The NCBI Pathogen Analysis Pipeline to Support Real Time Sequencing of Foodborne Pathogens

William Klimke
NCBI/NLM/NIH/DHHS
Other NCBI Talks

Tues. Nov 17th
4:00 AM – 6:00 PM
PulseNet Next Generation Methods Open Sessions
wgMLST pipeline development at NCBI

Fri. Nov 20th
9:00 AM – 10:30 AM
Whole Genome Sequencing Standardization
Standardization of Next Generation Sequencing in Support of Real Time Analysis for Foodborne Pathogen Outbreak Analysis
Weather as a Modern Global Infrastructure
Many Models on the Data, Fully Public, On the News
Citizens and Government All See the Power and Limits of Science
NCBI Pathogen Detection Pipeline

NCBI Submission Portal

- USDA
- FDA
- CDC
- New York State
- Public Health England
- fera
- Brigham and Women's Hospital

NCBI Pathogen Pipeline

- QC
  - Kmer analysis
- Genome Assembly
- Genome Annotation
- Genome Placement
  - Clustering
  - SNP analysis
- Tree Construction

BioProject
BioSamples
SRA
GenBank
Genome Assembly
Genome Annotation
Genome Placement
Clustering
SNP analysis
Tree Construction

Reports
Automated Bacterial Assembly

1. SRA Reads sample 1
2. Trim reads (Ns, adaptor)
3. Find closest reference genome(s)
4. Reference distance tree

De novo assembly panel
- SOAP denovo
- MauveRCA
- SPAdes
- GS-assembler (newbler)
- Celera Assembler

ArgoCA (Combined Assembly)

Reads remapped to combined assembly
- Contig fasta
- Read placements (bam)
- Quality profile
## NCBI Biosample - Pathogen Template
### (Foodborne Outbreaks)

<table>
<thead>
<tr>
<th>What</th>
<th>When</th>
<th>Where</th>
<th>Who</th>
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<td>OR</td>
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**Minimal metadata**

**NCBI Biosample – Pathogen Template (Foodborne Outbreaks)**
NCBI Pathogen Detection Pipeline Submissions (2015-11-13)

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<tr>
<th>Organism</th>
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## NCBI Pathogen Detection Pipeline Submissions

### Contributors: Campylobacter

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### Contributors: E.coli and Shigella

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### Contributors: Listeria monocytogenes

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### Contributors: Salmonella

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NCBI Pathogen Detection Pipeline Status (2015-05-01:2015-09-21)
NCBI Pathogen Detection Pipeline SNP Analysis
Reliable, *transparent*, high throughput, high resolution ERDs?

- Major challenge is to distinguish independent events (SNPs) from single events that generate multiple nucleotide differences
- i.e. collapsed repeats and other artifacts, alignment errors (reference-based alignments), sequence quality, & recombination
Fairly uniform distribution of differences along the two genomes...?
Iterative density filtering (Richa Agarwala modification of Science. 2011 Jan 28;331(6016):430-4.
SNP pipeline

1. Initial partition of isolates within each species by kmer distances
2. Within each partition blast comparison of all genomes
3. Single linkage clusters <100 SNPs
4. Within clusters, SNPs with respect to one reference (VCF file)
5. Density filtering to eliminate problematic SNP regions
6. Problematic genomes are eliminated at various points along the way
7. Generate final SNP list and phylogenetic trees
Graphs


- Non-Protein Coding genes
- Genes, 1 gene model shown

Alignments, total 41 objects shown
This SNP distinguishes Patient 8 from the other outbreak isolates.
## Assembly

### Quality profile

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NCBI Pathogen Pipeline:
Listeria pairwise SNP distances

Listeria kmer tree
PDG000000001.290
2015-08-21
4628 targets
351 Genbank genomes
4277 pathogen pipeline assemblies
21 outliers removed from further processing
4113 targets in clusters of size 3 or greater
NCBI Pathogen Pipeline:
Listeria clusters (size >2)
NCBI Pathogen Detection SNP Pipeline
CDC wgMLST

Median no. of allele differences (min–max)

- 3 (0–10)
- 6 (0–14)
- 4 (1–7)
- 10 (0–43)
- 11 (0–47)
- 12 (0–69)
- 2.5 (0–5)
- 3 (0–8)

- Isolates from recalled stone fruits
- Isolates from patients
- Isolates from nectarines
- Isolates from peaches
- Isolates from nectarines
- Isolates from peaches
- Isolates from nectarines and peaches

- Massachusetts isolate
- Minnesota isolate
- Illinois isolate
- South Carolina isolate

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6410a6.htm?s_cid=mm6410a6_e#Fig
NCBI Pathogen Detection SNP Pipeline

Pairwise SNP Distance Summary (Minimum, Mean, Maximum)

Outbreak or Cluster of Interest

Pairwise SNP Distance
NCBI Pathogen Detection SNP Pipeline
How Can NCBI Help Combat AMR?

• Improve the identification and annotation of resistance genes
  – Direct use in Pathogen Detection Pipeline
• Need for standardization of resistance gene nomenclature
• As more genomes are available, will be able to better understand genotype-phenotype map of antibiotic resistance:
  – predict resistance phenotypes from resistance genotypes

• Agricultural and clinical collaborators:
  – Center for Veterinary Medicine
  – Brigham & Women’s Hospital (Lynn Bry, Boston)
  – CDC/NIAID/Broad/NIHGRI
NCBI’s Role

“Create a repository of resistant bacterial strains (an “isolate bank”) and maintain a well-curated reference database that describes the characteristics of these strains.”

“Develop and maintain a national sequence database of resistant pathogens.”
Antibiogram Fields

- Fields designed to find balance between comprehensiveness and ease of submission
- Data dictionaries based on outside expertise (ASM, CLSI) standardize input and minimize ‘data drift’

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<th>Antibiotic</th>
<th>Resistance phenotype</th>
<th>Measurement sign</th>
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<th>Laboratory typing method</th>
<th>Laboratory typing platform</th>
<th>Vendor</th>
<th>Laboratory typing method version or reagent</th>
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Results: 1 to 20 of 718

1. Pathogen: clinical or host-associated sample from Citrobacter sp. CRE-46
   - Identifiers: BioSample: SAMN04014998; Sample name: AR_0157
   - Organism: Citrobacter sp. CRE-46
   - Package: Pathogen: clinical or host-associated; version 1.0
   - Accession: SAMN04014998 ID: 4014998

2. Pathogen: clinical or host-associated sample from Enterobacter cloacae
   - Identifiers: BioSample: SAMN04014977; Sample name: AR_0136
   - Organism: Enterobacter cloacae
   - Package: Pathogen: clinical or host-associated; version 1.0
   - Accession: SAMN04014977 ID: 4014977

3. Pathogen: clinical or host-associated sample from Enterobacter cloacae complex
   - Identifiers: BioSample: SAMN04015005; Sample name: AR_0164
   - Organism: Enterobacter cloacae complex
   - Package: Pathogen: clinical or host-associated; version 1.0
   - Accession: SAMN04015005 ID: 4015005

National Sequence Database of Resistant Pathogens

- Goal is to understand relationship between antibiotic resistance phenotypes and genotypes

- Will serve as infrastructure base for collecting and presenting antibiograms associated with any submitted bacterial genome
Building a Database Resource for AMR Genes

Domain experts
- Bush and Jacoby (beta-lactamases)
- Marilyn Roberts (MLS/tetracycline)
- Pasteur Institute (beta-lactamases)

Large scale databases
- FDA Center for Veterinary Medicine
- ResFinder
- The C.A.R.D.

Manual extraction from literature

ResFams
- Select
- Set cutoffs

New HMMs
- Group sequences
- Align
- Build HMM
- Set cutoffs

Validation
From Annotation to Resistance Genes

- Proteins
- AMR database
  - 3,337 resistance proteins
  - 33 drug classes resisted
  - ~50% beta-lactamases
- HMMs and BLAST
- Report on resistance genes in isolate
- New beta lactamase submissions
Assigning Function and Name

• Descriptive nomenclature matters as it describes possible function:
  – OXA-23 vs.
  – Class D beta-lactamase OXA-23 vs.
  – **Carbapenem-hydrolyzing** class D beta-lactamase OXA-23

• Relationship between genotype and resistance phenotype is difficult but assigning protein function is first step
  – resistance phenotypes are often incomplete

• BLAST-only approaches have troubling assigning function to novel alleles
• HMM can place proteins in functionally defined families

• 2930/3337 (88%) proteins are placed into 352 consistent, coherent AMR gene families
Resistance to carbapenems and other beta-lactam antibiotics.

**KPC family**

Likely resistance to carbapenems and other beta-lactam antibiotics.

Class A beta-lactamase of unknown specificity.

Prevents false-positive identification as a beta-lactamase. *Not reported.*
How Do We Determine If Our AMR Detection Works

• ‘Known Truth’ Datasets:
  – Finished quality genomes that also have Illumina reads and antibiogram data
  – serve as positive and negative controls
  – NIH CRE Outbreak (10)
  – VRE/MRSA (2)
  – CDRH genomes (29)
• Antibiogram data and reads/assemblies
  – ESBL enterobacteriaceae (139)
  – Carbapenem-resistant enterobacteriaceae (93)
  – MDRO Dept. of Defense (6; assemblies only)
  – CVM MDR E. coli (76)
  – B&W Hospital diverse clinical pathogens (86)
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NDM in Salmonella enterica AM49198 (SAMN03098832)

Vibrio cholerae 116-17a plasmid pNDM-116-17 (Cardiff University)

Salmonella enterica AM49198 contigs (CDC)
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pd-help@ncbi.nlm.nih.gov