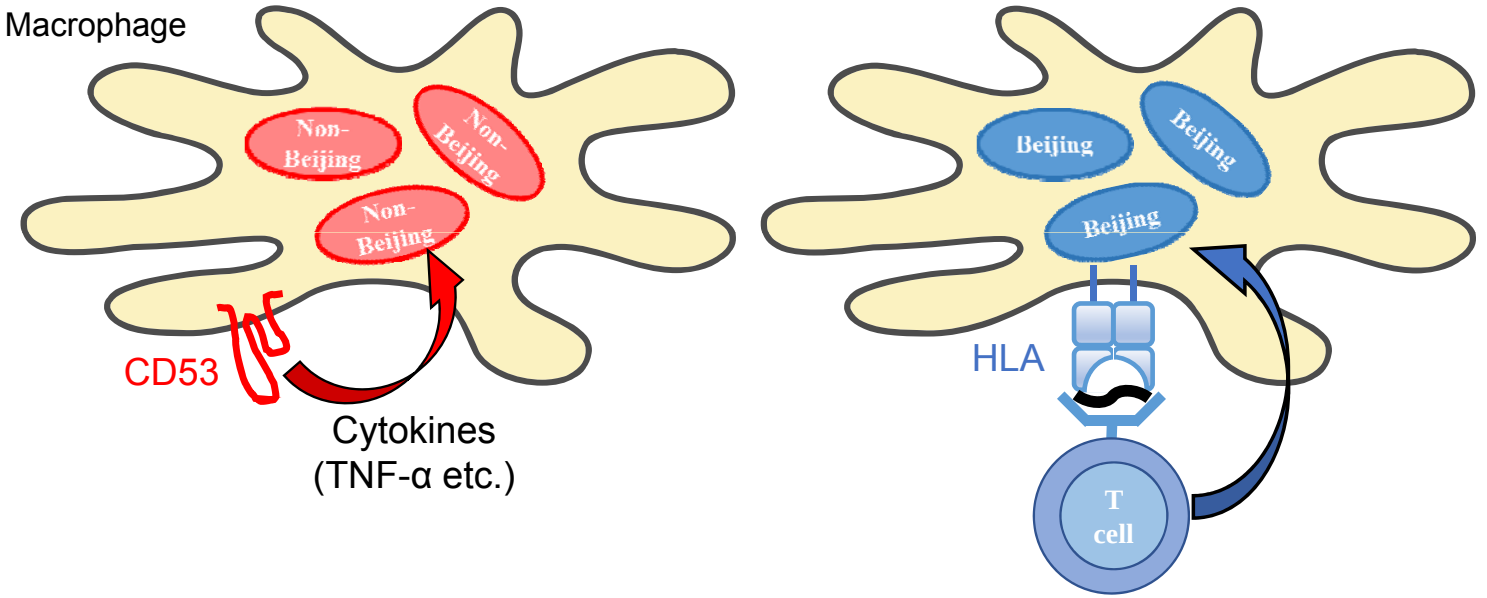
Updated from original table,
Toyo-oka L. *et al.* HLA. 2017;90:149-156



Stronger association was detected for HLA alleles after extracting cases infected by Beijing lineage.

HLA: Human Leukocyte antigen involved in peptide presentation

Proposed model from Lineage based analyses



Non-Beijing lineage infected
↓
Strong cytokine induction
(TNF-α etc.)
↓
Risk at cytokine regulation through CD53

⇔

Beijing lineage infected
↓
Weak cytokine induction
(Inhibition by MTB)
↓
Risk at pathogen recognition through HLA

Difference between Beijing and Non-Beijing: **RD105** (3.5kbp genome deletion in Beijing)

Summary

- In this study, we first conducted pathogen lineage-based genome-wide association studies and identified two SNPs around *CD53* that are a significant risk for old age TB onset under non-Beijing lineage-infected conditions.
- These SNPs did not show an association under Beijing lineage-infected conditions, indicating the lineage-dependent risk of host genetic factors.
- As *CD53* is a modulator of inflammatory responses, and the ability of non-Beijing lineages to induce inflammatory responses differs from that of the Beijing lineage.
- *HLA-DRB*09:01, HLA-DQB1*03:03* are associated with TB of Beijing lineages.
- In future study, the heterogeneity of the pathogen genome can provide a clue to identify the consistent genetic risk factors for TB among different populations and contribute to the effective control of TB.

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