A novel three-gene diagnostic test for pulmonary tuberculosis based on host gene response

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Background: Better diagnostics are needed for active pulmonary tuberculosis (ATB). A WHO consensus statement has called especially for non-sputum diagnostics that are effective in patients co-infected with HIV and in children.

Material/methods: We performed a systematic search for publicly available gene expression microarray datasets that studied patients with ATB. We applied our validated multi-cohort analysis framework to three whole-blood TB datasets (N=1,023) to uncover differentially expressed genes in ATB. We then algorithmically searched for a highly diagnostic gene set, revealing a three-gene signature that distinguishes patients with ATB from those with latent tuberculosis or other diseases.

Results: We validated the three-gene set in 11 independent cohorts (N=1,650). We created global ROC curves to measure performance across all validation datasets (as measured by area under the ROC curve (AUC)). The results were: healthy vs. ATB, AUC 0.9; latent TB vs. ATB, AUC 0.88, other diseases vs. ATB, AUC 0.84 (Figure 1). Further, the three-gene set achieved a mean sensitivity of 0.86 and mean specificity of 0.86 in diagnosing ATB in children. It was also robust to HIV status, BCG vaccination status, and TB drug resistance. Finally, the three-gene set normalized to baseline levels during anti-TB treatment, making it a potential marker for treatment-response.

Conclusions: We found a novel three-gene set in whole blood that shows great potential as a new diagnostic for ATB. The diagnostic power was confirmed in multiple independent cohorts, including in highly relevant populations such as culture-positive children and those with HIV co-infection. Prospective validation is needed prior to clinical application.
Figure 1. Global ROC curves across all validation datasets for the three-gene diagnostic set. (A) Healthy controls vs. ATB, AUC 0.90; (B) latent TB vs. ATB, AUC 0.88; (C) other diseases vs. ATB, AUC 0.84.