Molecular Epidemiology of Tuberculosis
Wendy A. Cronin, PhD, MT(ASCP)

Heartland National TB Center
June 19, 2009
Objectives

- Molecular epidemiology
- Methods used for genotyping in National TB Genotyping Service (NTGS)
- Ways to effectively integrate genotyping information in routine TB control efforts

What is Molecular Epidemiology?

- **Genotyping**: Uses specific elements of bacterial DNA that serve as markers for *M. tuberculosis* strains
- **Molecular epidemiology**: Combines bacterial genotyping (“DNA fingerprinting”) information with traditional epidemiology data
What is Molecular Epidemiology?

• Determines if patients’ TB isolates are:
  – Closely enough related genetically to suggest there is a high probability that the patients are linked by recent transmission

• Provides insights to:
  – Natural history of *M. tuberculosis*
  – Sources of transmission
  – Population of circulating genotypes

CDC’s National TB Genotyping Service

• Contracts with 2 reference laboratories since 2004

• Labs genotype up to 5,000 isolates/lab/year

• Goal: Universal genotyping (1 isolate for every new TB case in the U.S.)
National TB Genotyping Service

Proportions of Case-Isolates Submitted

- 2004: 47%
- 2007: 86%

Legend:
- 75 – 100%
- 50 – 74%
- 25 – 49%
- 0 – 24%
Isolate and Data Flow

Other Labs → ISOLATES & DATA

Genotyping Lab

CDC

RESULTS

State Lab

TB Program

Patient Names

Genotyping Techniques

• PCR = Polymerase Chain Reaction Tests
  – Spoligotyping = Spacer oligonucleotide typing
  – MIRU-VNTR = Variable-Number Tandem Repeats of Mycobacterial Interspersed Repetitive Units

• RFLP = Restriction Fragment Length Polymorphism

(Phenotypic characteristics: Drug Susceptibilities)
Spoligotyping

- Can be performed on non-viable isolates
- Standardized coding: digital results (000000000003771)
- Targets direct repeat locus of genome interspersed by spacer sequences
- 36 base pairs with 43 available identical sequences

Spoligotyping of *Mycobacterium tuberculosis*

MIRU

- Determines the #s of repeating units at targeted loci
  - 41 loci with direct tandem repeats of 50-70 base pairs
  - Number of repeats per locus varies between strains
  - “MIRU1” - 12 separate loci are targeted by 12 separate PCR assays for typing
  - “MIRU2” – additional 12 loci added in 2009

- Digital results: MIRU - 12 digits, e.g., 232234253322

MIRU locus 20 with 2 Tandem Repeating Units

- Genomic sequence
  ggctcgaage cgcatggccc gaaagcaagc gaggtgcaag tgcgacatg aegcggegecc
  atggcggcge ecgcegecg ctcggcctt gttggeggg gtcgacatgc aegcggegecc
gacgaggage ggegecaatg aegcggegecc ggcggegcg gtcgacatgc aegcggegecc
geggggggac aegcaghatag cggaggegecc gcgaatgc acgacatacc cggcagcgc

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**MIRU1**

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**Restriction Fragment Length Polymorphism (RFLP): Insertion Sequences (IS)**

- Only code for proteins needed to sponsor their own transposition (change of position, number)
- TB has a number of different insertion sequences
- IS6110 useful in strain typing
  - Stable: Single mutations every 2 to 4 years
  - Highly varied in number and position on chromosome: >>7,000
RFLP: Southern Blot Methodology

RFLP analysis reveals patterns matching of bands (copies of IS6110)

Comparisons of the Methods

• **IS6110-based fingerprinting**
  – Most discriminatory method
  – Slowest method: 3-6 weeks (4-6 months!)
  – Difficult to compare large numbers of patterns
  – Requires a lot of viable sample
  – Inter-lab reproducibility challenges (subjective)

• **PCR methods: Spoligotyping and MIRU-VNTR typing**
  – Less discriminatory than IS6110 typing
  – Rapid turnaround: 2 weeks
  – Yield digital results, facilitates comparisons
  – Do not require viable cultures
  – Amenable to multi-lab, international comparisons
Common Genotypes in the U.S.

<table>
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<th>Spoligo_MIRU Pattern</th>
<th>Spoligotype family</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>000000000003771_223325173533</td>
<td>Beijing</td>
<td>5512 (13%)</td>
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<tr>
<td>6767737777777600_2y2324153322</td>
<td><em>M. bovis</em></td>
<td>768 (2%)</td>
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<tr>
<td>470777777767671_236214233522</td>
<td><em>M. africanum</em></td>
<td>166 (&lt;1%)</td>
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<td></td>
<td>Euro-American</td>
<td>27,447 (65%)</td>
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<tr>
<td>43777760760771_122326153322</td>
<td>LAM</td>
<td>5,280 (12%)</td>
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<td>77776777760731_223325153322</td>
<td>X</td>
<td>6820 (16%)</td>
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<td>677777477413771_254326223432</td>
<td>Manila</td>
<td>3246 (8%)</td>
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<td>77777774020771_225325153323</td>
<td>Haarlem</td>
<td>3929 (9%)</td>
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<tr>
<td>776377777760771_233325153324</td>
<td>S</td>
<td>982 (2%)</td>
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</table>

Common strains – Beijing (spoligotyping only)
What is a genotype cluster?

The isolate genotypes from 2 or more patients are essentially identical

Spoligotyping
000000000003771
MIRU
223325173533

Spoligotyping
000000000003771
MIRU
223325173533

Genotype/PCR Cluster

NTGS: Genotype Cluster Terminology

**Genotype cluster:** 2 or more persons with the same genotype results in a jurisdiction

**PCR Results:**
- Spoligotype: 000000000003771
- MIRU: 223325173533

**State PCR cluster designation:**
- FL_042, IL_003, IN_020, MO_008

**National PCR type:** PCR00002
### CDC Cluster Naming Conventions

<table>
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<tr>
<th>Field name</th>
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<th>2009-2013</th>
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<td>PCRtype2</td>
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<tr>
<td>State cluster name</td>
<td>FL_042</td>
<td>FL_042 - 001</td>
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### Applications of genotyping

1) Identify or confirm false positive culture results

2) Enhance contact investigations:
   - unsuspected relationships between cases
   - new and unusual transmission settings

3) Define outbreaks; establish case definitions
Applications of genotyping – 2

4) Monitor trends through routine molecular surveillance: emergence of new and growing genotype clusters (recent transmission)

5) Differentiate between reactivation and re-infection episodes

6) Evaluate program performance and monitor TB control activities, such completeness of contact investigations

Applications of genotyping

1) Identify incorrect TB diagnoses based on false positive cultures
Names, Places, Identities, Photos

- Changed to protect the innocent

When Genotypes Match

- Organize data by cluster and specimen collection date

<table>
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<th>Accession Number</th>
<th>Cluster</th>
<th>Specimen Collection Data</th>
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<tr>
<td>MD0700R (D. Biby)</td>
<td>MD-003</td>
<td>December 3, 2007</td>
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<td>MD0700U (J. Jones)</td>
<td>MD-003</td>
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<td>MD0900P</td>
<td>MD-010</td>
<td>June 3, 2009</td>
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</table>
*Case 1 – Drew Biby*

- 40-year-old male
- U.S. born, white, non-hispanic
- Chronic sinusitis symptoms since November 2007
- Smear negative, 1 positive sputum culture in December 2007, CXR normal in January 2008
- Visited India in summer 2007
- TB reported to County A HD on January 30, 2008
- J Jones is a well-known AFB smear positive TB case

**False Positive Cultures**
False Positive Cultures

False Positive Cultures
False Positive Cultures

Causes

- Laboratory cross-contamination
- Clerical errors: mislabeling of patient specimens
- Clinical devices contamination: bronchoscope

Consequences

- Incorrect TB diagnoses
- Unnecessary anti-TB treatment
- Delay in correct diagnoses and treatment
- Overestimation of the TB case rate

When To Suspect False (+) Cultures?

- **Laboratory evidence**
  - Single positive culture
  - AFB smear negative
  - Slow growth = late report (6 or 7 weeks)
  - Known culture positive specimen processed on same day or +/- a few days

- **Clinical evidence**
  - Patient’s presentation inconsistent with TB
  - CXR not suggestive of TB
False Positives - 5 Year Review

42 false positives episodes

31 suspected false-positive specimens (non-cases)

11 UNSUSPECTED false-positive specimens ("cases")
  • 3 diagnosed after death
  • 3 treated until death (3 days, 10 days, 4 months)
  • 4 completed treatment
  • 1 true case’s treatment extended several months

False Positive Culture Investigation

• Review all lab reports (same lab?)
  – Type of specimen (sputum vs. bronch wash)
  – Track dates of specimen collection and processing times, patients, and locations
• Review dates of patients (symptoms and locations)
• Exclude possibility of epi-link or common source
• Review all labels and specimen handlers (difficult)
Applications of genotyping

2) Enhance contact investigations:
   unsuspected relationships between cases
   new and unusual transmission settings

*Case 2 – Lucy Lee

- 3-year-old female
- Asian, US-born
- Parents immigrated from China 10 years ago
- Coughing and difficulty breathing since May 5, ‘08
- Gastric aspirates culture-negative on May 21, ‘08
- Sputum culture-positive on June 10, ‘08
- Reported to state by local health department on June 11
*Case 3 – Anna Smith*

- 33-year-old female
- White, US-born, non-Hispanic
- Daycare worker
- Weight loss, cough, fatigue, and hoarseness since March 21, 2008
- Bilateral cavitary infiltrates on CXR
- Sputum smear-positive for AFB – July 10, 2008
- *M. tuberculosis* identified on culture – July 30

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**Florida Genotype Report**

<table>
<thead>
<tr>
<th>Genotyping Lab Accession No.</th>
<th>Submitter No.</th>
<th>Date Rec’d</th>
<th>Spoligotype</th>
<th>MI RU</th>
<th>Cluster name/PCRType</th>
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</table>
Applications of genotyping

1. Is this an outbreak?
2. Who is the source case?

*Case 4 – Bob Jones

- 28-year-old male
- White, US-born, non-Hispanic
- Bartender
- Coughing since January 14, 2008
- AFB smear positive, sputum culture positive and abnormal CXR – October 1, 2008
- HIV positive, alcohol, non-injecting drugs
- TB reported to Health Dept A on October 4
## Florida Genotype Report

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## Applications of genotyping

1. Now is this an outbreak?
2. Who is the source case?
Applications of genotyping

3) Defining outbreaks; establishing case definitions

*Case 5 – Rodney Holmes

- 42-year-old male
- US-born
- Homeless since last Thanksgiving
- Alcohol, drugs, malnutrition
- Frequents the bar where Bob Jones works
- Presented to ER with 2 week history of hemoptysis on January 4, 2008
- CXR-Extensive miliary patterns throughout the lung
- Had TB in 1990 but never completed treatment
Florida Genotype Report

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*Case 5 – Rodney Holmes*

- 42-year-old male
- US-born
- Homeless since last Thanksgiving
- Alcohol, drugs, malnutrition
- Frequents the bar where Bob Jones works
- Presented to ER with 2 week history of hemoptysis on January 14, 2008
- CXR-Extensive miliary patterns throughout the lung
- Had TB in 1990 but never completed treatment

*3 new cases enter cluster in August 2008; 4th in October 2008*
How do you define an outbreak?

- “... the occurrence, in a community or region, of cases of an illness clearly in excess of normal expectancy ...”

- “... number of cases needed varies according to agent, size and type of population exposed, time, and place of occurrence.”

- JM Last (1988). Dictionary of Epidemiology
Is this an outbreak?

- How many cases are in the cluster?
- What are the patient demographics?
- Are they occurring in the same location?
- Are there any potential venues for transmission (bars, social events, jails)?
- How are the patients who are named in contact investigation connected?
- If no epi-links, considering requesting RFLP to increase genotyping resolution

Applications of genotyping

4) Monitor trends through routine molecular surveillance: emergence of new and growing genotype clusters (may be recent transmission)
### A tale of 2 investigations...

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<th>Contact Investigation</th>
<th>Cluster Investigation</th>
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<td><strong>Who?</strong></td>
<td>One case</td>
<td>Multiple cases in a genotype cluster</td>
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<tr>
<td><strong>What?</strong></td>
<td>New cases/suspects and exposed contacts</td>
<td>Epidemiologic links between cases</td>
</tr>
<tr>
<td><strong>When?</strong></td>
<td>Upon identification of case/suspect</td>
<td>After recognizing genotype cluster</td>
</tr>
<tr>
<td><strong>Where?</strong></td>
<td>Household, Workplace, Congregate settings</td>
<td>Unusual transmission settings like bars, religious gatherings</td>
</tr>
<tr>
<td><strong>How?</strong></td>
<td>Interview, Record review, Home/work place visit</td>
<td>Review genotype data, Record re-review, Re-interview clustered cases, Additional social network analyses</td>
</tr>
<tr>
<td><strong>Why?</strong></td>
<td>Prevent new cases</td>
<td>Epidemiologic links between cases suggesting recent transmission and need to expand investigation</td>
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</table>

### When to launch a cluster investigation?

- Investigate clusters according to programmatic priorities
  - Unexpected cluster growth or new genotype
  - Suspected transmission among high-risk populations (HIV, IV drug use, dialysis)
  - Congregate settings
  - Pediatric cases
Applications of genotyping – 2

5) Differentiate between reactivation and reinfection episodes

*Case 5 – Rodney Holmes

- 42-year-old male
- US-born
- Homeless since last Thanksgiving
- Alcohol, drugs, malnutrition
- Frequents the bar where Bob Jones works
- Presented to emergency room with 2 week history of hemoptysis on January 14, 2008
- Extensive miliary patterns throughout the lung field found on chest radiograph
- Had TB in 1990 but never completed treatment

*Cases are fictitious and bare no resemblance to real people
Relapse vs Re-infection

**Relapse**
- Newly symptomatic after a period of improvement and treatment completion, caused by the same genotype of *M. tuberculosis*

**Re-infection**
- Exogenous re-infection caused by *M. tuberculosis* with a genotype that differs from the genotype that caused the initial infection
Applications of genotyping – 2

6) Evaluate program performance and monitor TB control activities, such completeness of contact investigations

Think about...

- Increase in number of clusters? Or cases in 1 cluster? (maybe recent transmission)
- Are we managing our cases adequately to prevent transmission?
- Did we overlook any contacts during our investigations?
- Endemic genotype vs. unique genotype?
- Truly recent transmission vs. increase in number of isolates being submitted for genotyping?
- What is the genotype profile of our county/state?
Tuberculosis Epidemiologic Studies Consortium
“Task Order 26”

Improving the utilization and integration of *Mycobacterium tuberculosis* genotyping into routine TB program practice

Molecular Surveillance and Aberration Detection?

- Automatic, real-time, algorithm for predicting potential TB outbreaks
- Events defined by genotype, and temporal and spatial dimensions, using readily available and routinely collected information
- Should be highly sensitive (detect true outbreaks)
- Should have high PPV (low false alarms)
CDC: Cluster aberration detection statistic:
Measures of geospatial concentration

- Log-Likelihood Ratio (LLR) measures the difference between the observed prevalence of a genotype and the expected prevalence, based on the prevalence of the genotype in the US.
- Measure based on geospatial concentration of clustered cases (county level).
- Higher the LLR, the more aberrant the cluster.

Purpose of LLR

- To predict genotype clusters that are, or are likely to become, outbreaks in need of public health intervention.

Evaluation of LLR

- By known outbreaks (geographic area).
- By expert opinion.
Purpose of Task Order 26

- To test Log Likelihood Ratio statistic
  - How well do high, medium, and low scores predict outbreaks and the need for public health intervention?

- To create a final predictive algorithm that incorporates the LLR plus epidemiologic (risk) and temporal information
**Future Genotyping Data Management**

<table>
<thead>
<tr>
<th>Current management</th>
<th>TB GISMS (2009)</th>
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</thead>
</table>
| Data exchange      | • Excel spreadsheets  
|                    | • local databases  
|                    | • standardized database  
|                    | • national database  
|                    | • immediate notification  |
| Data queries       | • ad-hoc / not available  
|                    | • genotype information  
|                    | • search by:  
|                    |   genotype information  
|                    |   individual records  
|                    |   geography  
|                    |   date  |
| Data reports       | • ad-hoc / not available  
|                    | • limited to local data  
|                    | • compare local / national genotype distribution  
|                    | • epidemiologic factors  |