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Figure 1

A. DISCOVERY AND VALIDATION COHORT

Adolescent Cohort Study (ACS)
n= 6,363 12-18 year olds

QFT- and TST<10mm
n=2,349

QFT+ and/or TST≥10mm
n=3,595

Exclude QFT and TST unknown
n=22

Developed intrathoracic TB
n=27

Exclude not per protocol TB
n=20

Developed intrathoracic TB
n=60

Remained healthy despite M.tb-infection
n=3,146

Exclude TB within 6 months of QFT/TST conversion
n=17

TB > 6 months after M.tb infection
n=8

Exclude incomplete sample set
n=4

TB progressors
n=46

Match healthy controls to progressors (2:1) by age, gender, ethnicity, school, TB history
n=107

Randomise training/test split

TRAINING

Progressors
n=37

Controls
n=77

TEST

Progressors
n=9

Controls
n=30

South Africa
n=1,197

The Gambia
n=1,948

Other African countries
n=1,321

Baseline

Remained healthy

Developed intrathoracic TB
n=43

Developed intrathoracic TB
n=34

Remained healthy

Match healthy controls to progressors (4:1) by age, gender, and recruitment year

Match healthy controls to progressors (4:1) by age, gender, and recruitment year

South Africa controls
n=172

South Africa progressors
n=43

The Gambia progressors
n=30

The Gambia controls
n=129

Exclude non-microbiologically confirmed TB
n=3

Exclude TB within 3 months of enrolment
n=1

Baseline

Study follow-up

Study follow-up

B. INDEPENDENT VALIDATION COHORT

GC6-74 healthy, HIV-HHC of index TB cases
n= 4,466 10-60 years old

South Africa
n=1,197

The Gambia
n=1,948

Other African countries
n=1,321

Baseline

Remained healthy

Developed intrathoracic TB
n=43

Developed intrathoracic TB
n=34

Remained healthy

Match healthy controls to progressors (4:1) by age, gender, and recruitment year

Match healthy controls to progressors (4:1) by age, gender, and recruitment year

South Africa controls
n=172

South Africa progressors
n=43

The Gambia progressors
n=30

The Gambia controls
n=129

Exclude TB within 3 months of enrolment
n=1

Exclude non-microbiologically confirmed TB
n=3

Study follow-up

Study follow-up

DISCOVERY AND VALIDATION COHORT

A.

INDEPENDENT VALIDATION COHORT

B.
Figure 2

A.

**DISCOVERY**

- ACS Training Set
  - Progressors
  - Latent TB Controls

- RNA-Seq model
- Reparameterised qRT-PCR model

**BLIND VALIDATION**

- ACS Test Set
  - Progressors
  - Latent TB Controls

- GC6-74 Validation Sets
  - South Africa
    - Progressors
    - Household Controls
  - The Gambia
    - Progressors
    - Household Controls

B.

- Days after study enrolment
  - 0, 180, 360, 540, 720

- Displacement map using cross validation.

- Days before TB diagnosis
  - 720, 540, 360, 180, TB

- Re-aligned for analysis

- Healthy samples used for biomarker discovery.

Aligned to baseline sample collection.
Time to TB diagnosis varies among participants.

Aligned to time of TB diagnosis.
Prospective samples used for biomarker discovery.
Figure 3

A.

B.

C.

D.

E.

F.
Supplementary Figure 1

A.

Gene
ETV7   FGRA1B   FGRIA   GBP2   GBP5   SERPINC1   SCARF1   STAT1   TAP1   Other

B.

Progressor
434 days before TB  243 days before TB  79 days before TB

Non-progressor
Control

Matched Control
Supplementary Figure 2

A. ACS Training: 1-180 days before TB

B. ACS Training: 181-360 days before TB

C. ACS Training: 361-540 days before TB

D. ACS Training: 541-720 days before TB

E. ACS Test: prediction all days

- PSVM
- Random Forest
Supplementary Figure 3

A. RNA-Seq model

- Berry et al. (2010): UK Test, SA Test (other disease)
- Bloom et al. (2012): SA (TB Treatment)
- Bloom et al. (2013): UK (other diseases)
- Kafourou et al. (2013): SA, Malawi (TB/HIV, other diseases)
- Anderson et al. (2014): SA, Malawi, Kenya (Pediatric TB, HIV, other diseases)

B. Berry et al. (2010)

C. Kafourou et al. (2013)

D. Bloom et al. (2013)

E. Kafourou et al. (2013)

F. Anderson et al. (2014)

G. Anderson et al. (2014)

H. Bloom et al. (2012)