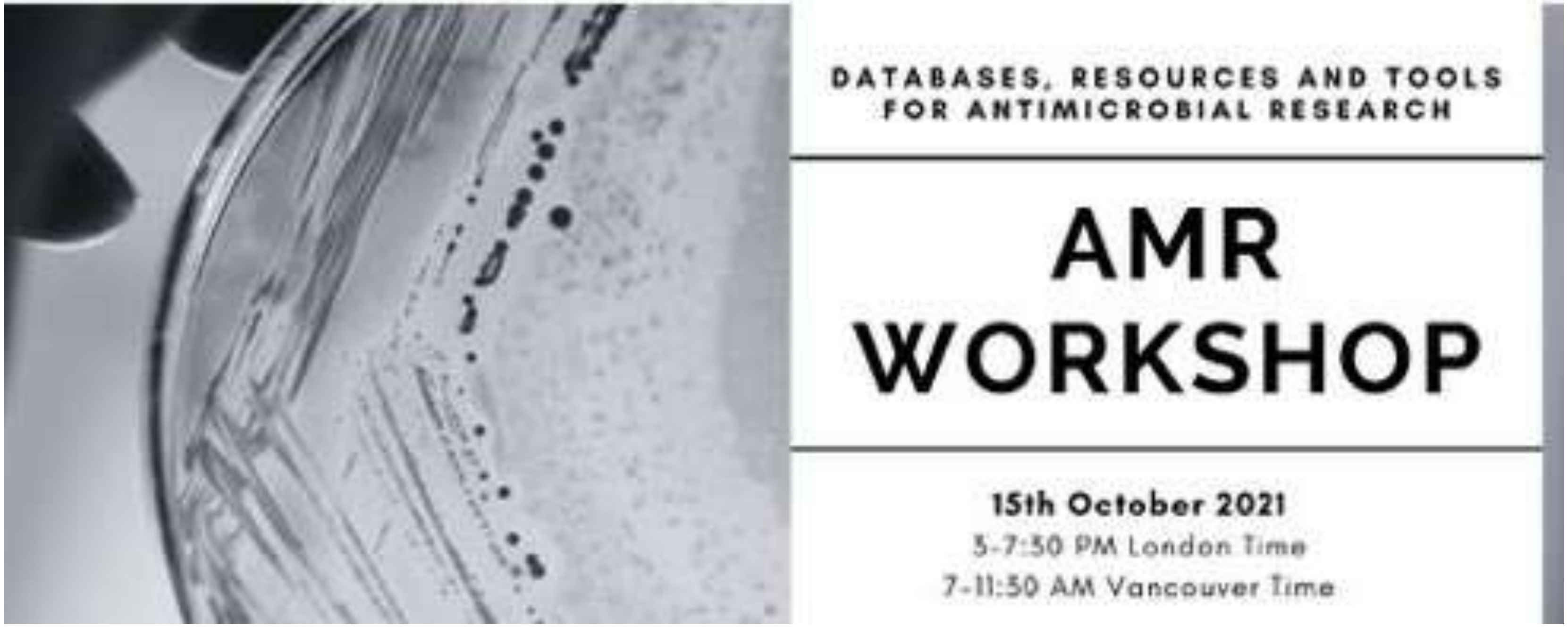


DATABASES, RESOURCES AND TOOLS FOR ANTIMICROBIAL RESEARCH

AMR WORKSHOP

15th October 2021
5-7:50 PM London Time
7-11:50 AM Vancouver Time

Introduction to databases and resources for AMR genomics

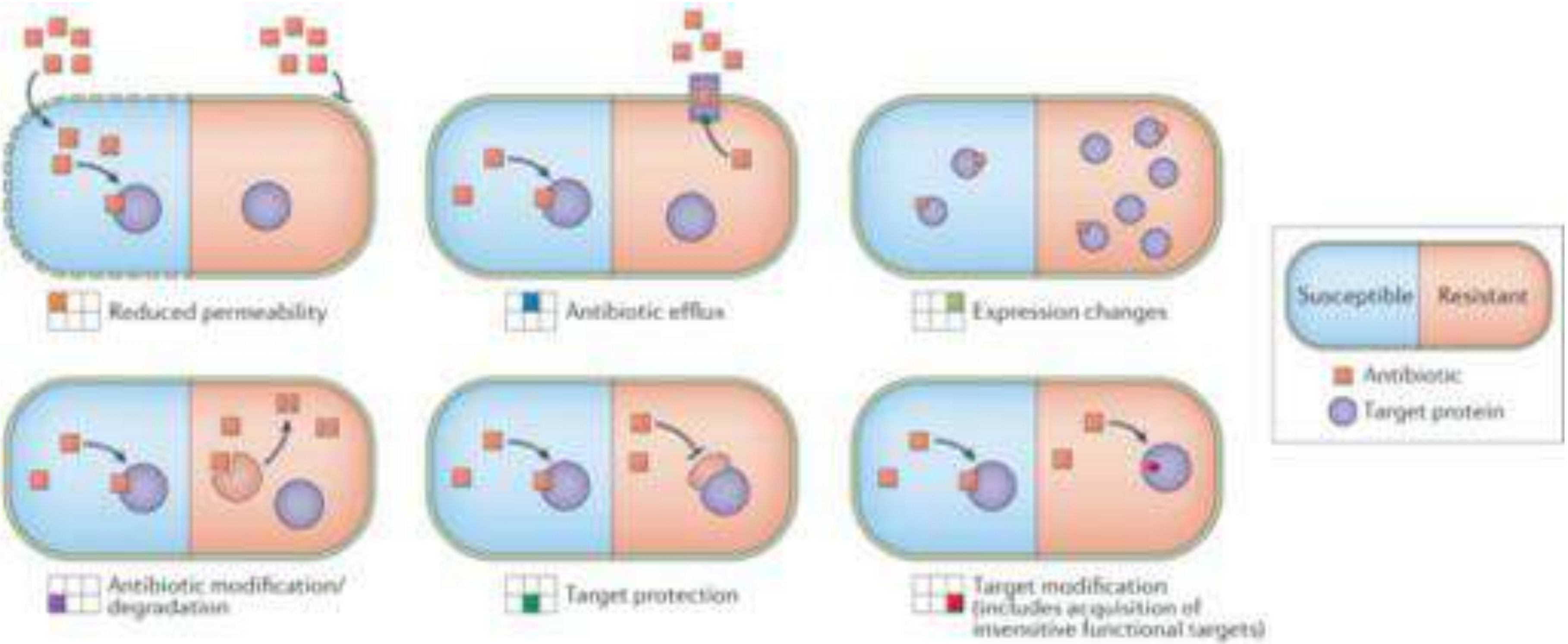
Kara Tsang
London School of Hygiene and Tropical Medicine (UK)

Public Health Alliance for Genomic Epidemiology

jpiamr
Joint Programming Initiative on Antimicrobial Resistance

CLIMB BIG DATA

Antimicrobial resistance (AMR) mechanisms

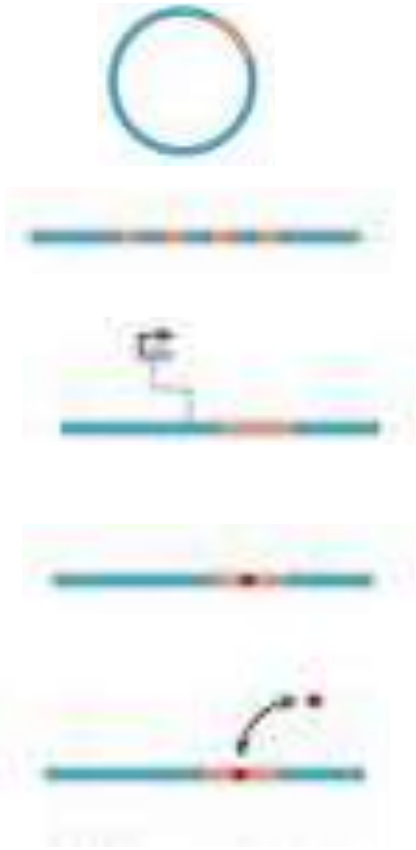


Boolchandani, et al. *Nat Rev Genet*, 2019.

Genetic determinants of AMR

▬ Resistance / target gene

▬ Promoter



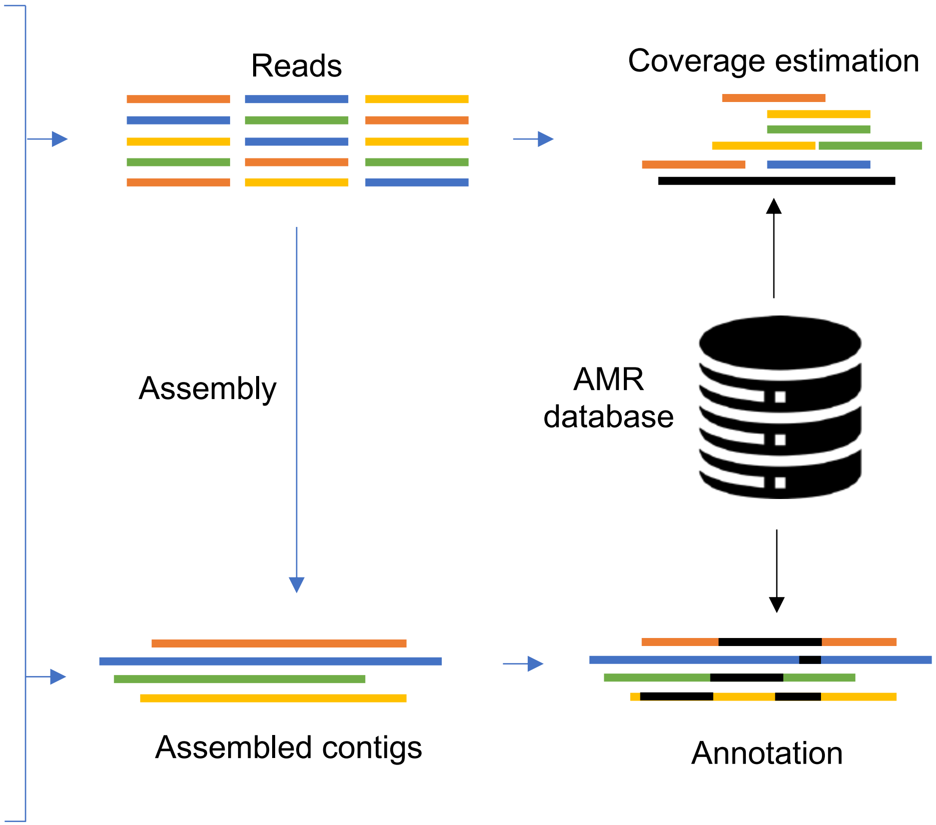
Horizontal gene transfer

Gene duplication

New promoter

Point mutation

Insertion or deletion



Reads

Coverage estimation

Assembly

AMR database

Assembled contigs

Annotation

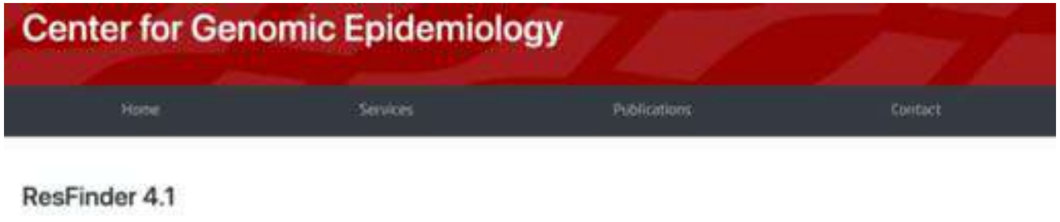
Boolchandani, et al. *Nat Rev Genet*, 2019.

AMR databases: overview

Database	Description	Link	Status
General databases			
CARD	• Ontology-based database that provides comprehensive information of AR genes and their resistance mechanisms • Currently contains >2,200 protein homologues and includes a curated set of resistance-conferring chromosomal mutations in protein-coding genes	https://card.mcmaster.ca/	Active; launched in 2013; updated monthly
Resfinder	Collation of AR genes involved in HGT events	https://cge.cbs.dtu.dk//services/ResFinder/	Active; started in 2012; update regularly; last update in February 2019
ResfinderFG	Collection of resistance gene variants identified in multiple functional metagenomics studies	https://cge.cbs.dtu.dk/services/ResFinderFG/	Active; last update in November 2016
Resfams	A profile HMM-based curated database confirmed for AR function	http://www.dantaslab.org/resfams/	Active; last update in January 2015
ARDB	• First centralized resource of AR gene information • Manually curated; contains >4,500 AR sequences	https://ardb.cbcb.umd.edu/	Archived; last updated in 2009
MEGARes	• Collation of multiple databases (CARD, ARG-ANNOT and ResFinder) to avoid redundancy between entries • For high-throughput screening and statistical analysis	https://megares.meglab.org/	Active; last update in December 2016
NDARO	• Collated and curated data from multiple databases (CARD, Lahey, Pasteur Institute β-Lactamases and ResFinder) • Contains 4,500 AR sequences	https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047	Active; started in 2016
ARG-ANNOT	• Repository of >1,800 AR sequences collated from scientific literature and online resources • Also includes point mutation data for select AR-associated chromosomal genes	Not available	Archived; last update in May 2018
Mustard	Resource containing 6,095 AR determinants from 20 families, including curated sets of AR genes identified in functional metagenomics studies	http://mgps.eu/Mustard/	Active; last update in November 2018
FARME database	Curated set of microbial sequences functionally screened to confer resistance in various functional metagenomics studies of different habitats	http://staff.washington.edu/jwallace/farme/	Active; last update in 2017
SARG (v2)	• Hierarchical structured database derived from ARDB, CARD and NCBI-NR database • Contains >12,000 AR genes; also includes profile HMMs for 189 AR genes subtypes	http://smile.hku.hk/SARGs	Active
Lahey list of β-lactamases	First initiative to compile known β-lactamases and assign nomenclature to novel ones	http://www.lahey.org/Studies/	Archived; last update in 2015
BLDB	Manually curated database for AR enzymes classified by class, family and subfamily	http://bldb.eu/	Active; last update in November 2018
LacED	Curated database of TEM and SHV β-lactamases, including a curated set of known TEM and SHV variants	http://www.laced.uni-stuttgart.de/	TEMLacED active; last update in 2017; SHVED archived; last update in April 2010
CBMAR	Database that identifies and characterizes novel β-lactamases on the basis of Ambler classification	http://proteininformatics.org/mkumar/lactamasedb/	Last update in September 2014

Boolchandani, et al. *Nat Rev Genet*, 2019.

AMR databases: focus



ResFinder 4.1

The Comprehensive Antibiotic Resistance Database

A bioinformatic database of resistance genes, their products and associated phenotypes.

6453 Ontology Terms, 4937 Reference Sequences, 1788 SNPs, 2775 Publications, 4983 AMR Detection Models

Resistome predictions: 263 pathogens, 14795 chromosomes, 2675 genomic islands, 30591 plasmids, 105556 WGS assemblies, 231629 alleles

CARD Bait Capture Platform 1.0.0 | State of the CARD 2021 Presentations & Demonstrations

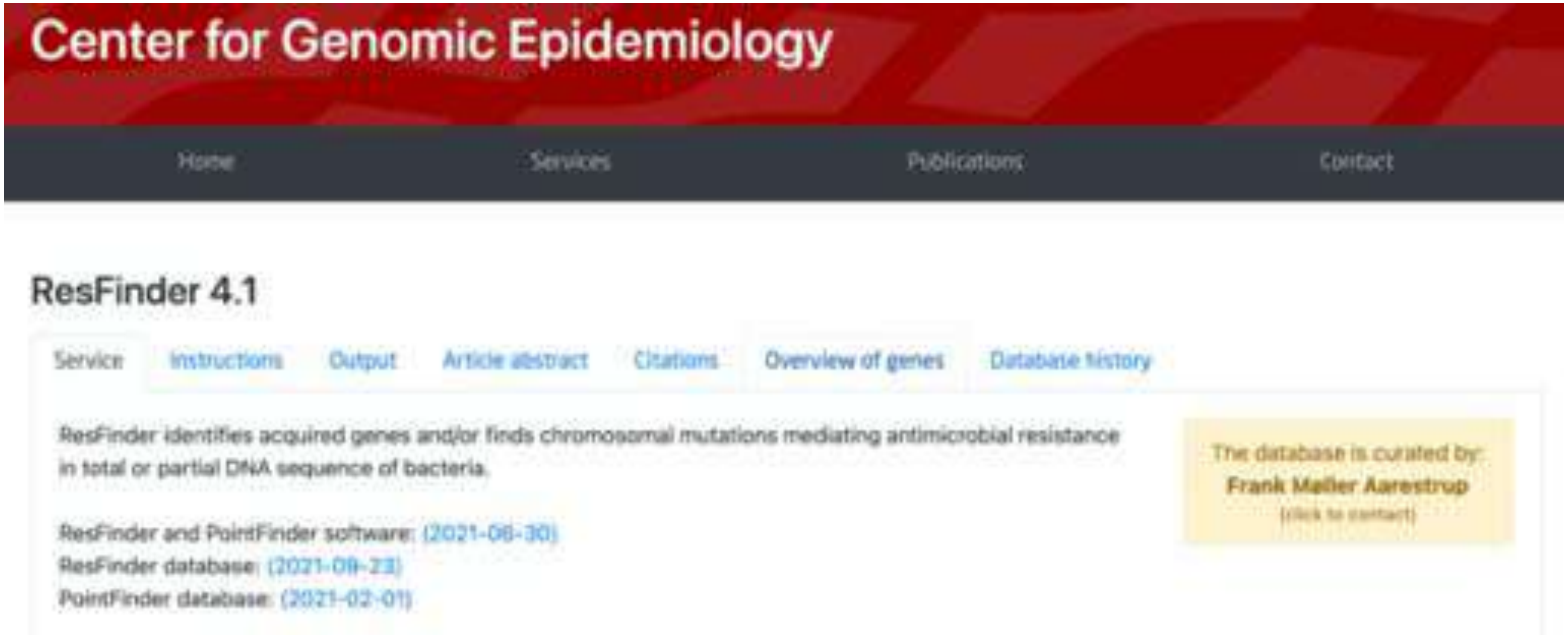
National Database of Antibiotic Resistant Organisms (NDARO)

BACTERIAL BIOINFORMATICS RESOURCE CENTER

PATRIC, the Pathosystems Resource Integration Center, provides integrated data and analysis tools to support biomedical research on bacterial infectious diseases.

- Broad in scope (species, AMR families, antibiotics)
- Build upon each other and add expertise
- Custom annotation tools
- Regularly updated and active

ResFinder: Overview



ResFinder 4.1

ResFinder identifies acquired genes and/or finds chromosomal mutations mediating antimicrobial resistance in total or partial DNA sequence of bacteria.

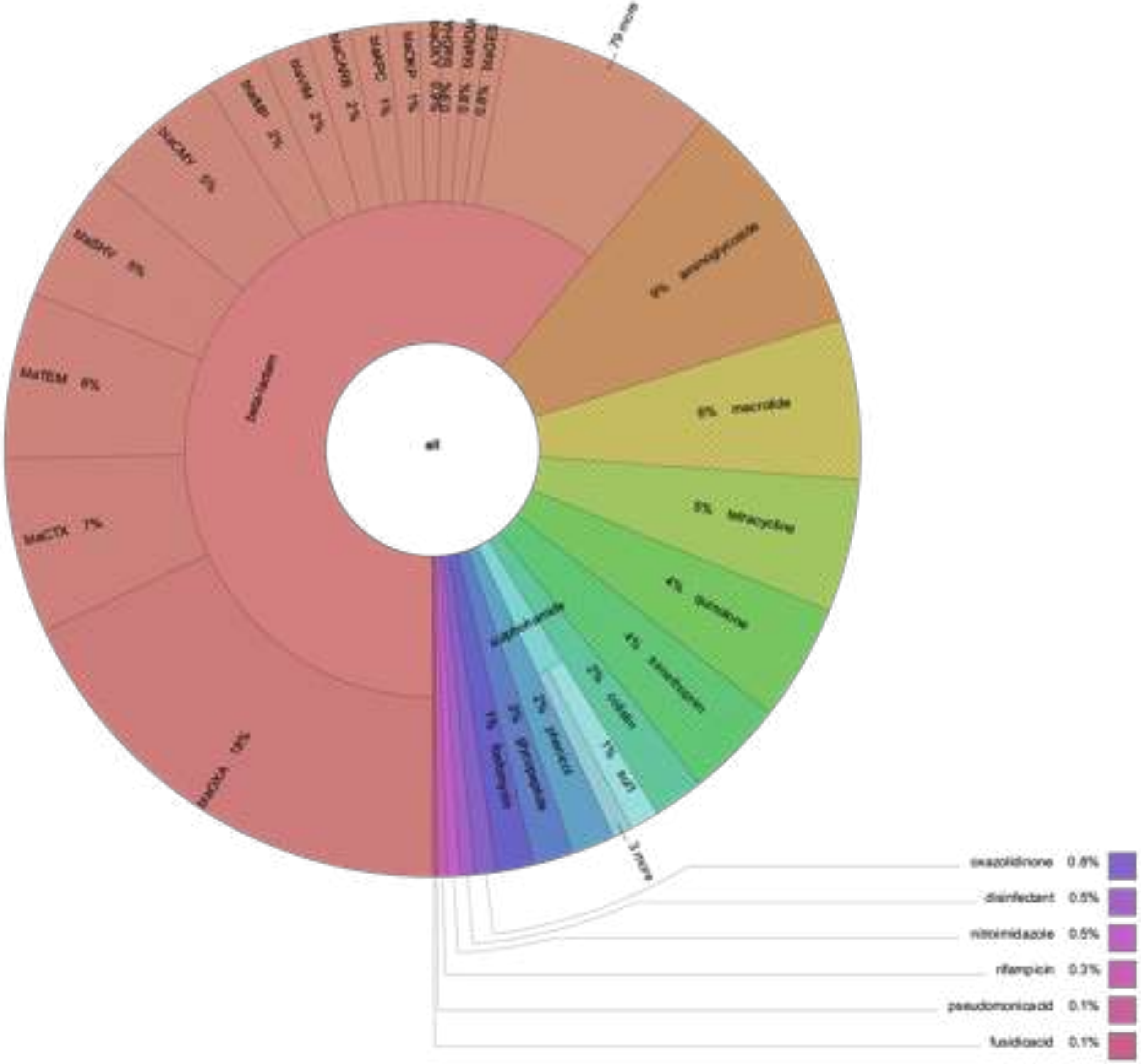
ResFinder and PointFinder software: (2021-06-30)
ResFinder database: (2021-08-23)
PointFinder database: (2021-02-01)

The database is curated by:
Frank Møller Aarestrup
(click to contact)

- Acquired genes (n=2919) and/or chromosomal mutations
    - *Campylobacter* spp.
    - *Campylobacter* jejuni
    - *Campylobacter* coli
    - *Escherichia coli*
    - *Salmonella* spp.
    - *Plasmodium falciparum*
    - *Neisseria gonorrhoeae*
    - *Mycobacterium tuberculosis*
    - *Enterococcus faecalis*
    - *Enterococcus faecium*
    - *Klebsiella*
    - *Helicobacter pylori*
    - *Staphylococcus aureus*

Bortolaia, et al. *J Antimicrob Chemother*, 2020. https://cge.cbs.dtu.dk/services/ResFinder/

ResFinder: Distribution of gene database



Bortolaia, et al. *J Antimicrob Chemother*, 2020. https://cge.cbs.dtu.dk/services/ResFinder/

ResFinder: Distribution of gene database

genomicepidemiology/resfinder_db

pseudomonicacid.fsa	9.21 KB	2021-03-09	added aac(3)-IIa_6_CP023555, blaCMY-150_...
quinolone.fsa	91.63 KB	2021-06-12	Fixed oqxA and oqxB gene names
rifampicin.fsa	4.77 KB	2020-08-28	Updated with genes ARR-8,blaIMI-4,ant(3'')-I...
sulphonamide.fsa	45.76 KB	2018-05-24	Reformat phenicol, rifampicin and sulphonami...
tetracycline.fsa	226.64 KB	2020-06-02	Update db with blaVMB-1,blaLMB-1,blaCMY-1...
trimethoprim.fsa	51.95 KB	2021-04-13	fixed dfra19_2 bug

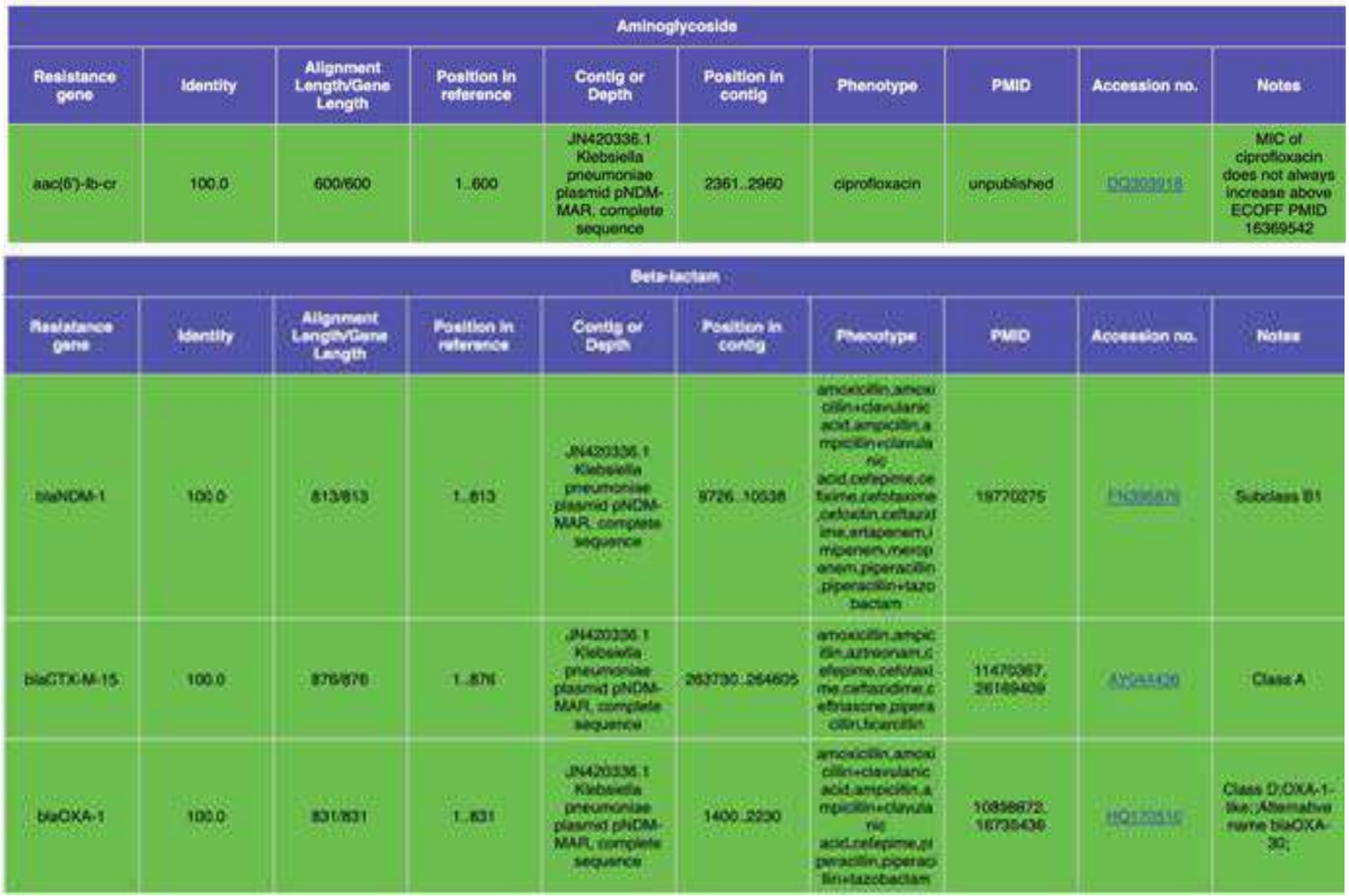
Bortolaia, et al. *J Antimicrob Chemother*, 2020. https://cge.cbs.dtu.dk/services/ResFinder/

ResFinder: AMR phenotype prediction results

ceftriaxone	beta-lactam	Resistant	blaCTX-M-15 (blaCTX-M-15_AY044436)
ceftazidime	beta-lactam	Resistant	blaCTX-M-15 (blaCTX-M-15_AY044436), blaNDM-1 (blaNDM-1_FN396876)
fortimicin	aminoglycoside	No resistance	
carbomycin	macrolide	No resistance	
ticarcillin	beta-lactam	Resistant	blaCTX-M-15 (blaCTX-M-15_AY044436)
azithromycin	macrolide	No resistance	
chlorhexidine	quaternary ammonium compound	No resistance	
kasugamycin	aminoglycoside	No resistance	
chloramphenicol	amphenicol	Resistant	catB3 (catB3_AJ009818), catA1 (catA1_V00622), catB3 (catB3_U13880)
cetylpyridinium chloride	quaternary ammonium compound	No resistance	
ampicillin+clavulanic acid	beta-lactam	Resistant	blaNDM-1 (blaNDM-1_FN396876), blaOXA-1 (blaOXA-1_HQ170510)
cefotaxime	beta-lactam	Resistant	blaCTX-M-15 (blaCTX-M-15_AY044436), blaNDM-1 (blaNDM-1_FN396876)

Bortolaia, et al. *J Antimicrob Chemother*, 2020. https://cge.cbs.dtu.dk/services/ResFinder/
ResFinder results using *Klebsiella pneumoniae* plasmid (JN420336.1)

ResFinder: AMR genotype results (genes and chromosomal mutations)

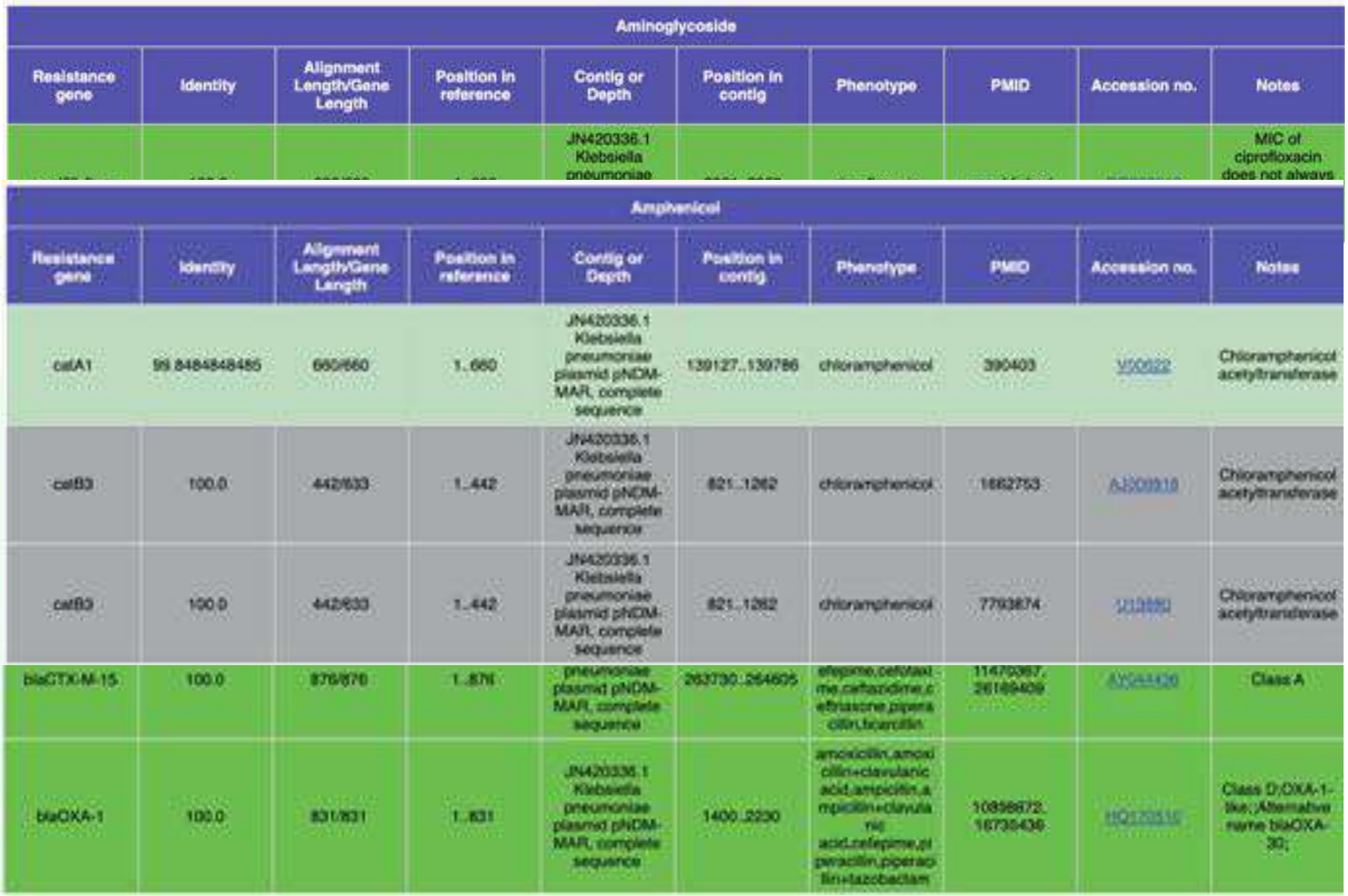


Aminoglycoside									
Resistance gene	Identity	Alignment Length/Gene Length	Position in reference	Contig or Depth	Position in contig	Phenotype	PMID	Accession no.	Notes
aac(6')-Ib-cr	100.0	600/600	1..600	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	2361..2960	ciprofloxacin	unpublished	DQ303918	MIC of ciprofloxacin does not always increase above ECOFF PMID 16369542

Beta-lactam									
Resistance gene	Identity	Alignment Length/Gene Length	Position in reference	Contig or Depth	Position in contig	Phenotype	PMID	Accession no.	Notes
blaNDM-1	100.0	813/813	1..813	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	9726..10538	amoxicillin,amoxicillin+clavulanic acid,ampicillin,ampicillin+clavulanic acid,cefepime,cefixime,cefotaxime,cefoxitin,ceftazidime,ertapenem,imipenem,meropenem,piperacillin,piperacillin+tazobactam	19770275	FN396876	Subclass B1
blaCTX-M-15	100.0	876/876	1..876	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	263730..264605	amoxicillin,ampicillin,aztreonam,cefepime,cefotaxime,ceftazidime,ceftriaxone,piperacillin,ticarcillin	11470367, 26169409	AY044436	Class A
blaOXA-1	100.0	831/831	1..831	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	1400..2230	amoxicillin,amoxicillin+clavulanic acid,ampicillin,ampicillin+clavulanic acid,cefepime,piperacillin,piperacillin+tazobactam	10858672, 16735436	HQ170510	Class D;OXA-1-like;;Alternative name blaOXA-30;

Bortolaia, et al. *J Antimicrob Chemother*, 2020. https://cge.cbs.dtu.dk/services/ResFinder/
ResFinder results using *Klebsiella pneumoniae* plasmid (JN420336.1)

ResFinder: AMR genotype results (genes and chromosomal mutations)



Aminoglycoside									
Resistance gene	Identity	Alignment Length/Gene Length	Position in reference	Contig or Depth	Position in contig	Phenotype	PMID	Accession no.	Notes
				JN420336.1 Klebsiella pneumoniae					MIC of ciprofloxacin does not always

Amphenicol									
Resistance gene	Identity	Alignment Length/Gene Length	Position in reference	Contig or Depth	Position in contig	Phenotype	PMID	Accession no.	Notes
catA1	99.8484848485	660/660	1..660	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	139127..139786	chloramphenicol	390403	V00622	Chloramphenicol acetyltransferase
catB3	100.0	442/633	1..442	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	821..1262	chloramphenicol	1662753	AJ009818	Chloramphenicol acetyltransferase
catB3	100.0	442/633	1..442	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	821..1262	chloramphenicol	7793874	U13880	Chloramphenicol acetyltransferase
blaCTX-M-15	100.0	876/876	1..876	pneumoniae plasmid pNDM-MAR, complete sequence	263730..264605	efepime,cefotaxime,ceftazidime,ceftriaxone,piperacillin,ticarcillin	11470367, 26169409	AY044436	Class A
blaOXA-1	100.0	831/831	1..831	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	1400..2230	amoxicillin,amoxicillin+clavulanic acid,ampicillin,ampicillin+clavulanic acid,cefepime,piperacillin,piperacillin+tazobactam	10898672, 16735436	HQ170510	Class D;OXA-1-like;;Alternative name blaOXA-30;

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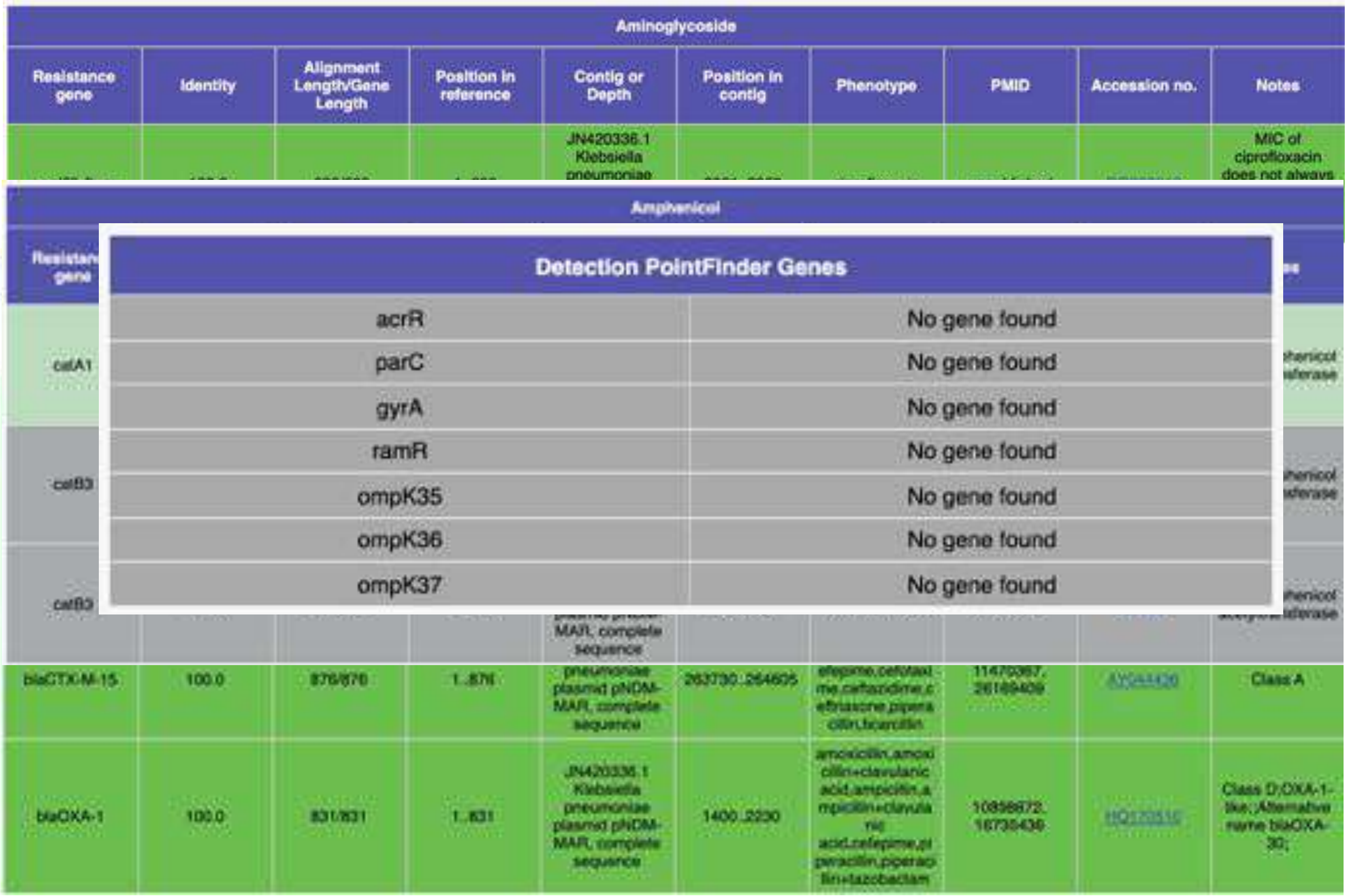

Aminoglycoside

Resistance gene	Identity	Alignment Length/Gene Length	Position in reference	Contig or Depth	Position in contig	Phenotype	PMID	Accession no.	Notes
				JN420336.1 Klebsiella pneumoniae					MIC of ciprofloxacin does not always

Amphenicol

Resistance gene		Notes
catA1		…phenicol …sferase
catB3		…phenicol …sferase
catB3	… plasmid pNDM-MAR, complete sequence	…phenicol acetyltransferase

Detection PointFinder Genes

acrR	No gene found
parC	No gene found
gyrA	No gene found
ramR	No gene found
ompK35	No gene found
ompK36	No gene found
ompK37	No gene found

Resistance gene	Identity	Alignment Length/Gene Length	Position in reference	Contig or Depth	Position in contig	Phenotype	PMID	Accession no.	Notes
blaCTX-M-15	100.0	876/876	1..876	… pneumoniae plasmid pNDM-MAR, complete sequence	263730..264605	…cefepime,cefotaxime,ceftazidime,ceftriaxone,piperacillin,ticarcillin	11470367, 26169409	AY044436	Class A
blaOXA-1	100.0	831/831	1..831	JN420336.1 Klebsiella pneumoniae plasmid pNDM-MAR, complete sequence	1400..2230	amoxicillin,amoxicillin+clavulanic acid,ampicillin,ampicillin+clavulanic acid,cefepime,piperacillin,piperacillin+tazobactam	10898672, 16735439	HQ170510	Class D;OXA-1-like;Alternative name blaOXA-30;

Bortolaia, et al. *J Antimicrob Chemother*, 2020. https://cge.cbs.dtu.dk/services/ResFinder/
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Comprehensive Antibiotic Resistance Database (CARD)

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A bioinformatic database of resistance genes, their products and associated phenotypes.

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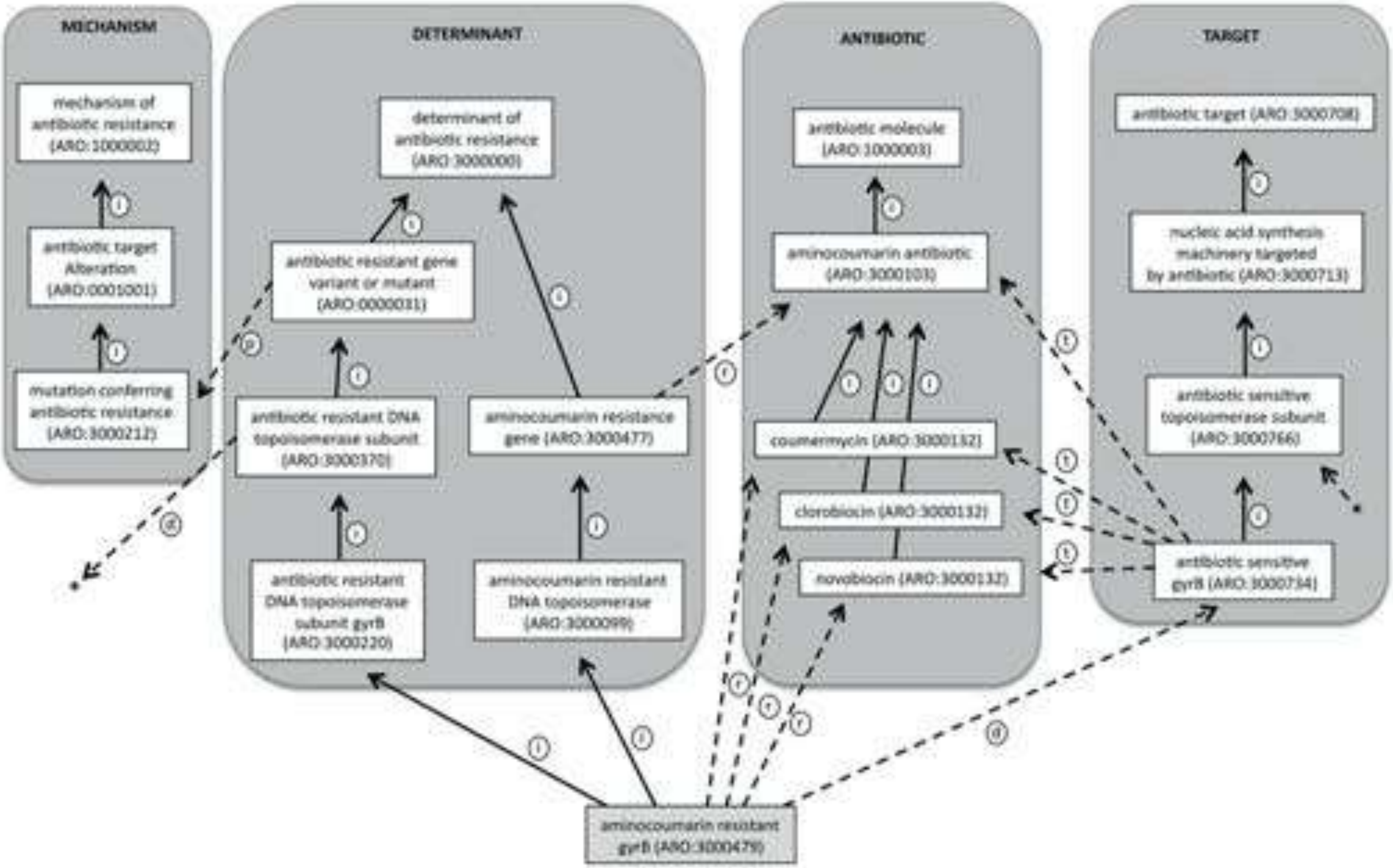
CARD Bait Capture Platform 1.0.0 | State of the CARD 2021 Presentations & Demonstrations

- ResFinder
- ARG-ANNOT
- NCBI National Database of Antibiotic Resistant Organisms (NDARO)
- Antibiotic Resistance Genes Database (ARDB)
- Beta-lactamase Database..and more
- Literature & domain knowledge experts

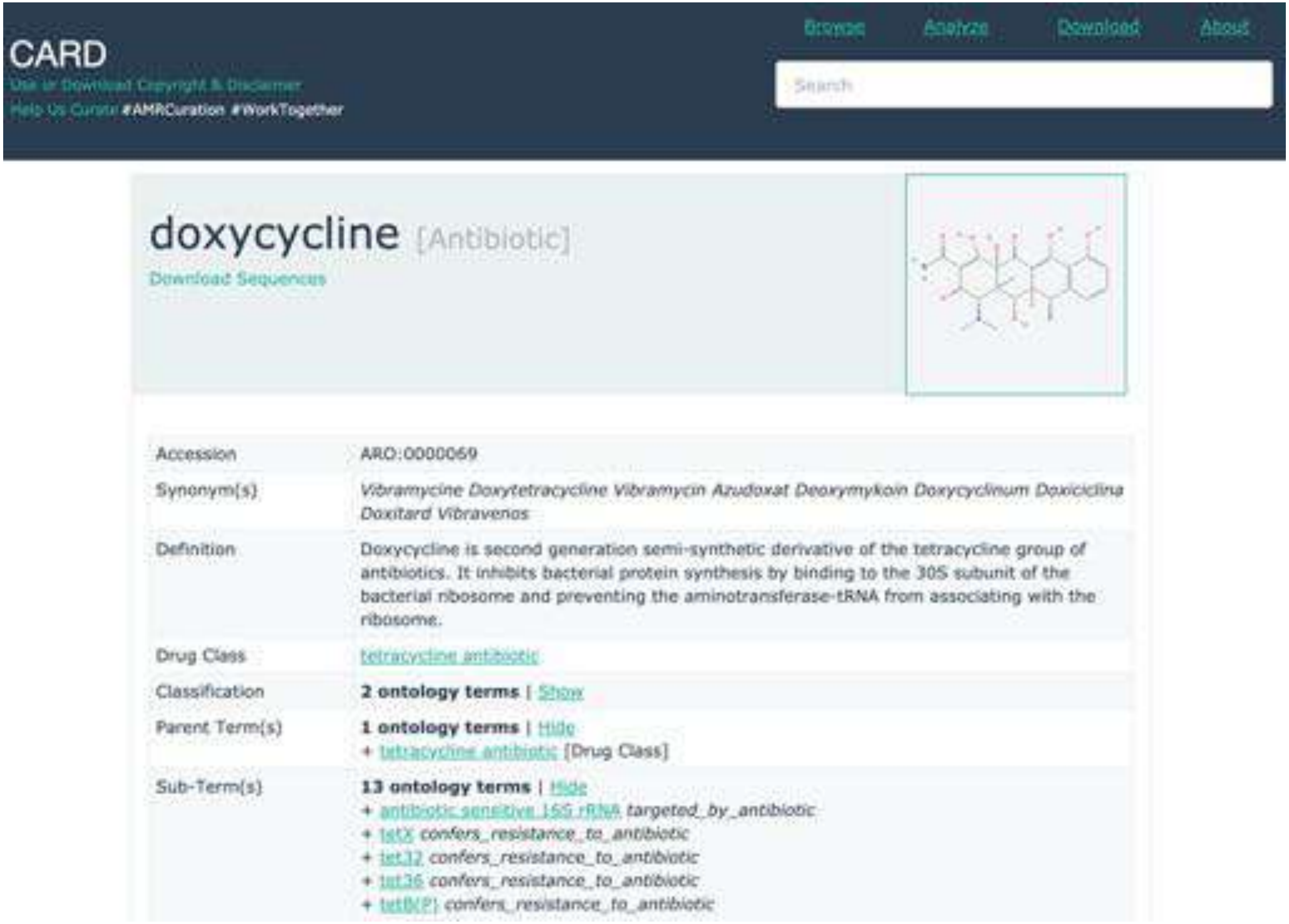
Alcock, et al. *Nucleic Acids Res*, 2020. https://card.mcmaster.ca/, https://github.com/arpcard/state-of-the-card-2021

Antibiotic Resistance Ontology (ARO)



McArthur, et al. *Antimicrob Agents Chemother*, 2013. https://card.mcmaster.ca/ontology/36006

Antibiotic Resistance Ontology (ARO)



doxycycline [Antibiotic]

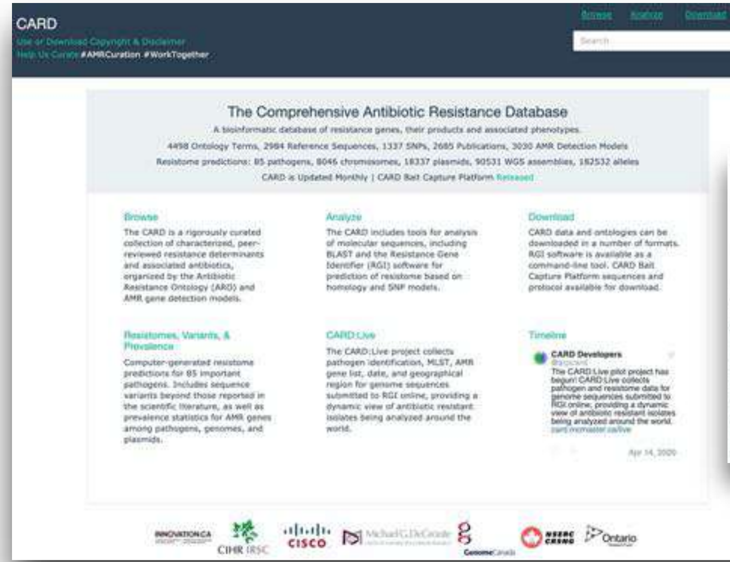
Download Sequences

Accession	ARO:0000069
Synonym(s)	*Vibramycine Doxytetracycline Vibramycin Azudoxat Deoxymykoin Doxycyclinum Doxiciclina Doxitard Vibravenos*
Definition	Doxycycline is second generation semi-synthetic derivative of the tetracycline group of antibiotics. It inhibits bacterial protein synthesis by binding to the 30S subunit of the bacterial ribosome and preventing the aminotransferase-tRNA from associating with the ribosome.
Drug Class	tetracycline antibiotic
Classification	**2 ontology terms** | Show
Parent Term(s)	**1 ontology terms** | Hide + tetracycline antibiotic [Drug Class]
Sub-Term(s)	**13 ontology terms** | Hide + antibiotic sensitive 16S rRNA *targeted_by_antibiotic* + tetX *confers_resistance_to_antibiotic* + tet32 *confers_resistance_to_antibiotic* + tet36 *confers_resistance_to_antibiotic* + tetB(P) *confers_resistance_to_antibiotic*

McArthur, et al. *Antimicrob Agents Chemother*, 2013. https://card.mcmaster.ca/ontology/36006

Predicting AMR determinants using Resistance Gene Identifier (RGI)

Comprehensive Antibiotic Resistance Database (CARD)



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Help Us Curate #AMRCuration #WorkTogether

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A bioinformatic database of resistance genes, their products and associated phenotypes.

4498 Ontology Terms, 2984 Reference Sequences, 1337 SNPs, 2685 Publications, 3030 AMR Detection Models

Resistome predictions: 85 pathogens, 8046 chromosomes, 18337 plasmids, 90531 WGS assemblies, 182532 alleles

CARD is Updated Monthly | CARD Bait Capture Platform Released

Browse

The CARD is a rigorously curated collection of characterized, peer-reviewed resistance determinants and associated antibiotics, organized by the Antibiotic Resistance Ontology (ARO) and AMR gene detection models.

Analyze

The CARD includes tools for analysis of molecular sequences, including BLAST and the Resistance Gene Identifier (RGI) software for prediction of resistome based on homology and SNP models.

Download

CARD data and ontologies can be downloaded in a number of formats. RGI software is available as a command-line tool. CARD Bait Capture Platform sequences and protocol available for download.

Resistomes, Variants, & Prevalence

Computer-generated resistome predictions for 85 important pathogens. Includes sequence variants beyond those reported in the scientific literature, as well as prevalence statistics for AMR genes among pathogens, genomes, and plasmids.

CARD:Live

The CARD:Live project collects pathogen identification, MLST, AMR gene list, date, and geographical region for genome sequences submitted to RGI online, providing a dynamic view of antibiotic resistant isolates being analyzed around the world.

Timeline

CARD Developers

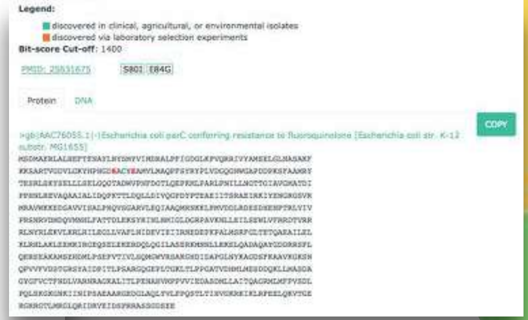
The CARD:Live pilot project has begun! CARD:Live collects pathogen and resistome data for genome sequences submitted to RGI online, providing a dynamic view of antibiotic resistant isolates being analyzed around the world. card.mcmaster.ca/live

Apr 14, 2020

card.mcmaster.ca

Genomics reference sequence database

Bioinformatics model



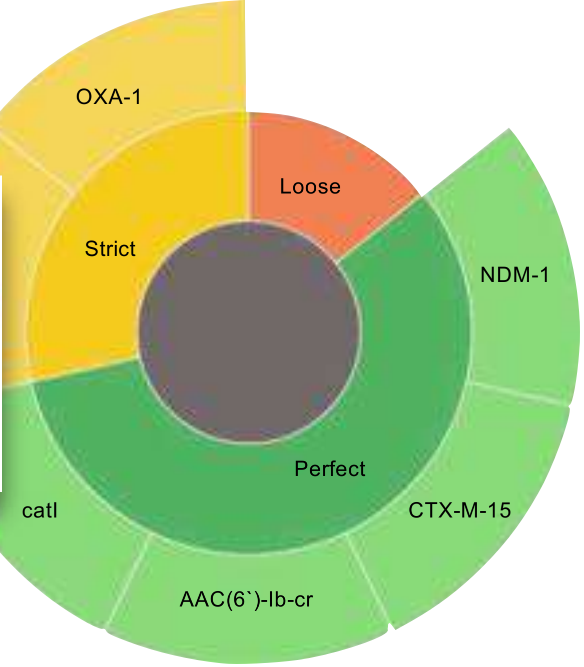
Legend:
- 🟩 discovered in clinical, agricultural, or environmental isolates
- 🟥 discovered via laboratory selection experiments

Bit-score Cut-off: 1400

PMID: 25831675 S80I E84G

>gb|AAC76055.1|-|Escherichia coli parC conferring resistance to fluoroquinolone [Escherichia coli str. K-12 substr. MG1655]

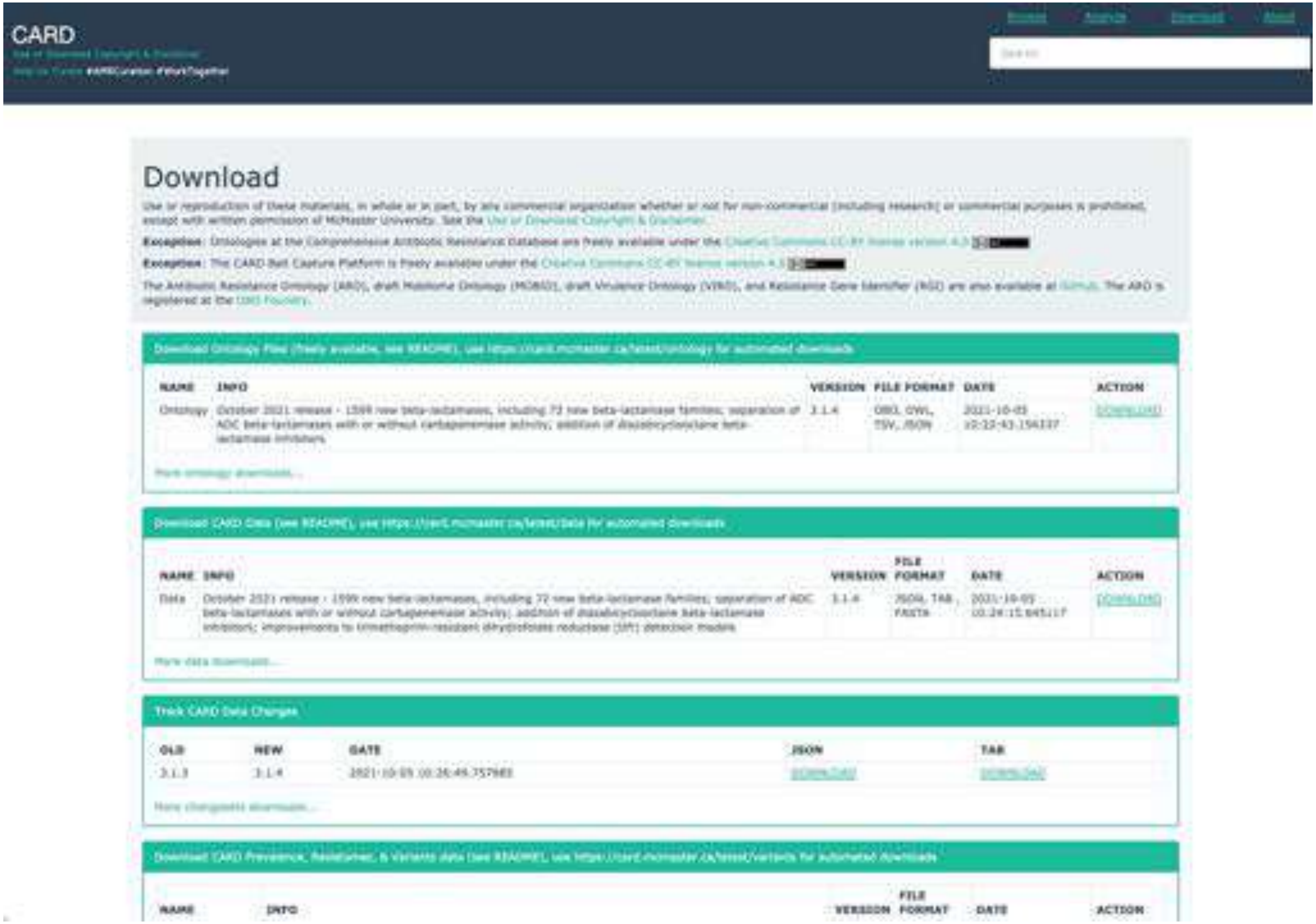
Resistance Gene Identifier (RGI)



Uses bioinformatics models to predict resistance determinants within clinical isolates

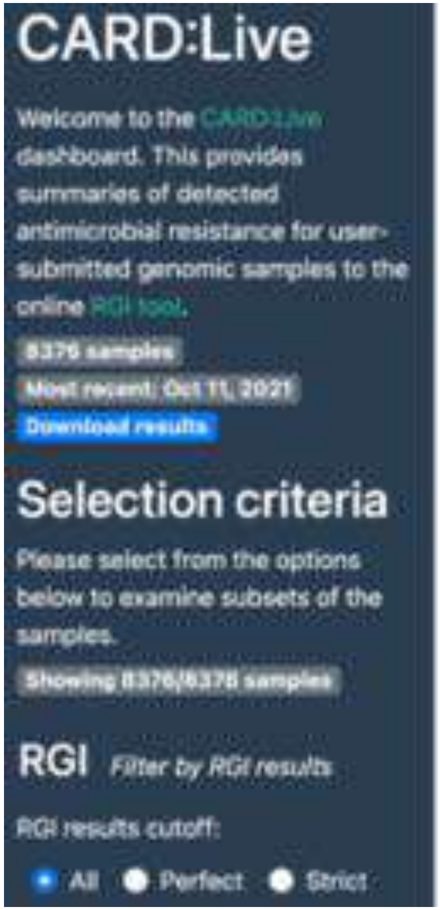
Alcock, et al. *Nucleic Acids Res*, 2020. https://card.mcmaster.ca/analyze

CARD: Download



Alcock, et al. *Nucleic Acids Res*, 2020. https://card.mcmaster.ca/download

CARD:Live – Summary of user-submitted genome sequences



CARD:Live

Welcome to the CARD:Live dashboard. This provides summaries of detected antimicrobial resistance for user-submitted genomic samples to the online RGI tool.

8376 samples

Most recent: Oct 11, 2021

Download results

Selection criteria

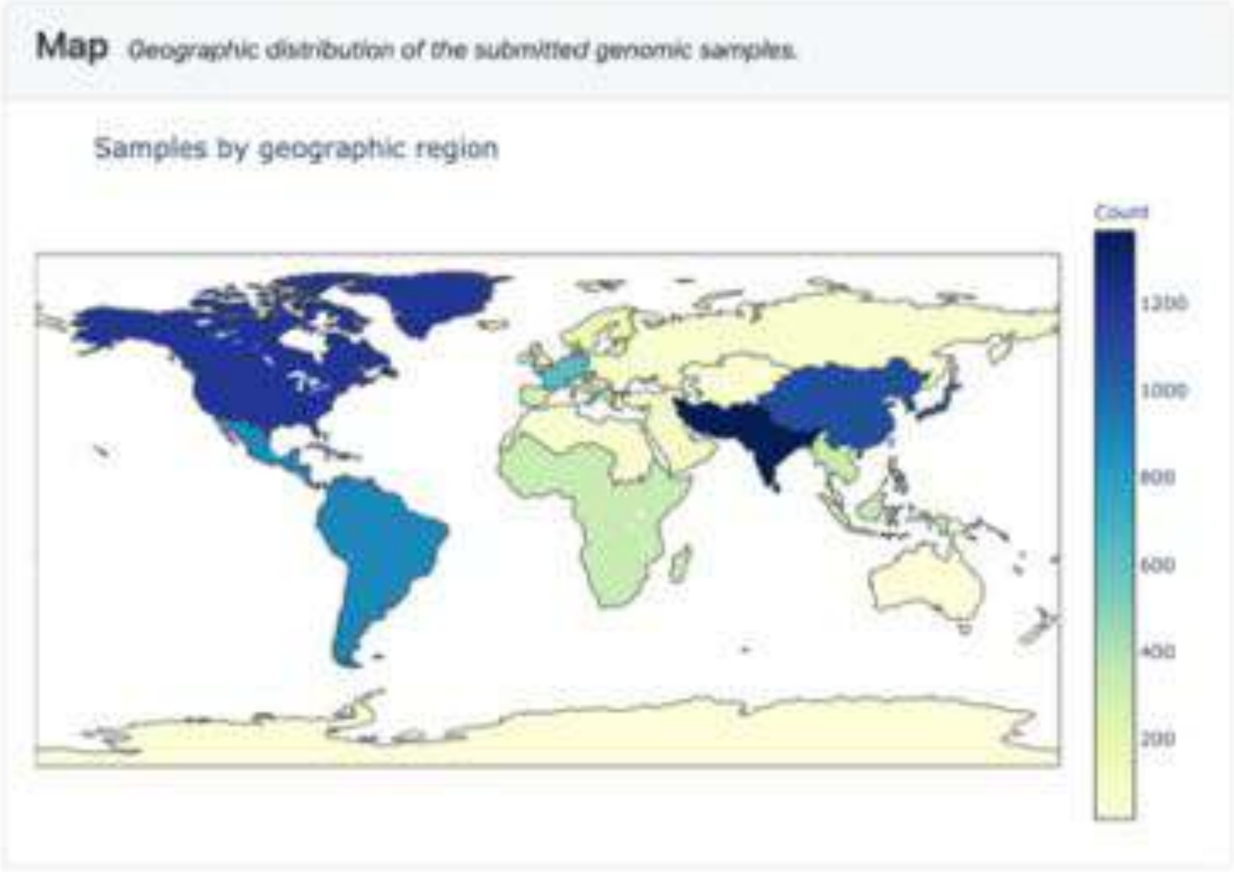
Please select from the options below to examine subsets of the samples.

Showing 8376/8376 samples

RGI *Filter by RGI results*

RGI results cutoff:

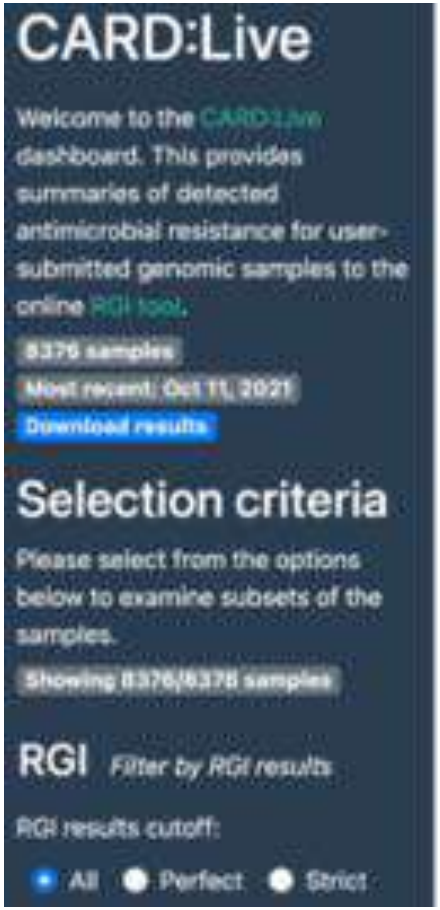
● All ○ Perfect ○ Strict



Map *Geographic distribution of the submitted genomic samples.*

https://card.mcmaster.ca/live

CARD:Live – Summary of user-submitted genome sequences



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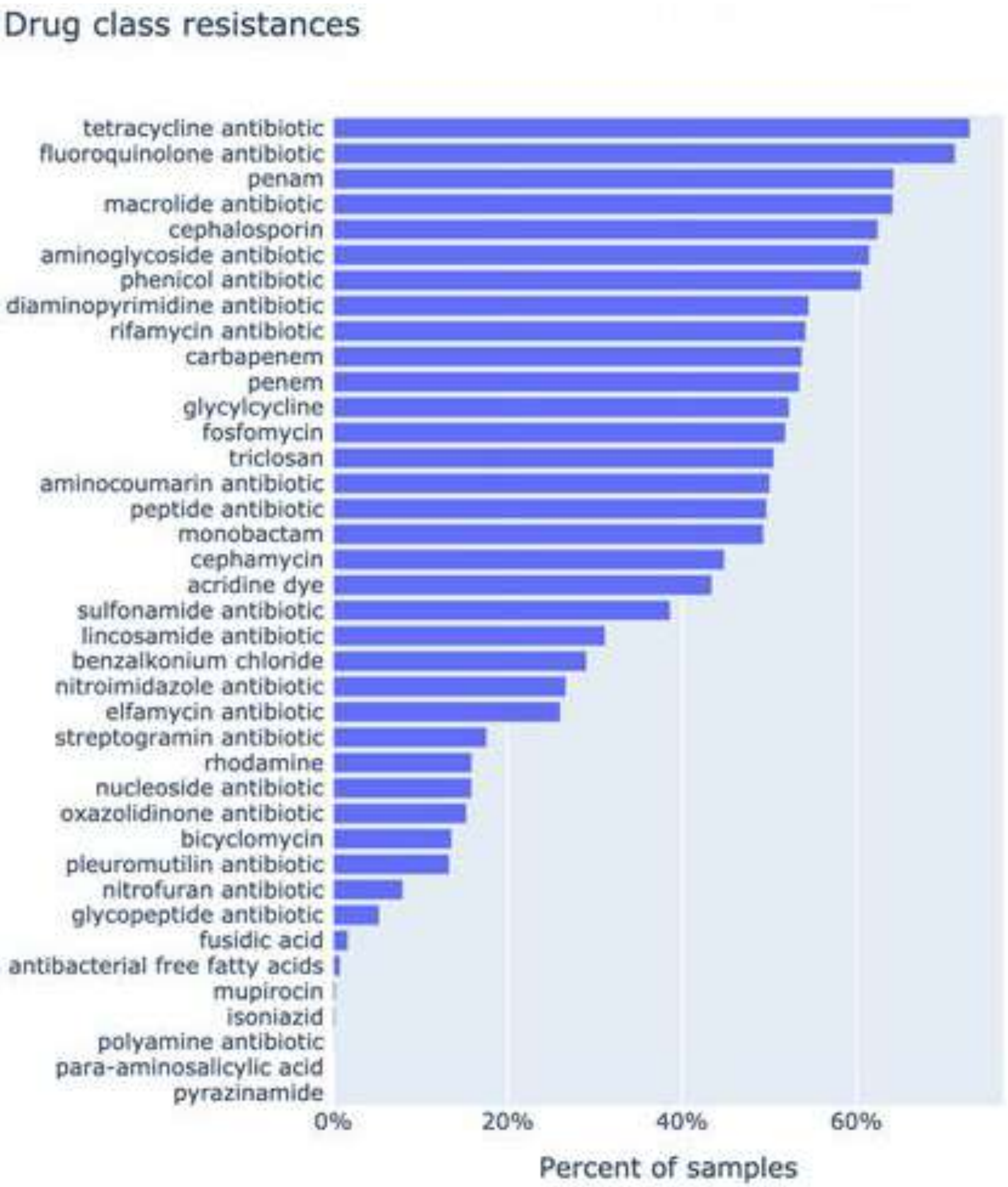

https://card.mcmaster.ca/live

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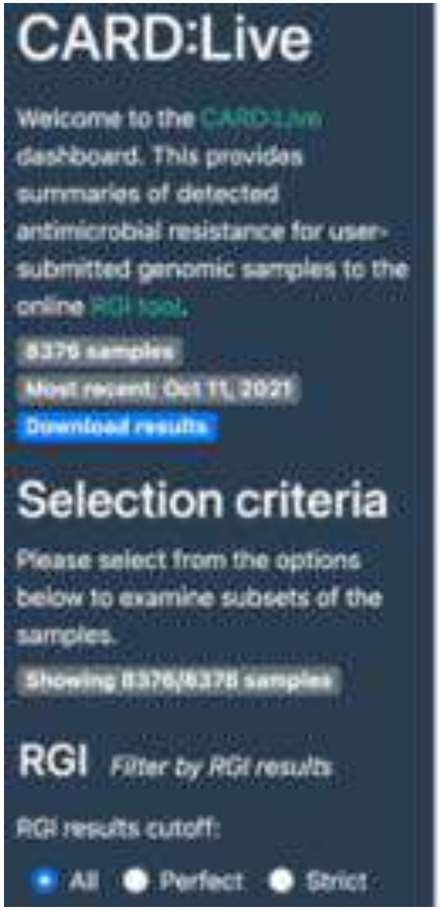

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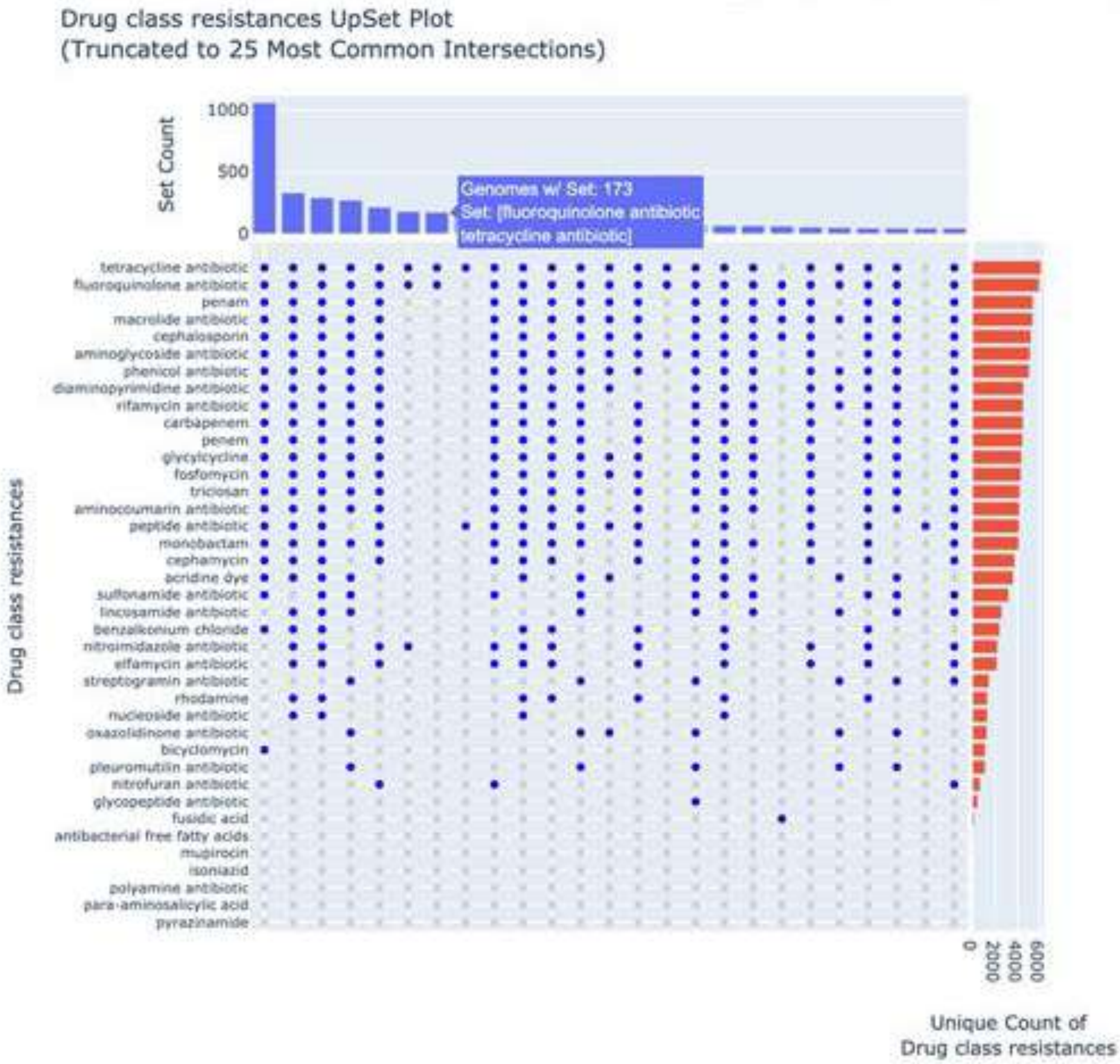
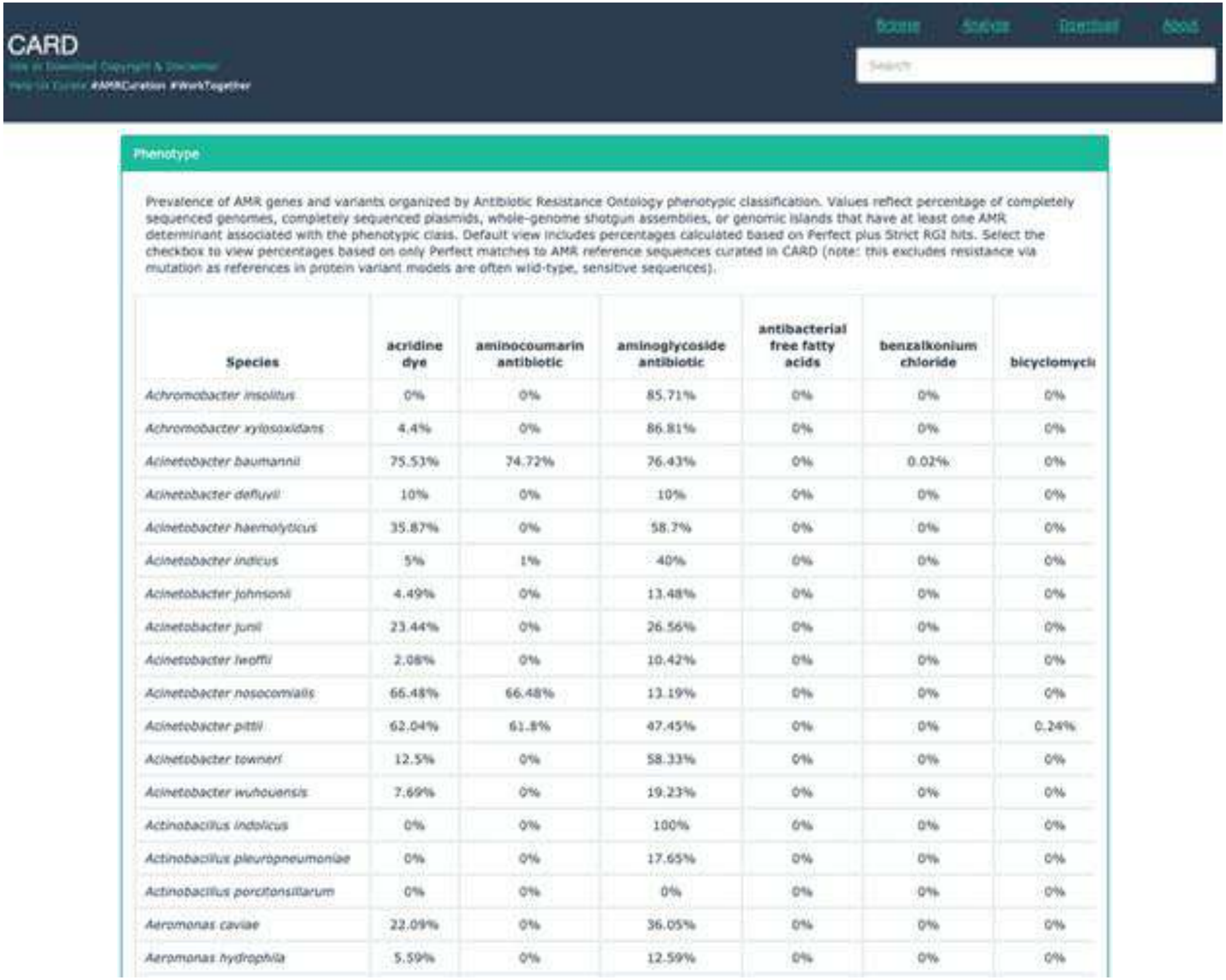
RGI results cutoff:

● All ○ Perfect ○ Strict



https://card.mcmaster.ca/live

CARD: Prevalence – Summary of NCBI genomes

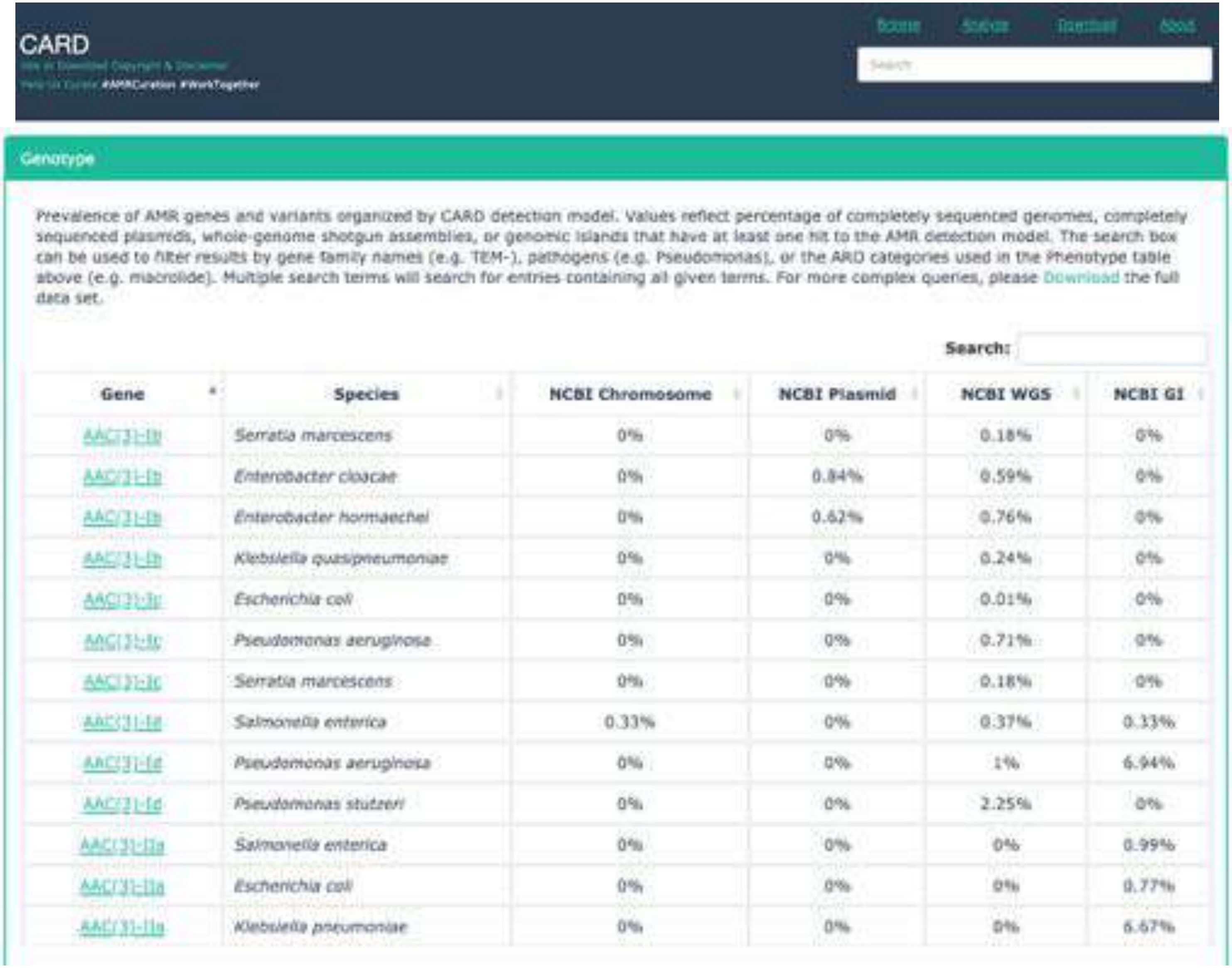


Prevalence of AMR genes and variants organized by Antibiotic Resistance Ontology phenotypic classification. Values reflect percentage of completely sequenced genomes, completely sequenced plasmids, whole-genome shotgun assemblies, or genomic islands that have at least one AMR determinant associated with the phenotypic class. Default view includes percentages calculated based on Perfect plus Strict RGI hits. Select the checkbox to view percentages based on only Perfect matches to AMR reference sequences curated in CARD (note: this excludes resistance via mutation as references in protein variant models are often wild-type, sensitive sequences).

Species	acridine dye	aminocoumarin antibiotic	aminoglycoside antibiotic	antibacterial free fatty acids	benzalkonium chloride	bicyclomyci
Achromobacter insolitus	0%	0%	85.71%	0%	0%	0%
Achromobacter xylosoxidans	4.4%	0%	86.81%	0%	0%	0%
Acinetobacter baumannii	75.53%	74.72%	76.43%	0%	0.02%	0%
Acinetobacter defluvii	10%	0%	10%	0%	0%	0%
Acinetobacter haemolyticus	35.87%	0%	58.7%	0%	0%	0%
Acinetobacter indicus	5%	1%	40%	0%	0%	0%
Acinetobacter johnsonii	4.49%	0%	13.48%	0%	0%	0%
Acinetobacter junii	23.44%	0%	26.56%	0%	0%	0%
Acinetobacter lwoffii	2.08%	0%	10.42%	0%	0%	0%
Acinetobacter nosocomialis	66.48%	66.48%	13.19%	0%	0%	0%
Acinetobacter pittii	62.04%	61.8%	47.45%	0%	0%	0.24%
Acinetobacter towneri	12.5%	0%	58.33%	0%	0%	0%
Acinetobacter wuhouensis	7.69%	0%	19.23%	0%	0%	0%
Actinobacillus indolicus	0%	0%	100%	0%	0%	0%
Actinobacillus pleuropneumoniae	0%	0%	17.65%	0%	0%	0%
Actinobacillus porcitonsillarum	0%	0%	0%	0%	0%	0%
Aeromonas caviae	22.09%	0%	36.05%	0%	0%	0%
Aerpmonas hydrophila	5.59%	0%	12.59%	0%	0%	0%

https://card.mcmaster.ca/prevalence

CARD: Prevalence – Summary of NCBI genomes



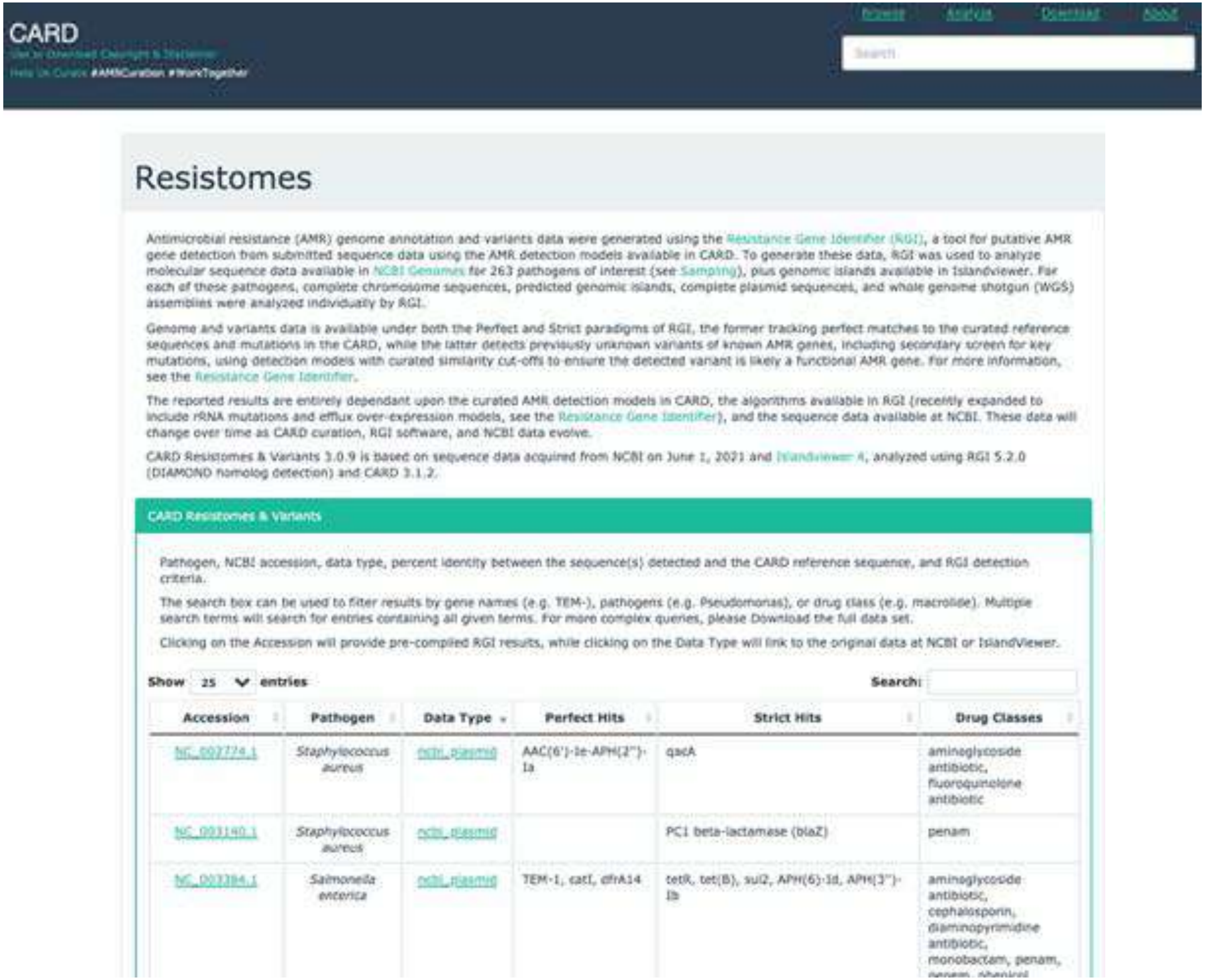
Prevalence of AMR genes and variants organized by CARD detection model. Values reflect percentage of completely sequenced genomes, completely sequenced plasmids, whole-genome shotgun assemblies, or genomic islands that have at least one hit to the AMR detection model. The search box can be used to filter results by gene family names (e.g. TEM-), pathogens (e.g. Pseudomonas), or the ARO categories used in the Phenotype table above (e.g. macrolide). Multiple search terms will search for entries containing all given terms. For more complex queries, please Download the full data set.

Search:

Gene	Species	NCBI Chromosome	NCBI Plasmid	NCBI WGS	NCBI GI
AAC(3)-Ib	*Serratia marcescens*	0%	0%	0.18%	0%
AAC(3)-Ib	*Enterobacter cloacae*	0%	0.84%	0.59%	0%
AAC(3)-Ib	*Enterobacter hormaechei*	0%	0.62%	0.76%	0%
AAC(3)-Ib	*Klebsiella quasipneumoniae*	0%	0%	0.24%	0%
AAC(3)-Ic	*Escherichia coli*	0%	0%	0.01%	0%
AAC(3)-Ic	*Pseudomonas aeruginosa*	0%	0%	0.71%	0%
AAC(3)-Ic	*Serratia marcescens*	0%	0%	0.18%	0%
AAC(3)-Id	*Salmonella enterica*	0.33%	0%	0.37%	0.33%
AAC(3)-Id	*Pseudomonas aeruginosa*	0%	0%	1%	6.94%
AAC(3)-Id	*Pseudomonas stutzeri*	0%	0%	2.25%	0%
AAC(3)-IIa	*Salmonella enterica*	0%	0%	0%	0.99%
AAC(3)-IIa	*Escherichia coli*	0%	0%	0%	0.77%
AAC(3)-IIa	*Klebsiella pneumoniae*	0%	0%	0%	6.67%

https://card.mcmaster.ca/prevalence

CARD: Resistomes & Variants – Details of NCBI genomes



Resistomes

Antimicrobial resistance (AMR) genome annotation and variants data were generated using the Resistance Gene Identifier (RGI), a tool for putative AMR gene detection from submitted sequence data using the AMR detection models available in CARD. To generate these data, RGI was used to analyze molecular sequence data available in NCBI Genomes for 263 pathogens of interest (see Sampling), plus genomic islands available in IslandViewer. For each of these pathogens, complete chromosome sequences, predicted genomic islands, complete plasmid sequences, and whole genome shotgun (WGS) assemblies were analyzed individually by RGI.

Genome and variants data is available under both the Perfect and Strict paradigms of RGI, the former tracking perfect matches to the curated reference sequences and mutations in the CARD, while the latter detects previously unknown variants of known AMR genes, including secondary screen for key mutations, using detection models with curated similarity cut-offs to ensure the detected variant is likely a functional AMR gene. For more information, see the Resistance Gene Identifier.

The reported results are entirely dependant upon the curated AMR detection models in CARD, the algorithms available in RGI (recently expanded to include rRNA mutations and efflux over-expression models, see the Resistance Gene Identifier), and the sequence data available at NCBI. These data will change over time as CARD curation, RGI software, and NCBI data evolve.

CARD Resistomes & Variants 3.0.9 is based on sequence data acquired from NCBI on June 1, 2021 and IslandViewer 4, analyzed using RGI 5.2.0 (DIAMOND homolog detection) and CARD 3.1.2.

CARD Resistomes & Variants

Pathogen, NCBI accession, data type, percent identity between the sequence(s) detected and the CARD reference sequence, and RGI detection criteria.

The search box can be used to filter results by gene names (e.g. TEM-), pathogens (e.g. Pseudomonas), or drug class (e.g. macrolide). Multiple search terms will search for entries containing all given terms. For more complex queries, please Download the full data set.

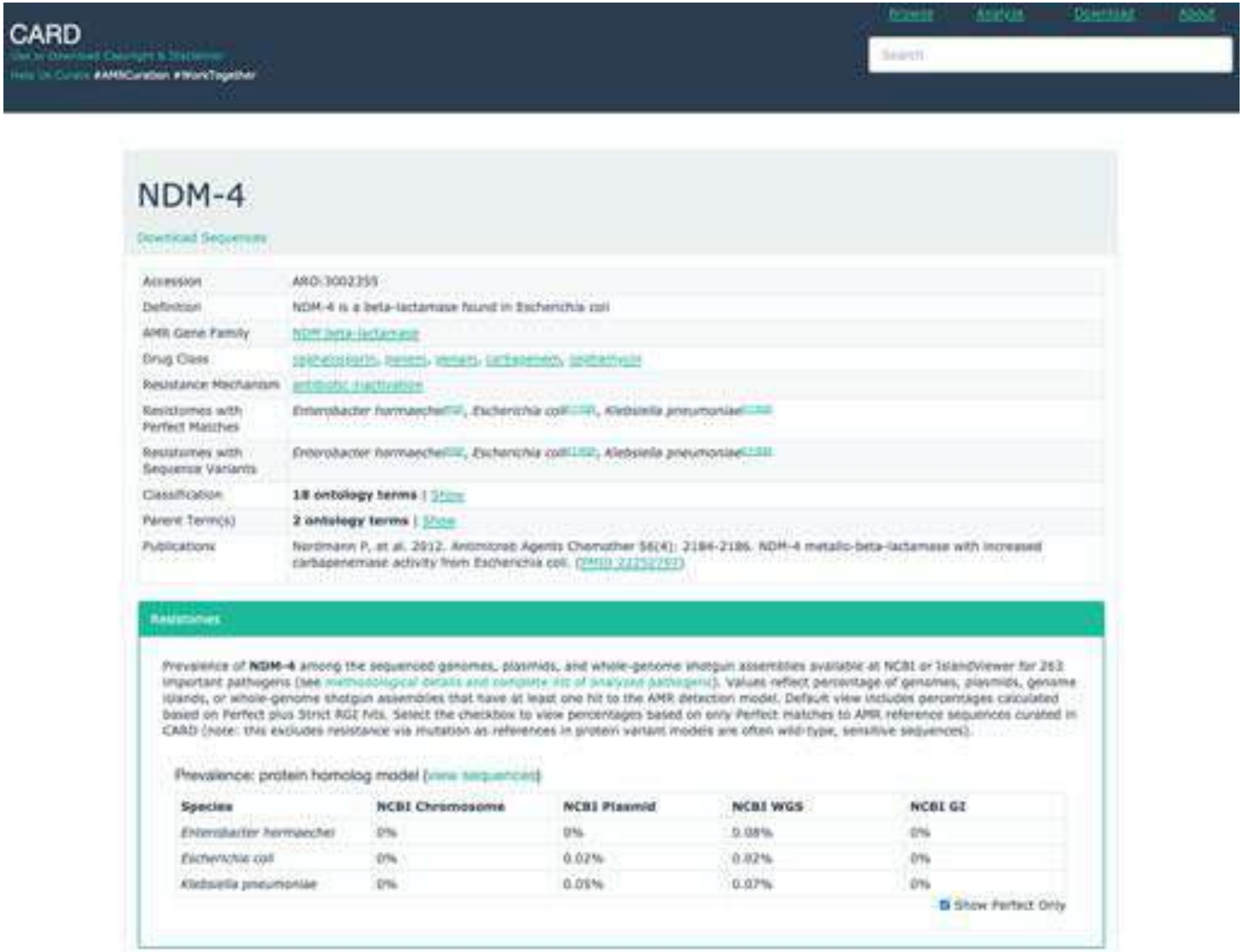
Clicking on the Accession will provide pre-compiled RGI results, while clicking on the Data Type will link to the original data at NCBI or IslandViewer.

Show 25 entries Search:

Accession	Pathogen	Data Type	Perfect Hits	Strict Hits	Drug Classes
NC_003774.1	*Staphylococcus aureus*	ncbi_plasmid	AAC(6')-Ie-APH(2")-Ia	qacA	aminoglycoside antibiotic, fluoroquinolone antibiotic
NC_003140.1	*Staphylococcus aureus*	ncbi_plasmid		PC1 beta-lactamase (blaZ)	penam
NC_003384.1	*Salmonella enterica*	ncbi_plasmid	TEM-1, catI, dfrA14	tetR, tet(B), sul2, APH(6)-Id, APH(3")-Ib	aminoglycoside antibiotic, cephalosporin, diaminopyrimidine antibiotic, monobactam, penam, penem, phenicol

https://card.mcmaster.ca/genomes

CARD: Resistomes & Variants – Details of NCBI genomes



NDM-4

Accession	ARO:3002355
Definition	NDM-4 is a beta-lactamase found in Escherichia coli
AMR Gene Family	NDM beta-lactamase
Drug Class	cephalosporin, penem, penam, carbapenem, cephamycin
Resistance Mechanism	antibiotic inactivation
Resistomes with Perfect Matches	*Enterobacter hormaechei*, *Escherichia coli*, *Klebsiella pneumoniae*
Resistomes with Sequence Variants	*Enterobacter hormaechei*, *Escherichia coli*, *Klebsiella pneumoniae*
Classification	**18 ontology terms** | Show
Parent Term(s)	**2 ontology terms** | Show
Publications	Nordmann P, et al. 2012. Antimicrob Agents Chemother 56(4): 2184-2186. NDM-4 metallo-beta-lactamase with increased carbapenemase activity from Escherichia coli. (PMID 22252797)

Resistomes

Prevalence of **NDM-4** among the sequenced genomes, plasmids, and whole-genome shotgun assemblies available at NCBI or IslandViewer for 263 important pathogens (see methodological details and complete list of analyzed pathogens). Values reflect percentage of genomes, plasmids, genome islands, or whole-genome shotgun assemblies that have at least one hit to the AMR detection model. Default view includes percentages calculated based on Perfect plus Strict RGI hits. Select the checkbox to view percentages based on only Perfect matches to AMR reference sequences curated in CARD (note: this excludes resistance via mutation as references in protein variant models are often wild-type, sensitive sequences).

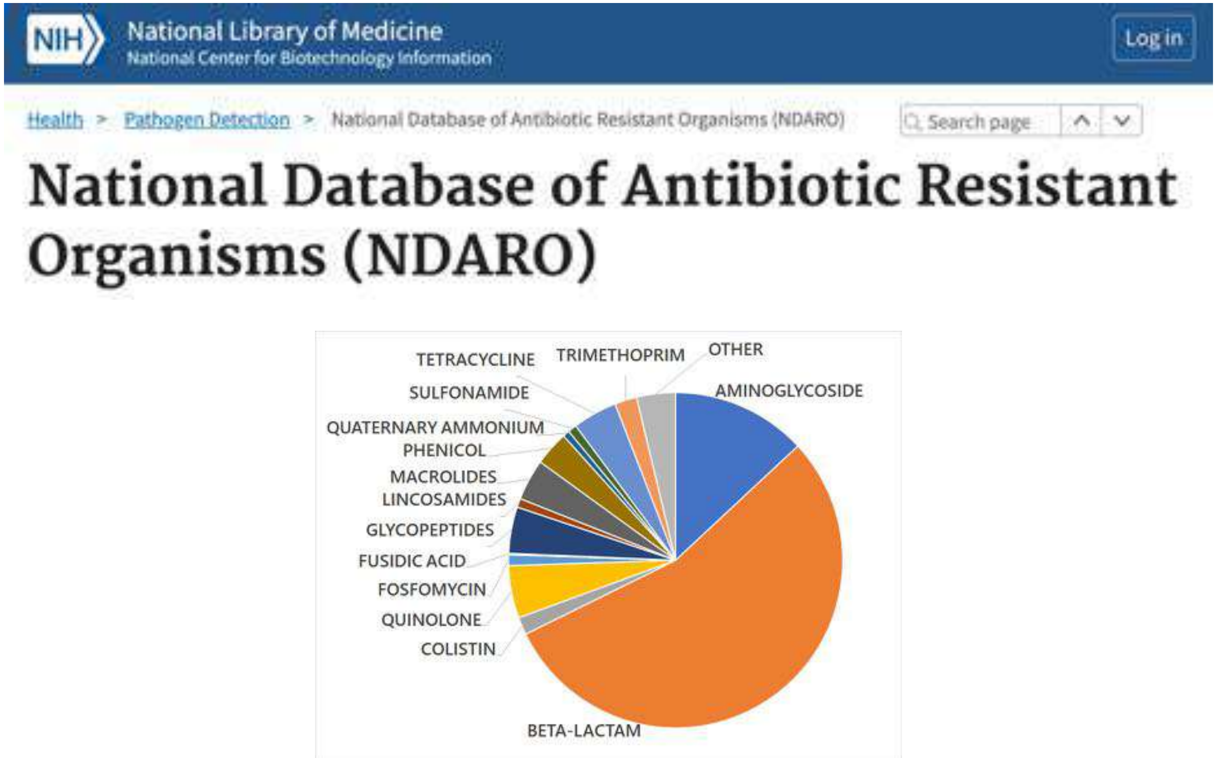
Prevalence: protein homolog model (view sequences)

Species	NCBI Chromosome	NCBI Plasmid	NCBI WGS	NCBI GI
Enterobacter hormaechei	0%	0%	0.08%	0%
Escherichia coli	0%	0.02%	0.02%	0%
Klebsiella pneumoniae	0%	0.05%	0.07%	0%

☑ Show Perfect Only

https://card.mcmaster.ca/genomes

NCBI: National Database of Antibiotic Resistant Organisms



National Database of Antibiotic Resistant Organisms (NDARO)

AMRFinderPlus

https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/AMRFinder/

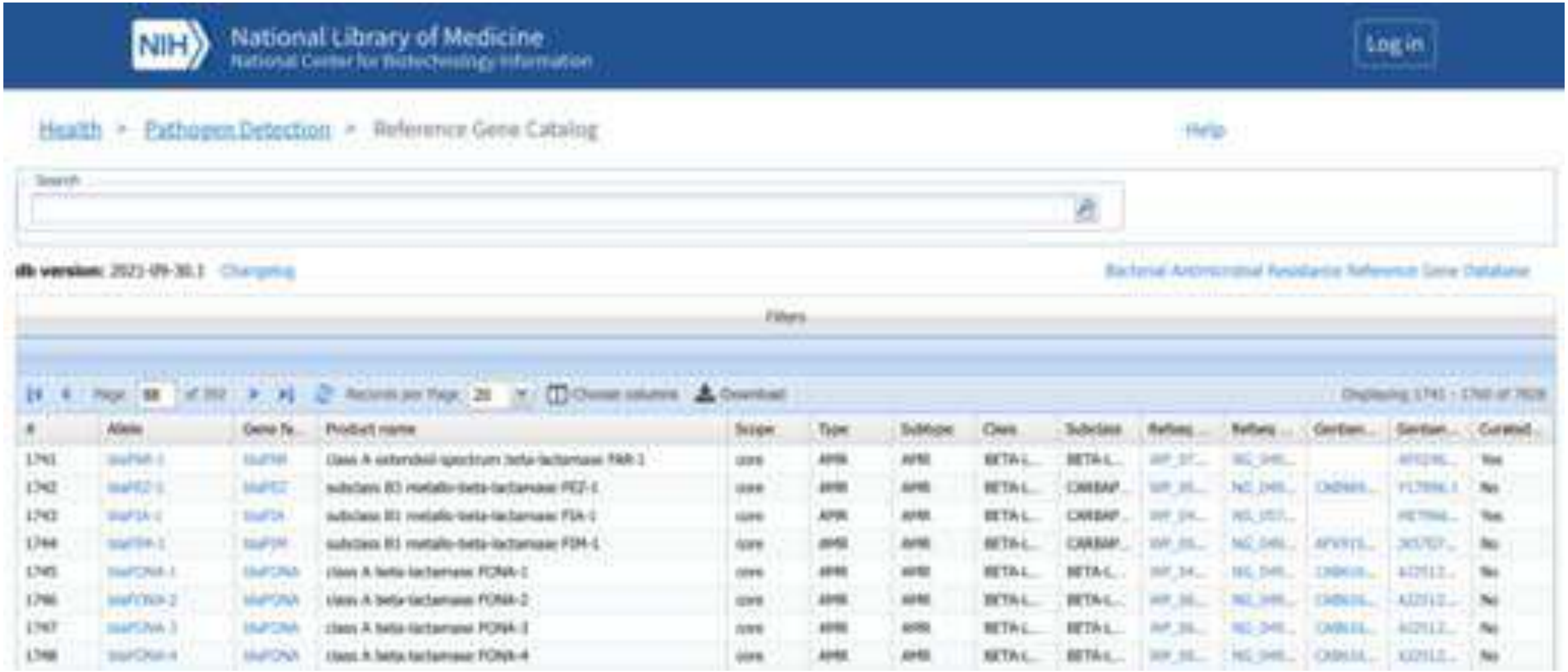
NCBI: AMRFinderPlus database (Reference Gene Catalog)

Database sources

- Lahey Clinic compilation of beta-lactamase sequences (http://www.lahey.org/studies/ and personal communications from Dr. George Jacoby and Karen Bush)
- Pasteur Institute collection of beta-lactamase sequences
- ResFinder
- Comprehensive Antibiotic Resistance Database (CARD)
- RAC and Integrall collections of AMR proteins found in integrons
- Center for Veterinary Medicine
- Marilyn Roberts personal communications
- "Oxford" - Derrick Crook personal communications

https://www.ncbi.nlm.nih.gov/pathogens/refgene/#, https://github.com/ncbi/amr/wiki/AMRFinderPlus-database

NCBI: AMRFinderPlus database (Reference Gene Catalog)



Health > Pathogen Detection > Reference Gene Catalog

db version: 2021-09-30.1 Changelog

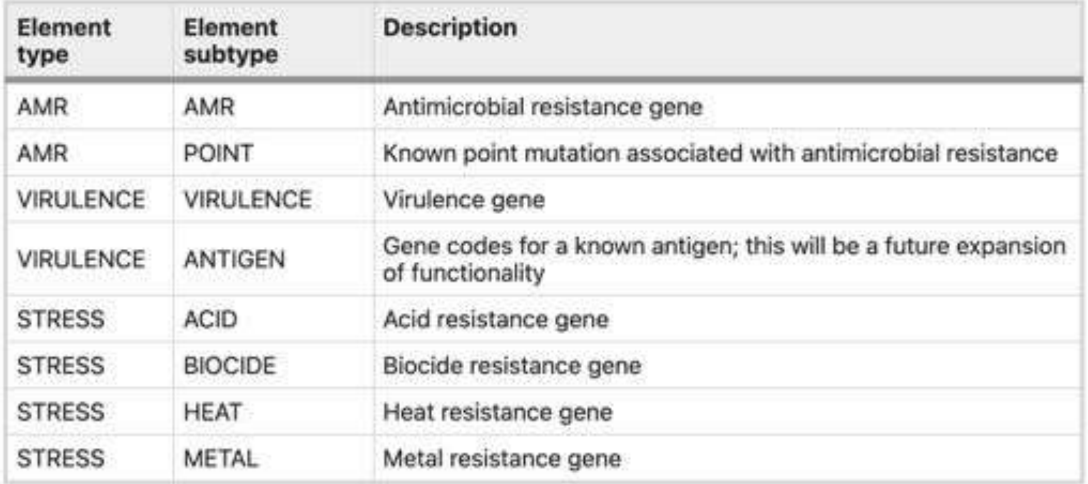
Bacterial Antimicrobial Resistance Reference Gene Database

Displaying 1741 - 1760 of 7828

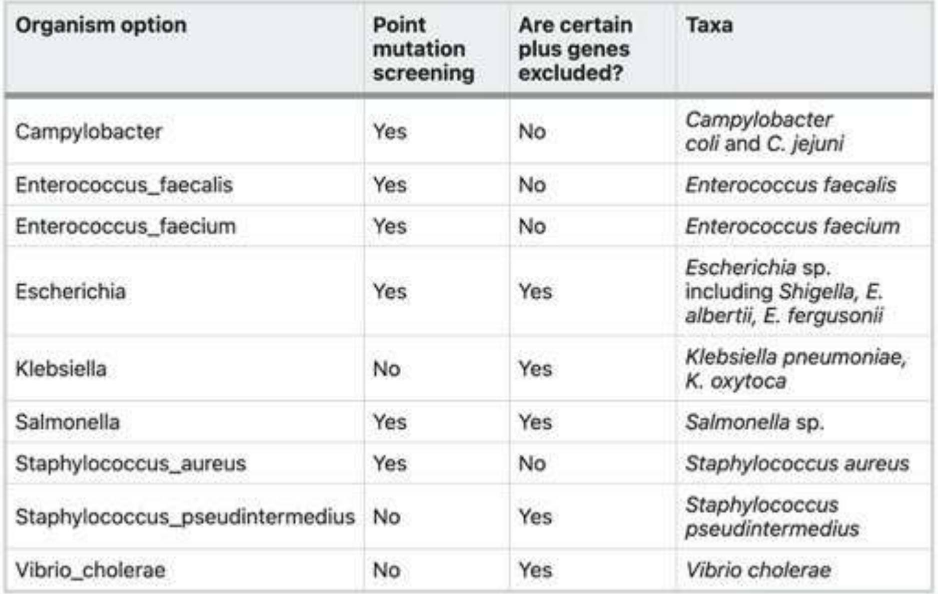
#	Allele	Gene fa...	Product name	Scope	Type	Subtype	Class	Subclass	Refseq ...	Refseq ...	Genban...	Genban...	Curated...
1741	blaFAR-1	blaFAR	class A extended-spectrum beta-lactamase FAR-1	core	AMR	AMR	BETA-L...	BETA-L...	[illegible]	[illegible]		[illegible]	Yes
1742	blaFEZ-1	blaFEZ	subclass B3 metallo-beta-lactamase FEZ-1	core	AMR	AMR	BETA-L...	CARBAP...	[illegible]	[illegible]	[illegible]	[illegible]	No
1743	blaFIA-1	blaFIA	subclass B1 metallo-beta-lactamase FIA-1	core	AMR	AMR	BETA-L...	CARBAP...	[illegible]	[illegible]		[illegible]	Yes
1744	blaFIM-1	blaFIM	subclass B1 metallo-beta-lactamase FIM-1	core	AMR	AMR	BETA-L...	CARBAP...	[illegible]	[illegible]	[illegible]	[illegible]	No
1745	blaFONA-1	blaFONA	class A beta-lactamase FONA-1	core	AMR	AMR	BETA-L...	BETA-L...	[illegible]	[illegible]	[illegible]	[illegible]	No
1746	blaFONA-2	blaFONA	class A beta-lactamase FONA-2	core	AMR	AMR	BETA-L...	BETA-L...	[illegible]	[illegible]	[illegible]	[illegible]	No
1747	blaFONA-3	blaFONA	class A beta-lactamase FONA-3	core	AMR	AMR	BETA-L...	BETA-L...	[illegible]	[illegible]	[illegible]	[illegible]	No
1748	blaFONA-4	blaFONA	class A beta-lactamase FONA-4	core	AMR	AMR	BETA-L...	BETA-L...	[illegible]	[illegible]	[illegible]	[illegible]	No

https://www.ncbi.nlm.nih.gov/pathogens/refgene/#, https://github.com/ncbi/amr/wiki/AMRFinderPlus-database

NCBI: AMRFinderPlus



Element type	Element subtype	Description
AMR	AMR	Antimicrobial resistance gene
AMR	POINT	Known point mutation associated with antimicrobial resistance
VIRULENCE	VIRULENCE	Virulence gene
VIRULENCE	ANTIGEN	Gene codes for a known antigen; this will be a future expansion of functionality
STRESS	ACID	Acid resistance gene
STRESS	BIOCIDE	Biocide resistance gene
STRESS	HEAT	Heat resistance gene
STRESS	METAL	Metal resistance gene

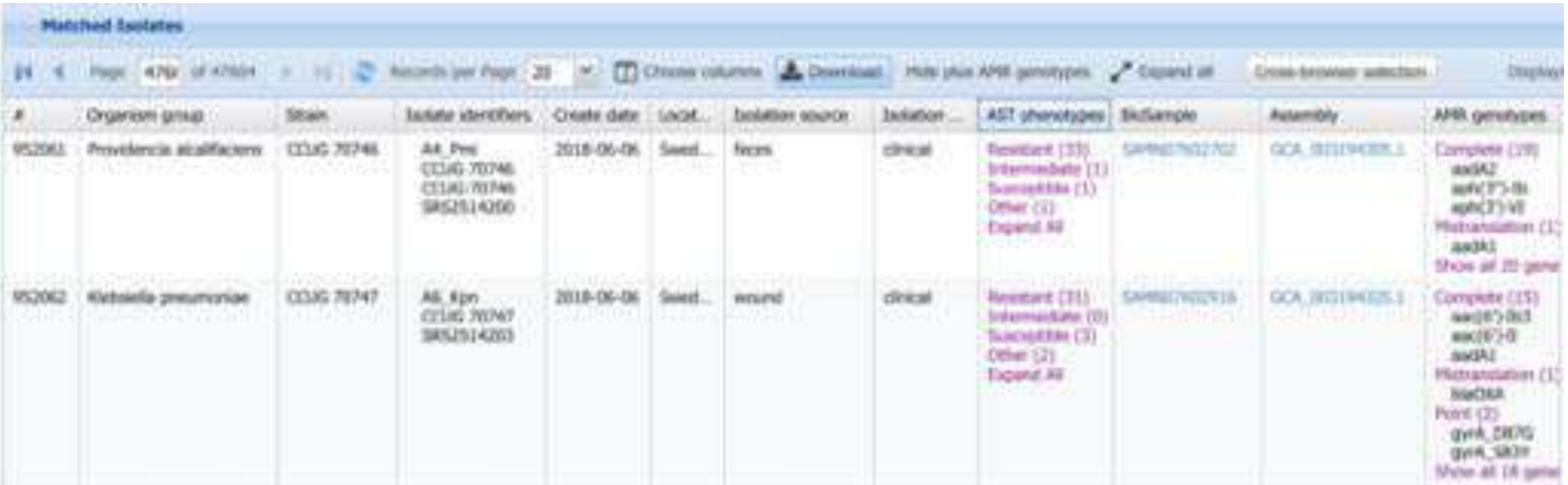


Organism option	Point mutation screening	Are certain plus genes excluded?	Taxa
Campylobacter	Yes	No	*Campylobacter coli* and *C. jejuni*
Enterococcus_faecalis	Yes	No	*Enterococcus faecalis*
Enterococcus_faecium	Yes	No	*Enterococcus faecium*
Escherichia	Yes	Yes	*Escherichia* sp. including *Shigella, E. albertii, E. fergusonii*
Klebsiella	No	Yes	*Klebsiella pneumoniae, K. oxytoca*
Salmonella	Yes	Yes	*Salmonella* sp.
Staphylococcus_aureus	Yes	No	*Staphylococcus aureus*
Staphylococcus_pseudintermedius	No	Yes	*Staphylococcus pseudintermedius*
Vibrio_cholerae	No	Yes	*Vibrio cholerae*

Feldgarden, et al. *Sci Rep*, 2021. https://github.com/ncbi/amr/wiki

NCBI: Other AMR resources

- Isolate browser

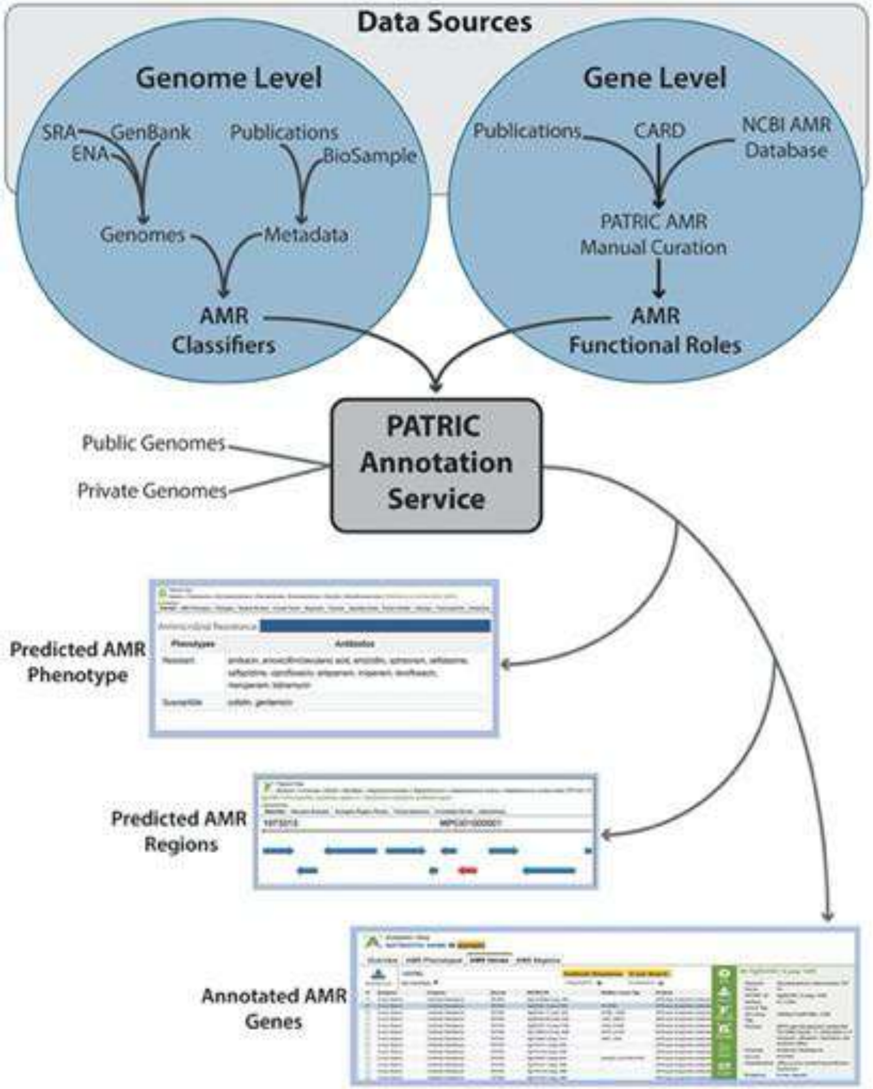


- Pathogen Detection Reference Hidden Markov Model (HMM) Catalog
- Microbial Browser for Identification of Genetic and Genomic Elements (MicroBIGG-E)

- Submit sequence and phenotype data

https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/resources/

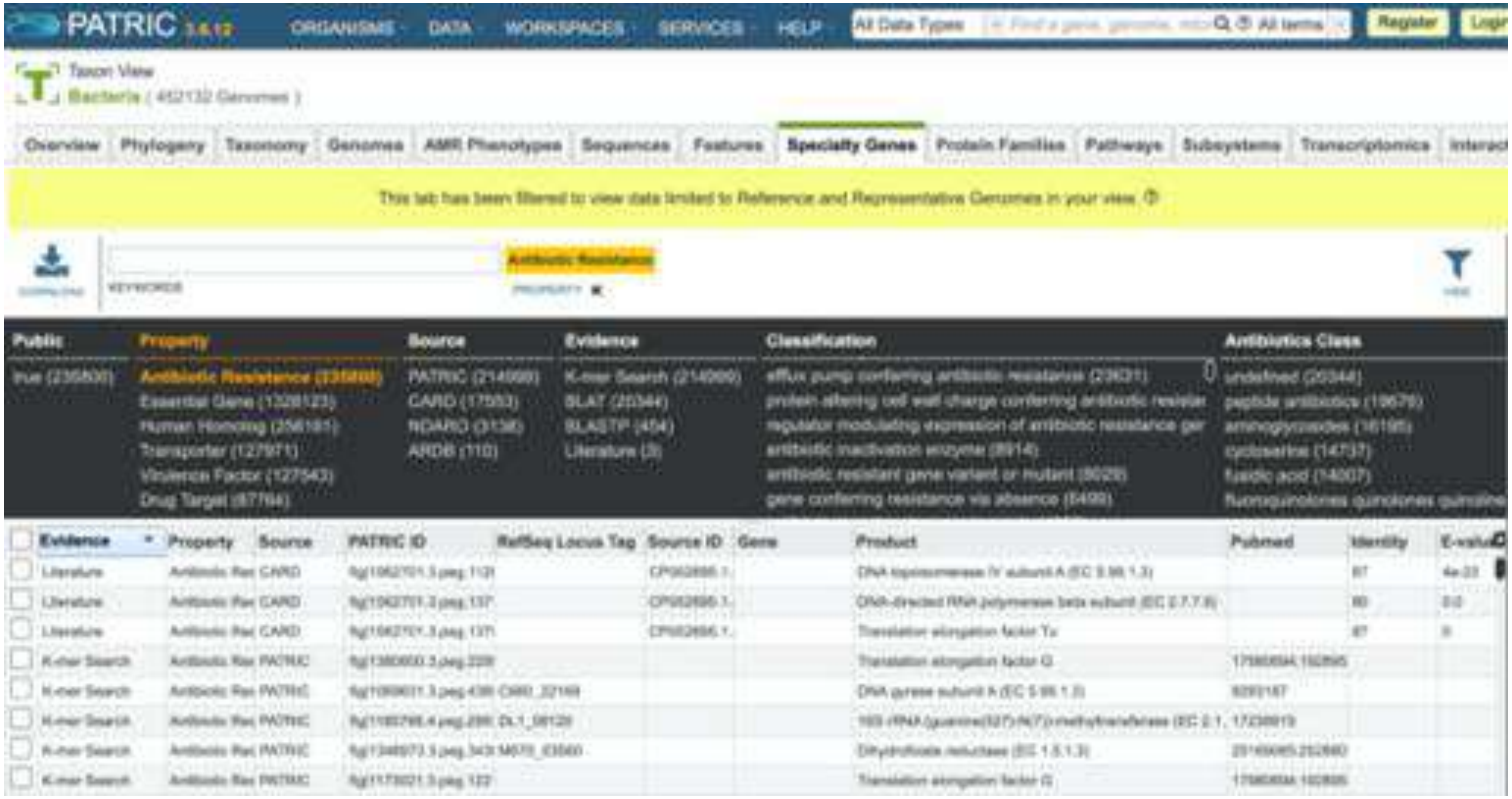
PathoSystems Resource Integration Center (PATRIC)



Davis, et al. *Nucleic Acids Res*, 2020. https://docs.patricbrc.org/user_guides/data/data_types/antimicrobial_resistance.html

PATRIC: AMR database

- PATRIC (in-house)
- CARD
- NCBI National Database of Antibiotic Resistant Organisms (NDARO)
- ARDB



This tab has been filtered to view data limited to Reference and Representative Genomes in your view.

Public: true (235830)

Property: Antibiotic Resistance (235830), Essential Gene (1328123), Human Homolog (256161), Transporter (127971), Virulence Factor (127543), Drug Target (87794)

Source: PATRIC (214099), CARD (17553), NDARO (3138), ARDB (110)

Evidence: K-mer Search (214099), BLAT (20344), BLASTP (454), Literature (3)

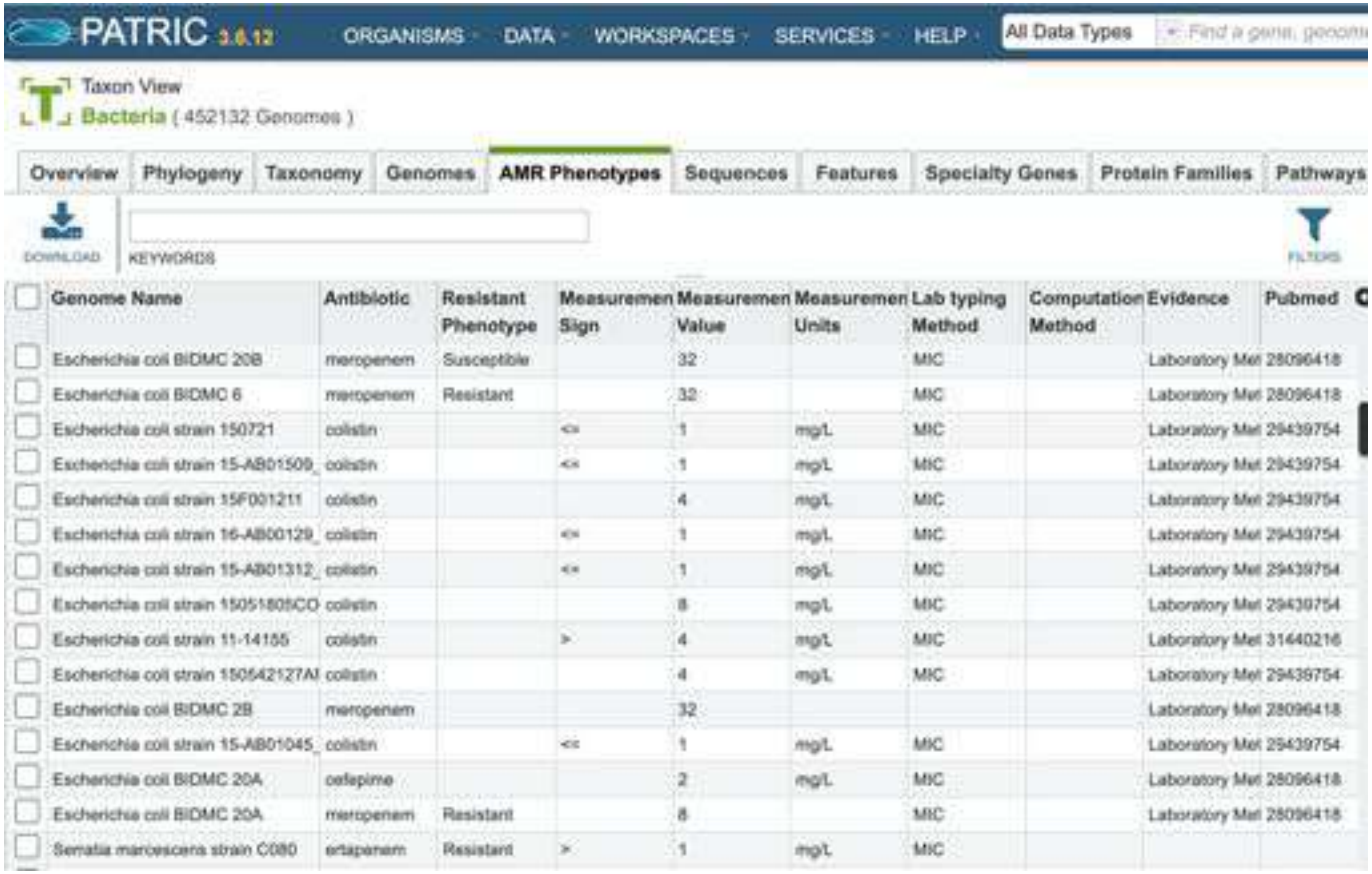
Classification: efflux pump conferring antibiotic resistance (23631), protein altering cell wall charge conferring antibiotic resistar, regulator modulating expression of antibiotic resistance ger, antibiotic inactivation enzyme (8914), antibiotic resistant gene variant or mutant (8028), gene conferring resistance via absence (6499)

Antibiotics Class: undefined (20344), peptide antibiotics (19676), aminoglycosides (16195), cycloserine (14737), fusidic acid (14007), fluoroquinolones quinolones quinoline

Evidence	Property	Source	PATRIC ID	RefSeq Locus Tag	Source ID	Gene	Product	Pubmed	Identity	E-valu
Literature	Antibiotic Res	CARD					DNA topoisomerase IV subunit A (EC 5.99.1.3)			
Literature	Antibiotic Res	CARD					DNA-directed RNA polymerase beta subunit (EC 2.7.7.6)			
Literature	Antibiotic Res	CARD					Translation elongation factor Tu			
K-mer Search	Antibiotic Res	PATRIC					Translation elongation factor G			
K-mer Search	Antibiotic Res	PATRIC					DNA gyrase subunit A (EC 5.99.1.3)			
K-mer Search	Antibiotic Res	PATRIC					16S rRNA (guanine(527)-N(7))-methyltransferase (EC 2.1.			
K-mer Search	Antibiotic Res	PATRIC					Dihydrofolate reductase (EC 1.5.1.3)			
K-mer Search	Antibiotic Res	PATRIC					Translation elongation factor G			

Davis, et al. *Nucleic Acids Res*, 2020. https://docs.patricbrc.org/user_guides/data/data_types/antimicrobial_resistance.html

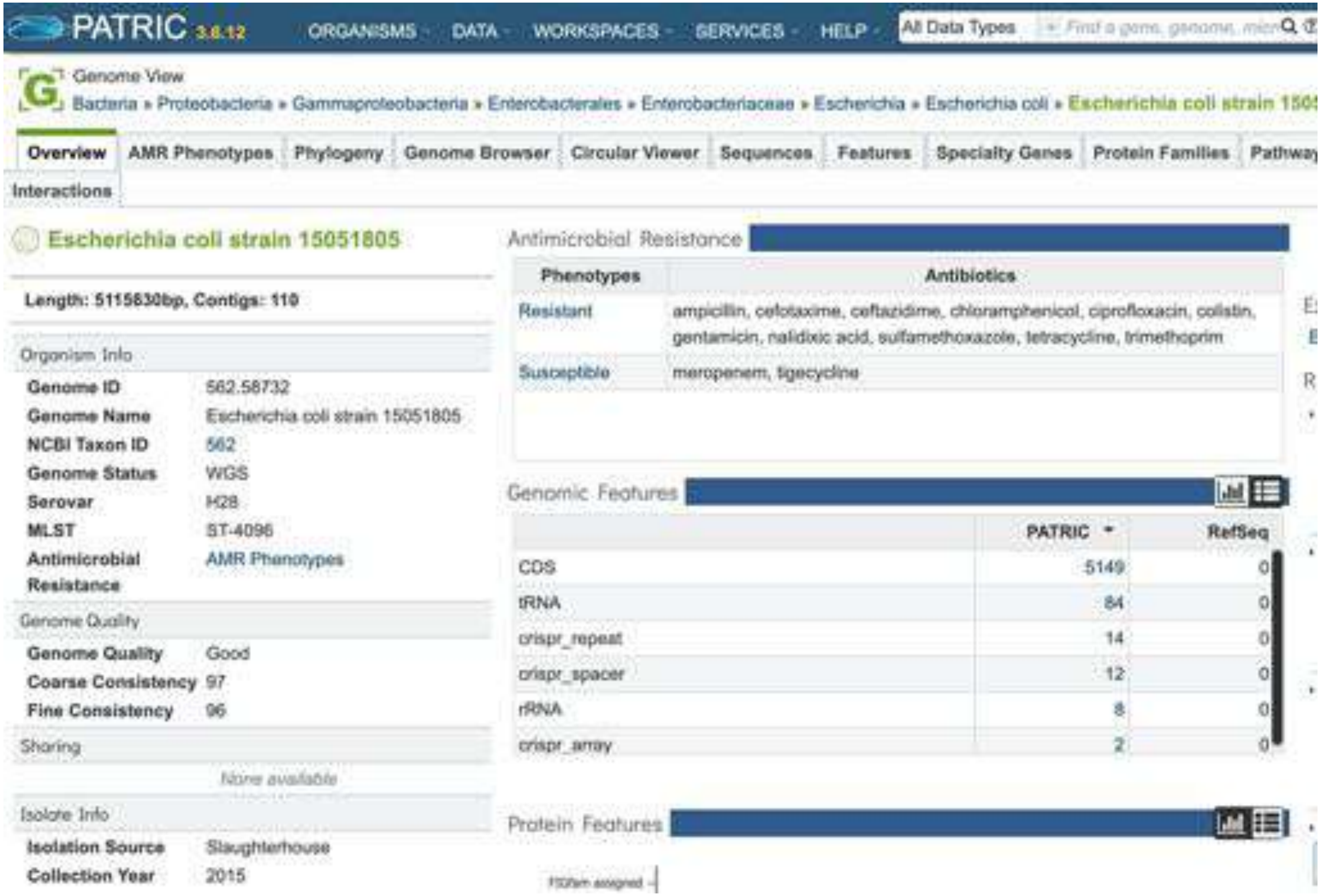
PATRIC: AMR phenotypes



☐	Genome Name	Antibiotic	Resistant Phenotype	Measuremen Sign	Measuremen Value	Measuremen Units	Lab typing Method	Computation Method	Evidence	Pubmed
☐	Escherichia coli BIDMC 20B	meropenem	Susceptible		32		MIC		Laboratory Met	28096418
☐	Escherichia coli BIDMC 6	meropenem	Resistant		32		MIC		Laboratory Met	28096418
☐	Escherichia coli strain 150721	colistin		<=	1	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli strain 15-AB01509_	colistin		<=	1	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli strain 15F001211	colistin			4	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli strain 16-AB00129_	colistin		<=	1	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli strain 15-AB01312_	colistin		<=	1	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli strain 15051805CO	colistin			8	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli strain 11-14155	colistin		>	4	mg/L	MIC		Laboratory Met	31440216
☐	Escherichia coli strain 150542127AI	colistin			4	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli BIDMC 2B	meropenem			32				Laboratory Met	28096418
☐	Escherichia coli strain 15-AB01045_	colistin		<=	1	mg/L	MIC		Laboratory Met	29439754
☐	Escherichia coli BIDMC 20A	cefepime			2	mg/L	MIC		Laboratory Met	28096418
☐	Escherichia coli BIDMC 20A	meropenem	Resistant		8		MIC		Laboratory Met	28096418
☐	Serratia marcescens strain C080	ertapenem	Resistant	>	1	mg/L	MIC			

Davis, et al. *Nucleic Acids Res*, 2020. https://docs.patricbrc.org/user_guides/data/data_types/antimicrobial_resistance.html

PATRIC: Genomes



Bacteria » Proteobacteria » Gammaproteobacteria » Enterobacterales » Enterobacteriaceae » Escherichia » Escherichia coli » **Escherichia coli strain 1505**

Escherichia coli strain 15051805

Length: 5115830bp, Contigs: 110

Organism Info

Genome ID	562.58732
Genome Name	Escherichia coli strain 15051805
NCBI Taxon ID	562
Genome Status	WGS
Serovar	H28
MLST	ST-4096
Antimicrobial Resistance	AMR Phenotypes

Genome Quality

Genome Quality	Good
Coarse Consistency	97
Fine Consistency	96

Sharing

None available

Isolate Info

Isolation Source	Slaughterhouse
Collection Year	2015

Antimicrobial Resistance

Phenotypes	Antibiotics
Resistant	ampicillin, cefotaxime, ceftazidime, chloramphenicol, ciprofloxacin, colistin, gentamicin, nalidixic acid, sulfamethoxazole, tetracycline, trimethoprim
Susceptible	meropenem, tigecycline

Genomic Features

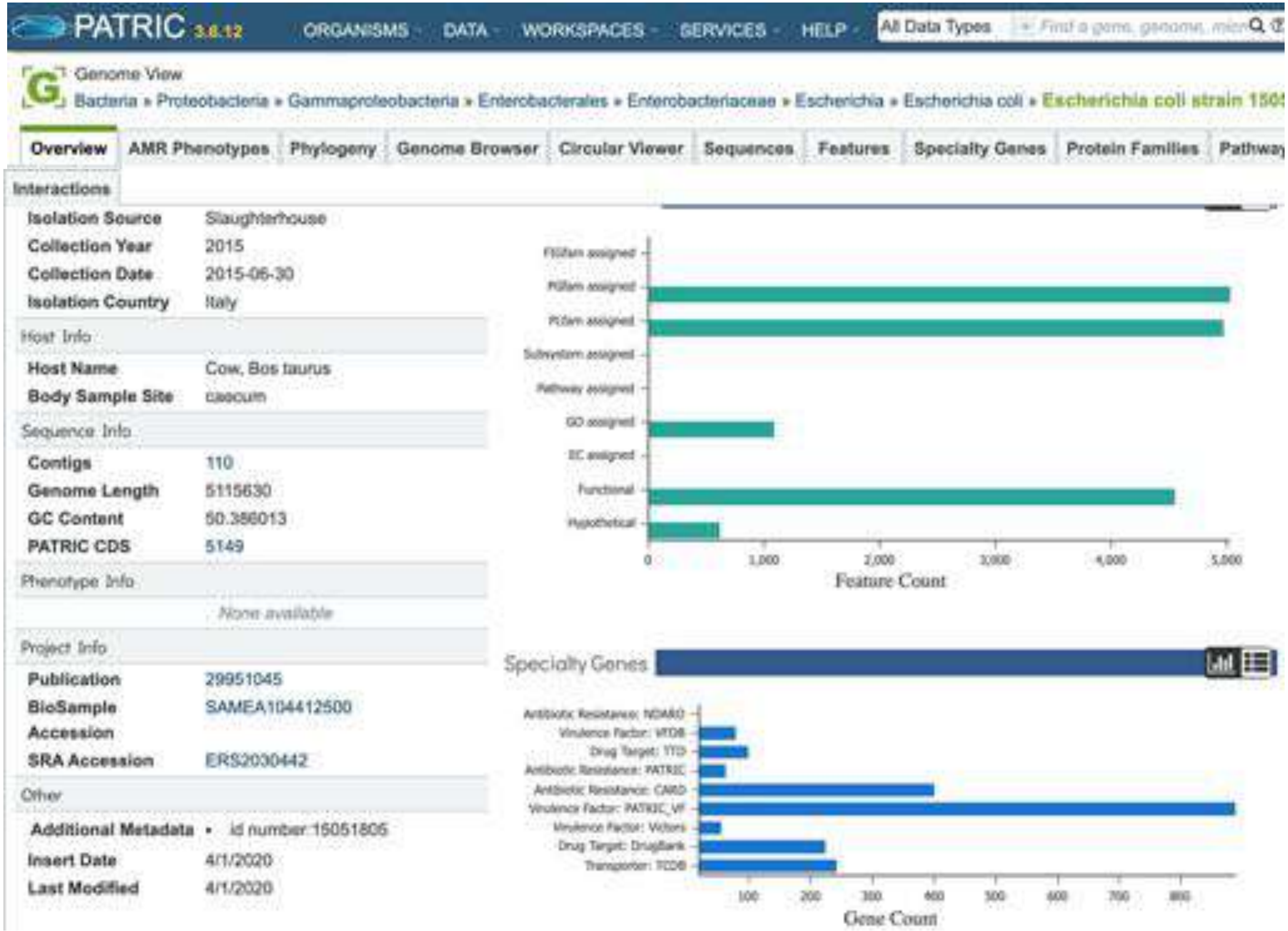
	PATRIC	RefSeq
CDS	5149	0
tRNA	84	0
crispr_repeat	14	0
crispr_spacer	12	0
rRNA	8	0
crispr_array	2	0

Protein Features

FIGfam assigned

Davis, et al. *Nucleic Acids Res*, 2020. https://docs.patricbrc.org/tutorial/

PATRIC: Genomes



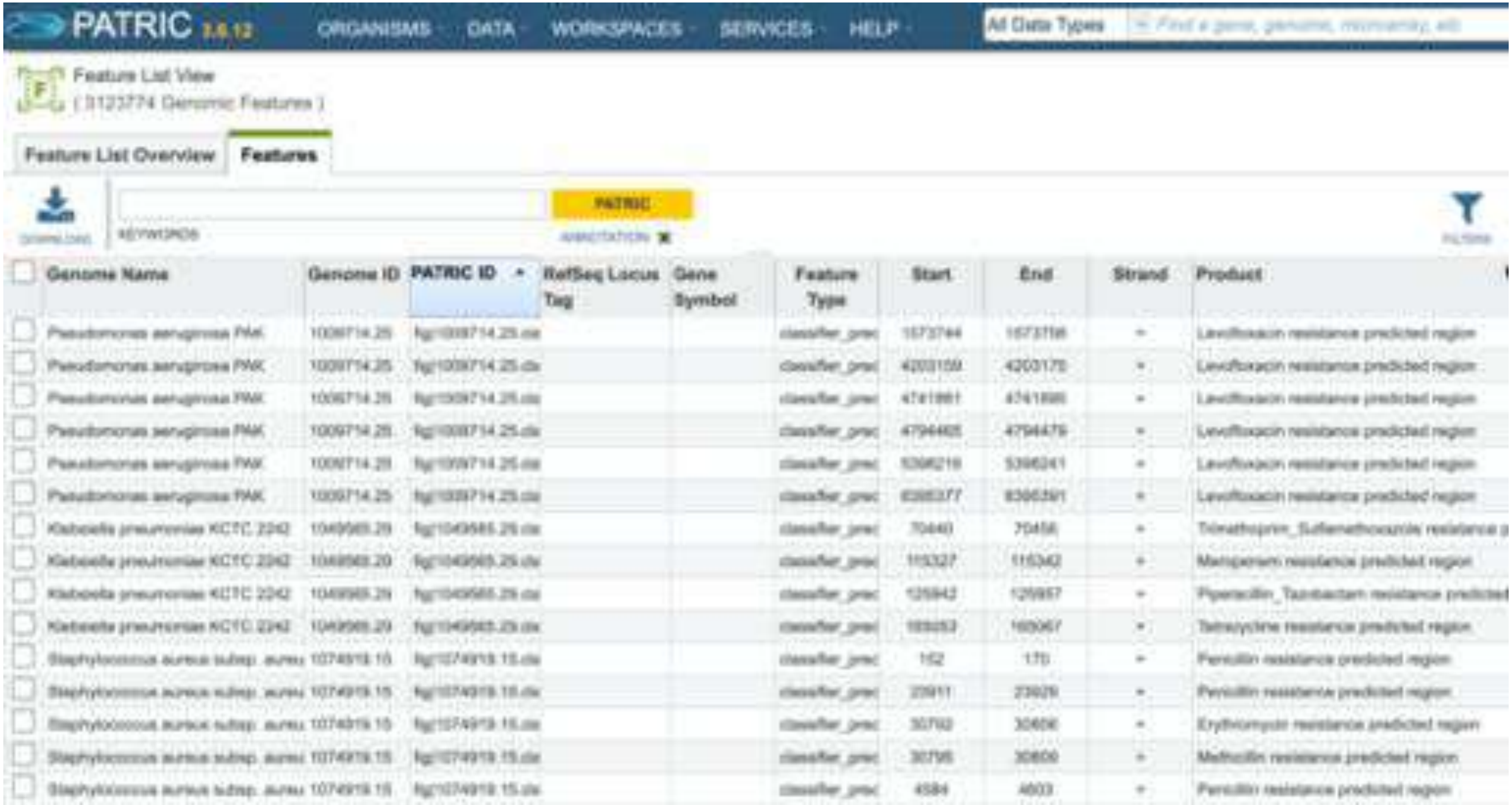
Bacteria » Proteobacteria » Gammaproteobacteria » Enterobacterales » Enterobacteriaceae » Escherichia » Escherichia coli » Escherichia coli strain 150

Isolation Source	Slaughterhouse
Collection Year	2015
Collection Date	2015-06-30
Isolation Country	Italy
Host Info	
Host Name	Cow, Bos taurus
Body Sample Site	caecum
Sequence Info	
Contigs	110
Genome Length	5115630
GC Content	50.386013
PATRIC CDS	5149
Phenotype Info	
	None available
Project Info	
Publication	29951045
BioSample Accession	SAMEA104412500
SRA Accession	ERS2030442
Other	
Additional Metadata	• id number:15051805
Insert Date	4/1/2020
Last Modified	4/1/2020

Davis, et al. *Nucleic Acids Res*, 2020. https://docs.patricbrc.org/tutorial/

PATRIC: Regions

- Computationally predicted small genomic regions associated with AMR



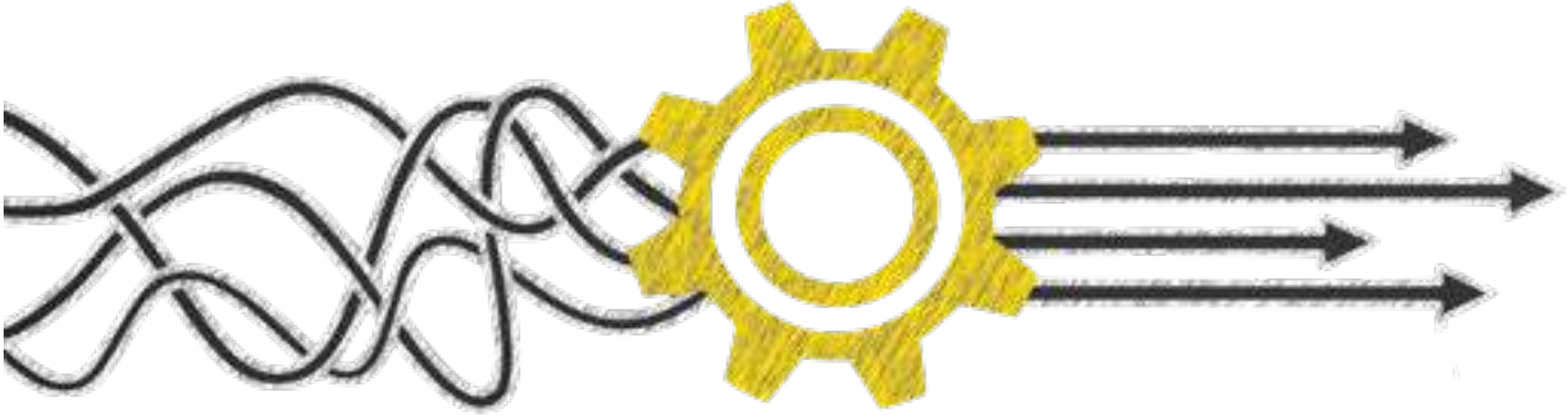
☐	Genome Name	Genome ID	PATRIC ID	RefSeq Locus Tag	Gene Symbol	Feature Type	Start	End	Strand	Product
☐	Pseudomonas aeruginosa PAK	1009714.25	fig|1009714.25.cla			classifier_pred	1573744	1573758	-	Levofloxacin resistance predicted region
☐	Pseudomonas aeruginosa PAK	1009714.25	fig|1009714.25.cla			classifier_pred	4203159	4203175	+	Levofloxacin resistance predicted region
☐	Pseudomonas aeruginosa PAK	1009714.25	fig|1009714.25.cla			classifier_pred	4741881	4741895	-	Levofloxacin resistance predicted region
☐	Pseudomonas aeruginosa PAK	1009714.25	fig|1009714.25.cla			classifier_pred	4794465	4794479	+	Levofloxacin resistance predicted region
☐	Pseudomonas aeruginosa PAK	1009714.25	fig|1009714.25.cla			classifier_pred	5396219	5396241	-	Levofloxacin resistance predicted region
☐	Pseudomonas aeruginosa PAK	1009714.25	fig|1009714.25.cla			classifier_pred	6395377	6395391	+	Levofloxacin resistance predicted region
☐	Klebsiella pneumoniae KCTC 2242	1049565.29	fig|1049565.29.cla			classifier_pred	70440	70456	-	Trimethoprim_Sulfamethoxazole resistance p
☐	Klebsiella pneumoniae KCTC 2242	1049565.29	fig|1049565.29.cla			classifier_pred	115327	115342	+	Meropenem resistance predicted region
☐	Klebsiella pneumoniae KCTC 2242	1049565.29	fig|1049565.29.cla			classifier_pred	125942	125957	-	Piperacillin_Tazobactam resistance predicted
☐	Klebsiella pneumoniae KCTC 2242	1049565.29	fig|1049565.29.cla			classifier_pred	165053	165067	+	Tetracycline resistance predicted region
☐	Staphylococcus aureus subsp. aureu	1074919.15	fig|1074919.15.cla			classifier_pred	152	170	-	Penicillin resistance predicted region
☐	Staphylococcus aureus subsp. aureu	1074919.15	fig|1074919.15.cla			classifier_pred	23911	23929	+	Penicillin resistance predicted region
☐	Staphylococcus aureus subsp. aureu	1074919.15	fig|1074919.15.cla			classifier_pred	30702	30606	-	Erythromycin resistance predicted region
☐	Staphylococcus aureus subsp. aureu	1074919.15	fig|1074919.15.cla			classifier_pred	30795	30809	+	Methicillin resistance predicted region
☐	Staphylococcus aureus subsp. aureu	1074919.15	fig|1074919.15.cla			classifier_pred	4584	4603	-	Penicillin resistance predicted region

Davis, et al. *Nucleic Acids Res*, 2020.
https://www.patricbrc.org/view/FeatureList/?eq(feature_type,classifier_predicted_region)#view_tab=features&filter=or(eq(annotation,%22PATRIC%22))

Summary of AMR databases and resources

	ResFinder	CARD/RGI	NCBI AMRFinderPlus	PATRIC
AMR context	Acquired resistance, chromosomal mutations	• Website • Command-line	All (can include additional classes of genes)	All
Annotation Usage	• Website • Command-line	• Website • Command-line	• Command-line	• Website • Command-line
Matched genotype-phenotype isolates	No	No	Yes	Yes
Other resources	• PointFinder	• Antibiotic Resistance Ontology • CARD:Live • CARD:Prevalence • CARD:Resistomes&Variants	• Isolate Browser • Hidden Markov Model (HMM) Catalog • MicroBIGG-E	• PATRIC:Antibiotics • PATRIC:Phenotypes • PATRIC:Regions

Future directions



- Standardization of AMR databases
- Inclusion of metadata in AMR databases
- Specialized databases and tools for species (e.g., *Mycobacterium tuberculosis*)
- Harmonization of AMR resources

Public Health Alliance for Genomic Epidemiology

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