An RNA signature for TB risk in pregnant women: A prospective cohort study from India

J Mathad[1], A Queiroz[2], R Bhosale[3,4], M Alexander[4], S Naik[3], V Kulkarni[4], B Andrade[2], A Gupta[5]
[1]Weill Cornell Medicine, [2]MONSTER, [3]BJ Gov't Medical College, [4]BJMC-JHU CTU, [5]Johns Hopkins University

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Background

- Identifying patients at high-risk for developing active tuberculosis (TB) is a research priority.
- The highest risk time for women to develop active TB is immediately postpartum.[1]
- Transcriptional studies have identified gene signatures that predict the development of active TB up to 12 months before symptoms appear.[2-4]
  - ***Pregnant women were excluded from all TB transcriptional studies.***
- **The objective of this study was to identify differentially expressed genes (DEGs) in pregnant women who did and did not progress to active TB in Pune, India.**

Results

Table 1. *Baseline Characteristics*

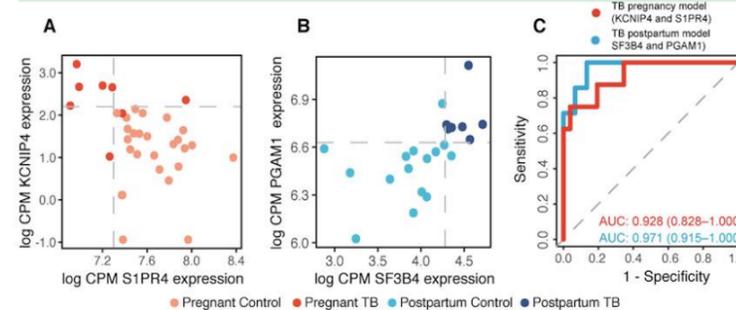| Characteristic	Cases (n=9)	Controls (n=18)	p
Med. age, yrs (IQR)	24 (21-29)	26.5 (25-28)	0.29
HIV positive	4 (44%)	8 (44%)	*
Med. CD4, entry (IQR)	428 (123-586)	402 (169-491)	0.82
Med. CD4, TB dx (IQR)	456 (131-826)	NA	--
TST+ at entry	4 (44%)	14 (77%)	0.08
Med. time to TB, days	60 (30-150)	NA	--

* Matching criteria

Results

Figure 1. *Dot plots from the log CPM values of the Machine Learn model genes in the (A) Predictive model and (B) Diagnosis model. (C) ROC of the Machine Learn model genes.*
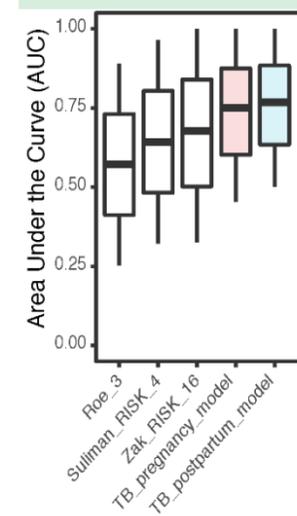

Figure 2. *Barplot of AUC values from published signatures in non-pregnant cohorts, the DEGs and decision tree set for TB pregnancy (predictive) and TB postpartum (diagnostic)*

RESULTS

- Expression of KCNIP4 >2.2 log CPM and S1PR4 <7.3 log CPM indicated a high probability of developing active TB postpartum.
- SF3B4 >4.3 log CPM and PGAM1 >6.6 log CPM correctly classified postpartum women with and without TB.
- Both pairs displayed elevated accuracy with an AUC >0.9. and were unique from 27 published signatures.

Design/Methods

- *Study Design*: A prospective longitudinal study.
- *Study Site*: Antenatal clinic at Sassoon Hospital in Pune, India.
- *Study Population*: Pregnant women > 18 years old, no evidence of active TB at study entry
  - Cases: Women who developed active TB within 12 months postpartum
  - Controls: Women who did not develop active TB, matched to cases by HIV status and gestational age at entry.
- *Study Procedures*:
  - All women had interferon gamma release assay and tuberculin skin test performed at entry (2nd/3rd trimester)
  - Whole blood was collected in PAXgene tubes at study entry, 6 weeks, and 12 months postpartum.
    - Additional sample collected if a woman developed active TB.
- *Analysis*: We used machine learning analysis and count gene expression to identify DEGs in:
  1. Samples from cases versus controls during pregnancy *before* development of active TB (Predictive Model)
  2. Samples from cases versus controls at the time of active TB diagnosis (Diagnostic Model)

The changes in gene expression levels were considered significant when statistical test values (FDR adjusted p-value) were lower than 0.05 and the fold change/difference higher than ±1.4.

Conclusions

1. We identified a **novel set of genes** whose expression levels differentiated pregnant women who developed active TB postpartum from those who did not.
   - **KCNIP4 > 2.2 log CPM and S1PR4 < 7.3 log CPM**
   - Needs to be validated in larger cohorts
2. These genes were **unique** from those identified in 27 published non-pregnant TB signatures and had a higher predictive value.
3. Genes could be used to develop targeted TB prevention therapies in pregnancy.

References
1. Zenner D, Kruijshaar ME, Andrews N, Abubakar I. *Am J Respir Crit Care Med.* 2012; 185(7):779-84.
2. Zak DE, Penn-Nicholson A, Scriba TJ, et al. *Lancet* 2016; 387:2312-2322.
3. Suliman S, Thompson EG, Sutherland J, et al. *Am J Respir Crit Care Med* 2018; 197: 1198-1208.

Questions? Please email: jsm9009@med.cornell.edu