Genome-Wide Association in Peru Demonstrates that Progression to Active Tuberculosis is a Polygenic and Highly Heritable Trait

S. Raychaudhuri[1,2], R. Calderon[3], L. Lecca[3], S. Leon[3], J. Jimenez[3], B.D. Moody[8], M. Murray[3,4,5,6,7], Y. Luo[1,2]

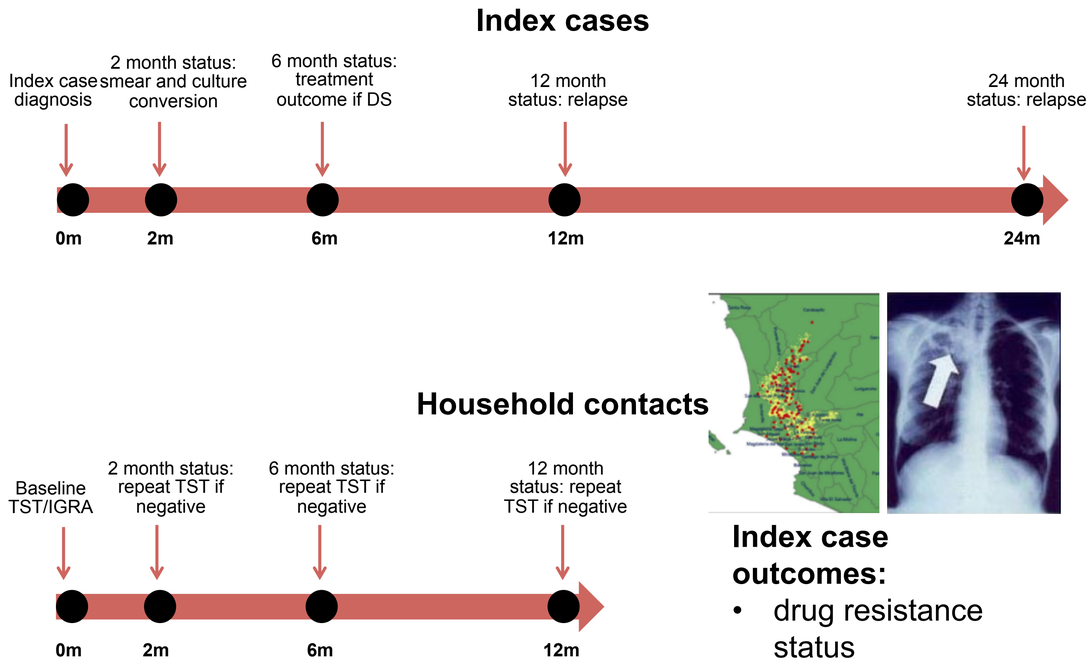
Study design & main findings

Since only ∼10% of the 1.5 billion Mycobacterium tuberculosis (Mtb) infected individuals worldwide go on to develop active tuberculosis (TB), host genetic factors that control disease progression have emerged as a central question in TB pathogenesis. To dissect the genetic basis of TB progression we conducted

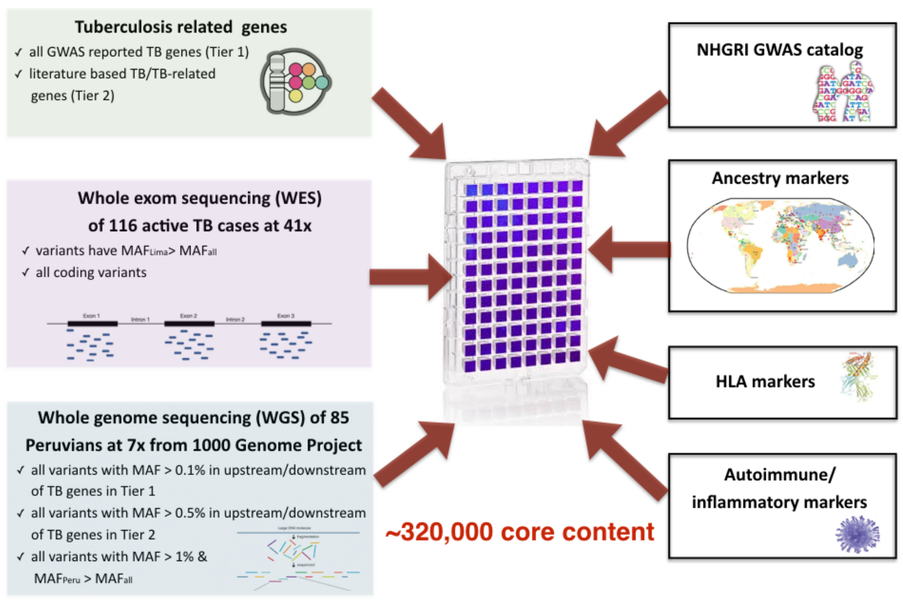
- the **first** and the **largest** genome-wide association study (GWAS) in Lima, Peru to date
- a GWAS of **2000** active TB cases and **2000** *Mycobacterium tuberculosis* (*M.tb*) infected household contact controls
- the largest GWAS of TB progression

We show that:

- Peru has a unique genetic heritage
- TB progression is a highly heritable trait ($h_g^2 = 0.243$)
- a novel TB progression locus on chromosome **3q23**
- there are multiple allelic-specific binding sites using Electrophoretic Mobility Shift Assay (EMSA)
- TB progression has different genetic bases to TB infection

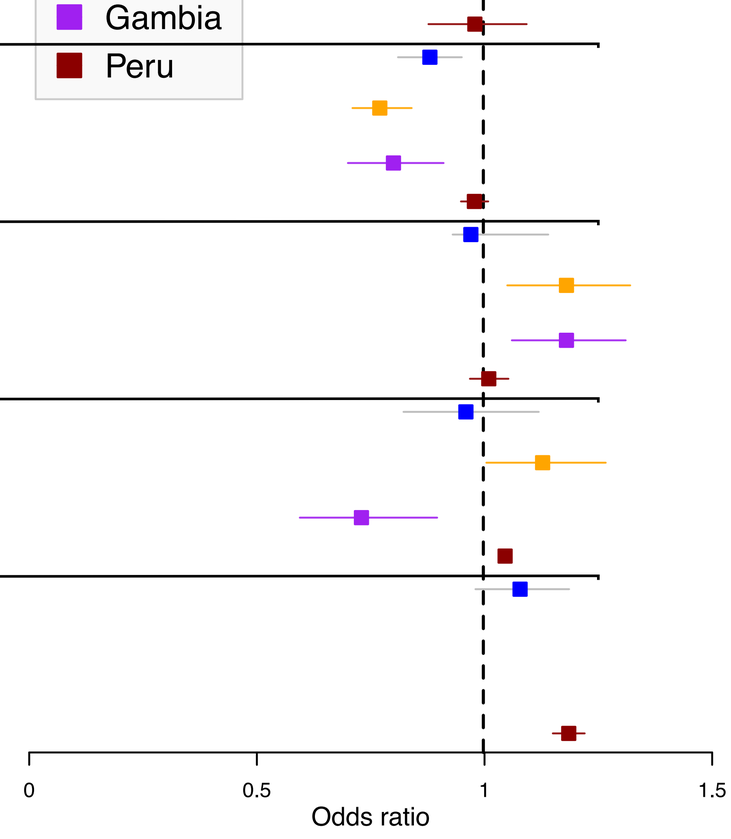


Unique LIMAArray tailored for Peruvian population



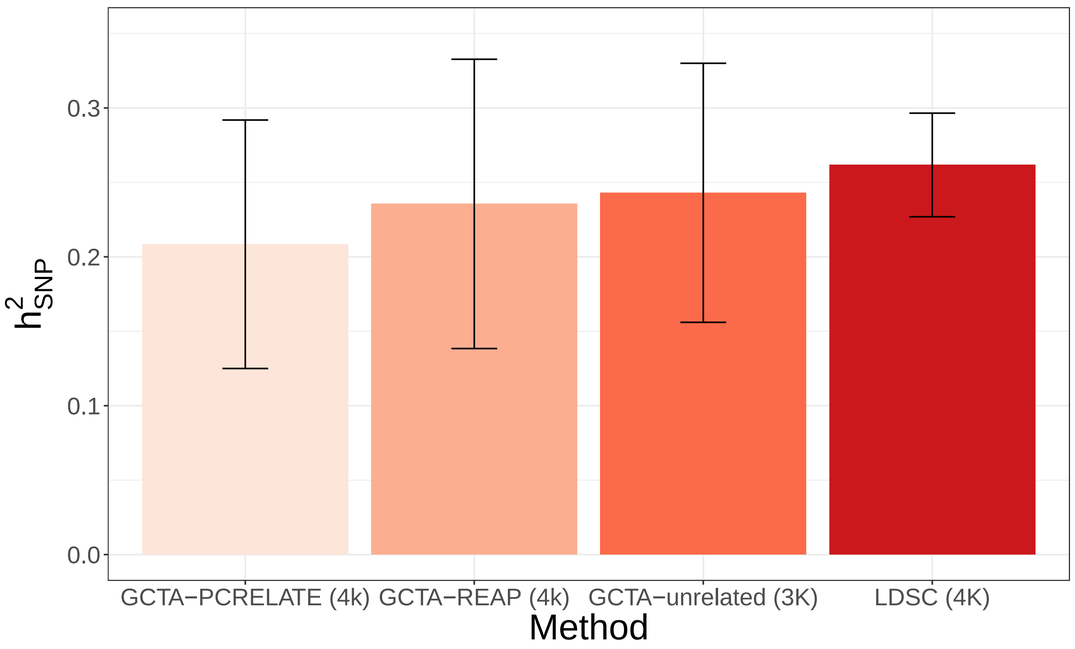
TB progression has different genetic bases to TB infection

Gene	MAF	Pvalue
ASAP1	0.31	2.60e−11
	0.12	2.60e−01
	0.09	2.30e−01
	0.33	**3.72e−01**
11p13	0.13	6.80e−04
	0.3	2.60e−09
	0.29	4.90e−04
	0.036	**4.61e−01**
18q11.2	0.03	7.10e−01
	0.47	4.30e−03
	0.5	2.90e−03
	0.021	**8.24e−01**
HLA−DQA1	0.03	7.94e−01
	0.31	1.88e−02
	0.11	2.79e−04
	0.41	**1.01e−04**
3q23	0.08	6.51e−02
	0.009	NA
	0.011	NA
	0.019	**2.98e−08**

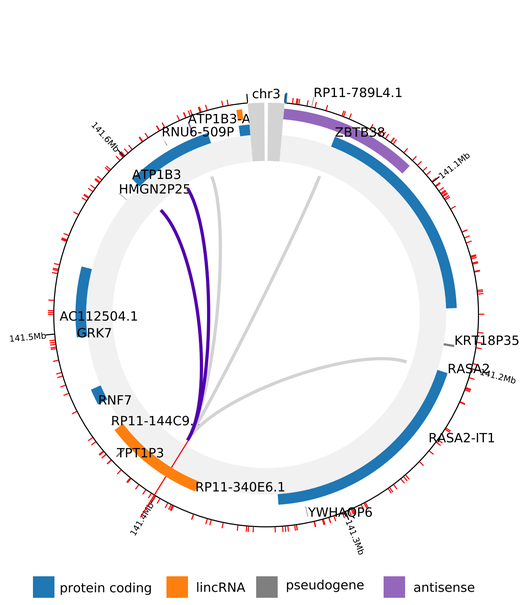


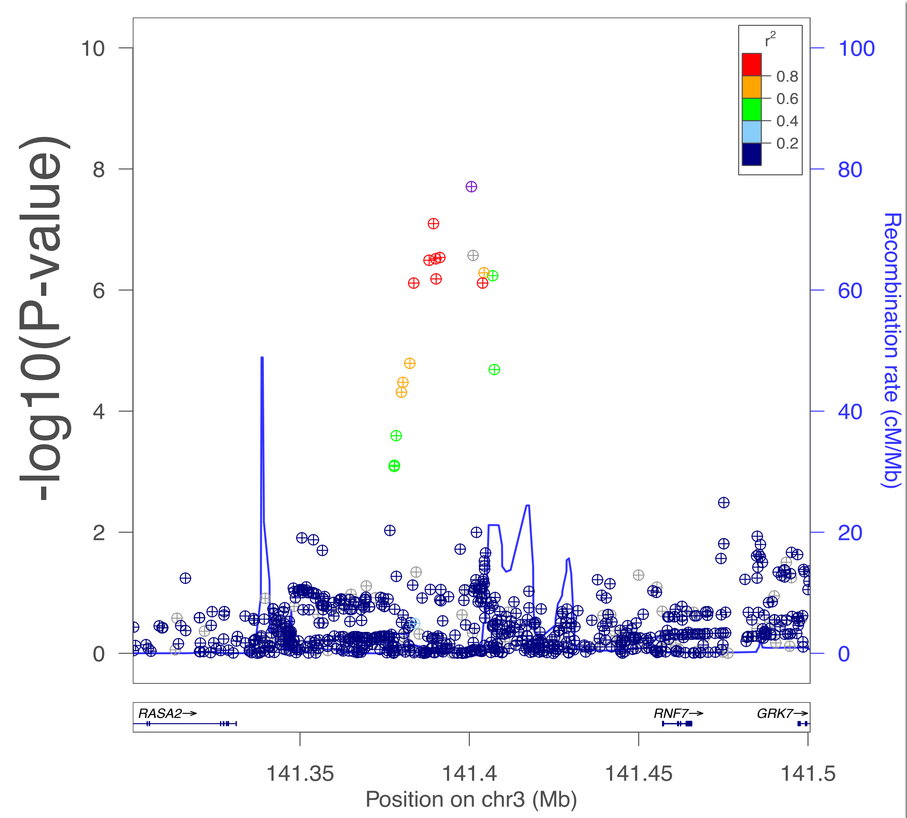
Heritablilty analyses demonstrate TB progression is a highly heritable trait

Multiple heritability analyses yield robust estimations. In total, we report 24.3% (s.e. 0.087) variation can be explained for TB progression on observed scale.



Linear mixed model highlights novel locus associated with TB progression





Contact information

Yang Luo, PhD
yangluo@broadinstitute.org

[1]Division of Genetics and Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.; [2] Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA; [3] Socios En Salud, Lima, Peru; [4] Partners In Health, Boston, MA, USA; [5] Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA; [6] Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA; [7] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [8] Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA