

# GENETIC, SOCIAL, AND BEHAVIORAL RISK FACTORS FOR TUBERCULOSIS: PRELIMINARY RESULTS FROM A MATCHED CASE-CONTROL STUDY IN KAZAKHSTAN

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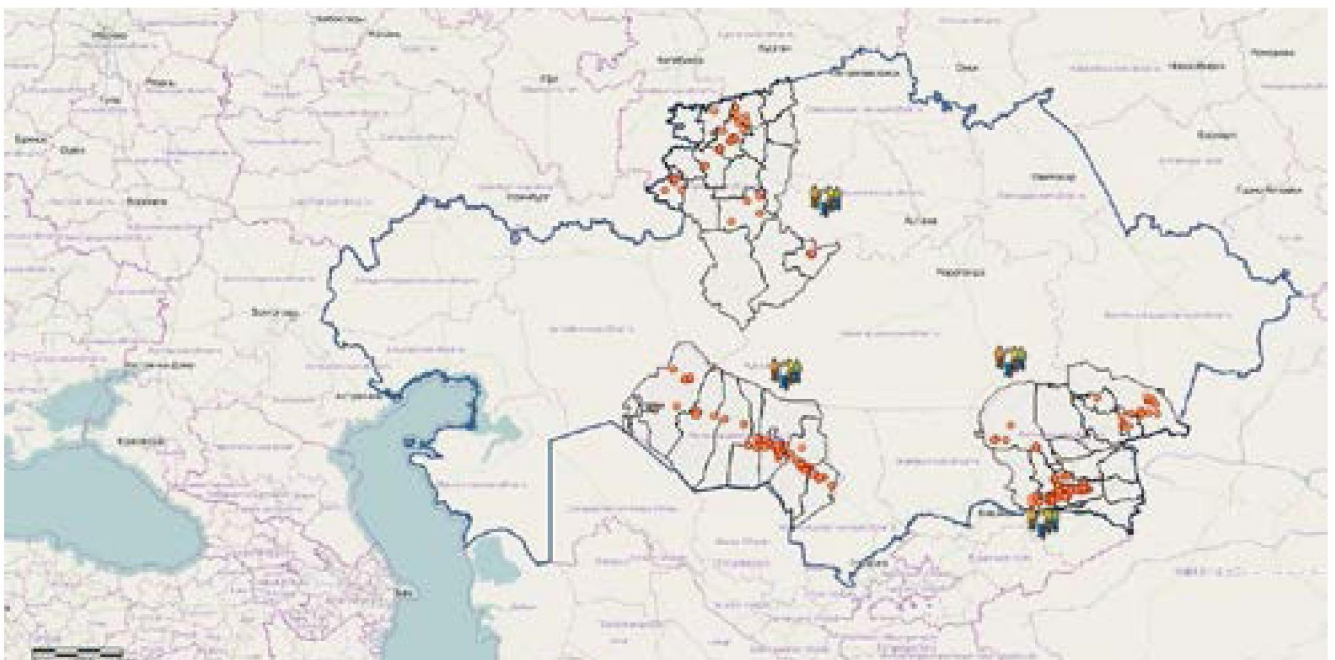
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## INTRODUCTION.

Tuberculosis control is among the most critical health concerns presently confronting Kazakhstan; however, detailed data on the specific TB risk factors in the country are yet undetermined. Rising multidrug resistant tuberculosis (MDR-TB) rates provide a new challenge to controlling TB nationwide.

## MATERIALS AND METHODS.

We designed a case-control study to examine demographic, clinical, social and cultural factors associated with tuberculosis in four regions of Kazakhstan. Cases included persons identified by the national tuberculosis program as having primary pulmonary tuberculosis, and controls were healthy household members and randomly selected community residents. We collected Mtb culture for TB cases to identify and compare different Mtb genotypes and assess their population variability and roles in epidemiology of drug resistance and transmission of TB and MDRTB. Finally, we collected venous blood samples from all the respondents to assess genetic host susceptibility. The study is ongoing and we have recruited 935 participants in all study regions thus far with the goal to reach the overall sample of 1600 by June, 2014. We have conducted preliminary statistical analysis with 324 respondents recruited from Almaty oblast, Kostanay oblast and Kyzylorda oblast (see Figure 1). Univariate and multivariate statistical analysis was performed to assess the relationships between TB and different socio-demographic characteristics, risk behaviors, and comorbid health conditions. We developed three separate models to compare TB cases to household control, TB cases to community controls and TB cases to household and community controls together.



*Figure 1. Mapping of new cases of pulmonary tuberculosis in three regions in our study.*

For candidate gene host susceptibility study, we conducted allele discrimination for 3 SNP markers associated with MDR-TB in other studies: (FokI(rs2228570), IL1(rs16944), TLR8(rs3764880)) in 182 samples. 154 clinical isolates of *M.tuberculosis* were genotyped for genes *katG*, *rpoB*, *oxyR-ahpC*, *fabG-inhA* and two MIRU-VNTR loci (VNTR 49 and 52).

#### RESULTS AND DISCUSSION.

TB cases were more likely to be younger persons (OR=11.36, 95%CI=1.67-77.49 for 18-24; OR=7.41, 95%CI=1.29-42.52 for 25-34; OR=1.99, 95%CI=0.35-11.47 for 35-44; OR=1.5, 95%CI=0.23-9.6 for 45-54 years old), recent smokers (OR=3.27, 95%CI=1.10-9.68) and have diabetes (OR=48.59, 95%CI=3.05-773.01), when compared to household controls. Between TB cases and community controls, TB is significantly associated with age (18-24 as compared to 55 plus, OR=5.13, 95%CI=1.01-26.18), non-married family status (OR=3.21, 95%CI=1.28-8.05), living in rented home (OR=5.15, 95%CI=1.39-19.05), recent smokers (OR=4.07, 95%CI=1.16-14.32), and having diabetes (OR=23.43, 95%CI=1.86-295.49). Comparing TB cases and with both control groups, we found that foreign birth (OR=3.16, 95%CI=1.08-9.29) was also associated with incident TB case status.

In candidate-gene study prevailing genotype for SNP markers – FokI(rs2228570) and IL1(rs16944) was heterozygous variant (46.7% and 49.5% accordingly), for SNP marker TLR8(rs3764880) – two variants prevailed: AA genotype (37.4%) and GG genotype (37.9%). 39% of mutations were revealed in *In katG* in 315 codone gene with amino-acid substitution Ser (serine)→Thr (treonine). 20% of mutations were in *rpoB* gene 4 mutations variants were revealed in codones (531, 516, 533 and 526), prevailing mutation in gene *rpoB* was mutation in 531 codone with substitution Ser (serin) → Leu (leucine), and only two cases (1.3%) had mutations in *rpoB* gene only; the remaining 33 cases were characterised by double mutations in genes *rpoB* and *katG*. Out of 154 *M. tuberculosis* strains combined mutations in genes *rpoB*, *katG* and *fabG-inhA* were found in two cases (1.3%).

#### CONCLUSIONS.

Preliminary analysis of 324 cases confirmed roles of major risk factors for TB: young age, single marital status, living in rented apartment, smoking, diabetes and migration. Next steps in the study will include: complete data collection by June 2014, continue MIRU-VNTR-typing per other loci, genotyping per SNP markers of human genes, screening of mutations in mycobacteria genes involved in forming of the first-line drug resistance, association and outcome analysis.

#### ACKNOWLEDGMENTS.

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