California’s Experiences Using Tuberculosis Whole Genome Sequencing

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Objective

Describe how whole-genome sequencing (WGS) data has been used to better understand outbreak-related tuberculosis (TB) transmission dynamics and focus public health action
Tuberculosis in California

7.5% Importation
Cases diagnosed within 1 year of arrival in U.S.

79.5% Reactivation
of remote infection

~2,100 TB Cases in 2015

13% Recent Transmission
CDC plausible source case method*

Discriminatory Power of Molecular Methods

Discriminatory Power:

LOW
- Spoligotype
- MIRU-12
- MIRU-24
- RFLP (>6 bands)

HIGH
- Whole-genome sequencing

Typical genotyping methods only look at ≈ 0.03% of *M. tb* genome

>90% of *M. tb* genome
CDC Outbreak Detection Using TB Genotyping*

• TB genotype cluster alerts:
  – Generated when a genotype has a higher than expected concentration within a county compared to other counties in the US in a 3-year window

• Large outbreak surveillance:
  – ≥10 TB cases in a 3-year period related by recent transmission

*Spoligotype and MIRU-24
CDC TB Genotype Cluster Alerts in CA, 2011-2015

Number of Alerts

Year of Alert

2011 2012 2013 2014 2015

19 25 28 33 40
Steps of a TB Genotype Cluster Investigation

TB genotype cluster alert received by TB outbreak team

Prioritize genotype clusters

Higher priority
- Notify local health departments

Lower/no priority
- Monitor genotype

Investigation

Implement interventions
CA’s Criteria for Requesting TB WGS

• Inform decisions on where to focus public health action
• Help confirm or refute that a genotype cluster is an outbreak
• Confirm transmission hypotheses
• Determine which cases are due to recent versus remote transmission in large multi-year outbreaks
TB WGS in California, 2013-2015

13 clusters

10 clusters with complete WGS results

6 clusters refuted as large outbreaks

2 outbreaks confirmed

3 clusters with pending WGS results

2 pending epi data to confirm outbreak
Example 1: Suspected TB Outbreak Refuted By WGS

• Preliminary epidemiologic investigation findings:
  – 2 likely transmission groups in 3 different counties
• WGS confirmed findings
• Background:
  – CDC alert, higher priority cluster
  – 10 cases in 5 central CA counties reported since 2013
  – Mostly Asian-born cases, one US-born child
  – Majority had infectious TB
  – Rare genotype: only one other TB case outside of CA
Example 1

4 cases in County A

2 cases in County B and C

Most Recent Common Ancestor (MRCA)
Example 2: TB Genotype Cluster Refuted as a Large Outbreak by WGS

• Investigation identified epidemiologic links among a small subset of cases in the large cluster
  – Epi links were confirmed and refuted by WGS

• Background: higher priority cluster
  – Genotype primarily found in one CA county
  – High percentage of US-born blacks
Example 2

Two 2010 cases lived in close proximity to each other
Example 3: TB Genotype Cluster Confirmed as a Large Outbreak by WGS

WGS helped to:

- Confirm outbreak transmission hypotheses
- Determine which cases are due to recent versus remote transmission in large multi-year outbreaks
- Identify previously unsuspected transmission links
Background

• Large confirmed outbreak of 26 cases 2012-2015
• Investigation priorities based largely on hypothesis of a single patient identified as most likely source case for 15 secondary cases
• 7 TB cases with the same genotype diagnosed before 2012, some in other CA counties or States
Example 3

Pre-2012 cases
Summary of California’s Experiences Using Tuberculosis WGS

• Save resources
  – Refute large outbreaks before launching an investigation

• Improve efficacy of outbreak investigations
  – Focus investigations on small sub-clusters of cases that may be linked by recent transmission
  – Distinguish which cases are due to recent vs. remote transmission in large multi-year outbreaks
  – Test outbreak transmission hypotheses
Next Steps

• Build TB program capacity to interpret and apply WGS to outbreak investigations:
  – Training
  – Visual analysis tools
• Evaluation of WGS results to inform which clusters should be selected for sequencing
• Continue collaboration in the CDC/APHL WGS project
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  – APHL
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