

## A four-gene pan-African blood signature predicts progression to tuberculosis

With tuberculosis (TB) now known to be the leading infectious cause of death worldwide, the battle to find an effective preventive strategy is becoming ever more urgent. One approach to the problem is to identify individuals with latent TB infection (LTBI) who are at high risk of progressing to active disease, with a view to intervention. The currently available methods of identifying LTBI, the tuberculin skin test (TST) and interferon- $\gamma$  release assays (IGRAs), unfortunately have very low positive predictive values of 1.5% and 2.7%, respectively, for progression to active TB.

Suliman *et al.*<sup>1</sup> reported on their efforts to identify a genetic signature in individuals among household contacts (HHCs) of known TB cases who are more likely to progress to active TB. This was a nested case-control study from within the Grand Challenges 6-74 (GC6-74, GC6) HHC study cohort conducted in South Africa (SA), Ethiopia, Uganda and The Gambia, with external validation on the subjects of the Adolescent Cohort Study (also a local cohort). The investigators enrolled 4 466 HIV-negative healthy HHCs of 1 098 index TB cases between 2006 and 2010 into the GC6-74 cohorts, and generated site-specific signatures of TB risk using complex RNA sequencing techniques and transcriptomics. A pooled multisite signature was then identified. The RISK4 signature, which comprises four unique genes – *GAS6* (growth arrest-specific 6) and *SEPT4* (septin 4), which were upregulated, and *CD1C* (cluster of differentiation 1C) and *BLK* (B lymphocyte kinase), which were downregulated in progressors (defined as individuals who developed active TB 3 - 24 months after household contact) – was compared with matched control subjects. On external validation, the RISK4 signature significantly predicted progression in the entire combined test set (area under the curve (AUC) 0.67; 95% CI 0.57 - 0.77;  $p=2.6 \times 10^{-4}$ ) and in each individual site (SA, The Gambia and Ethiopia, with AUCs of 0.66 - 0.72;  $p<0.03$ ). RISK4 performed similarly well in the samples collected within 2 months of the index case being diagnosed. The researchers then compared the RISK4 signature with three other previously reported prediction scores, finding that it had equal efficacy but was the only one which validated across all four of the sites. Lastly, the investigators found that when the components of the RISK4 score were individually validated, the ratio between the *SEPT4* and *BLK* primers reproduced the performance of the RISK4 signature

on all test set cohorts, which suggests that a highly simplified version of RISK4 may be feasible.

This highly complex article includes a post hoc meta-analysis of the combined datasets to determine whether the accuracy could be further improved for a signature performing well at all sites. They identified an optimal pair of upregulated and downregulated transcripts, consisting of C1QC (complement C1q C-chain; upregulated) and TRAV27 (T-cell receptor alpha variable gene 27; downregulated), which achieved an AUC >0.76 on all sites. The AUC was further increased to 0.79 when the C1QC/TRAV27 ratio was combined with the ratio between ANKRD22 (ankyrin repeat domain 22; upregulated with TB progression) and OSBPL10 (oxysterol-binding protein-related protein 10; downregulated with progression); however, on external validation with a cohort of adolescents with LTBI, the ANKRD22/OBSPL10 ratio strongly predicted TB progression, but the C1QC/TRAV27 ratio and the combination performed poorly.

Overall, this vast and complex body of work must be seen as a signal that the potential for a simple polymerase chain reaction-based blood test to identify individuals likely to progress from LTBI to active TB exists, and may even be feasible in the near future. The authors identify the next steps in investigating this potential as: (i) the assessment of the performance of RISK4 and the two-transcript C1QC/TRAV27 signature in other settings, including non-African populations; and (ii) a determination of the feasibility of developing a near-patient test for targeted intervention. Watch this space.

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1. Suliman S, Thompson EG, Sutherland J, et al. Four-gene pan-African blood signature predicts progression to tuberculosis. *Am J Respir Crit Care Med* 2018;197(9):1198-1208. <https://doi.org/10.1164/rccm.201711-2340OC>