LECTURE SERIES

Klebsiella pneumoniae Genomic Epidemiology and Antimicrobial Resistance

Introduction to *Klebsiella pneumoniae*

Kat Holt, London School of Hygiene and Tropical Medicine

Intended Learning Objectives

KlebNET-GSP

Specific objectives of this session:

1. Understand the basic features of *Klebsiella pneumoniae* genomes
2. Learn about genetic diversity relevant to public health, including:
    1. Population structure and lineages
    2. Polysaccharide loci (capsule and O antigen)
    3. Antimicrobial resistance mechanisms
    4. Virulence and hypervirulence factors
3. Understand the challenges of defining hypervirulence, and convergence of hypervirulence with resistance
4. Learn where to find resources to support genomic surveillance and typing of *Klebsiella pneumoniae*

Outline

KlebNET-GSP

This session consists of the following elements

1. Introduction to *Klebsiella pneumoniae*
2. Overview of genomic features and strain diversity
3. Challenges interpreting virulence markers and hypervirulence
4. KlebNET Genomic Surveillance Platform: resources and collaborative opportunities

Klebsiella pneumoniae (Kp)

KlebNET-GSP

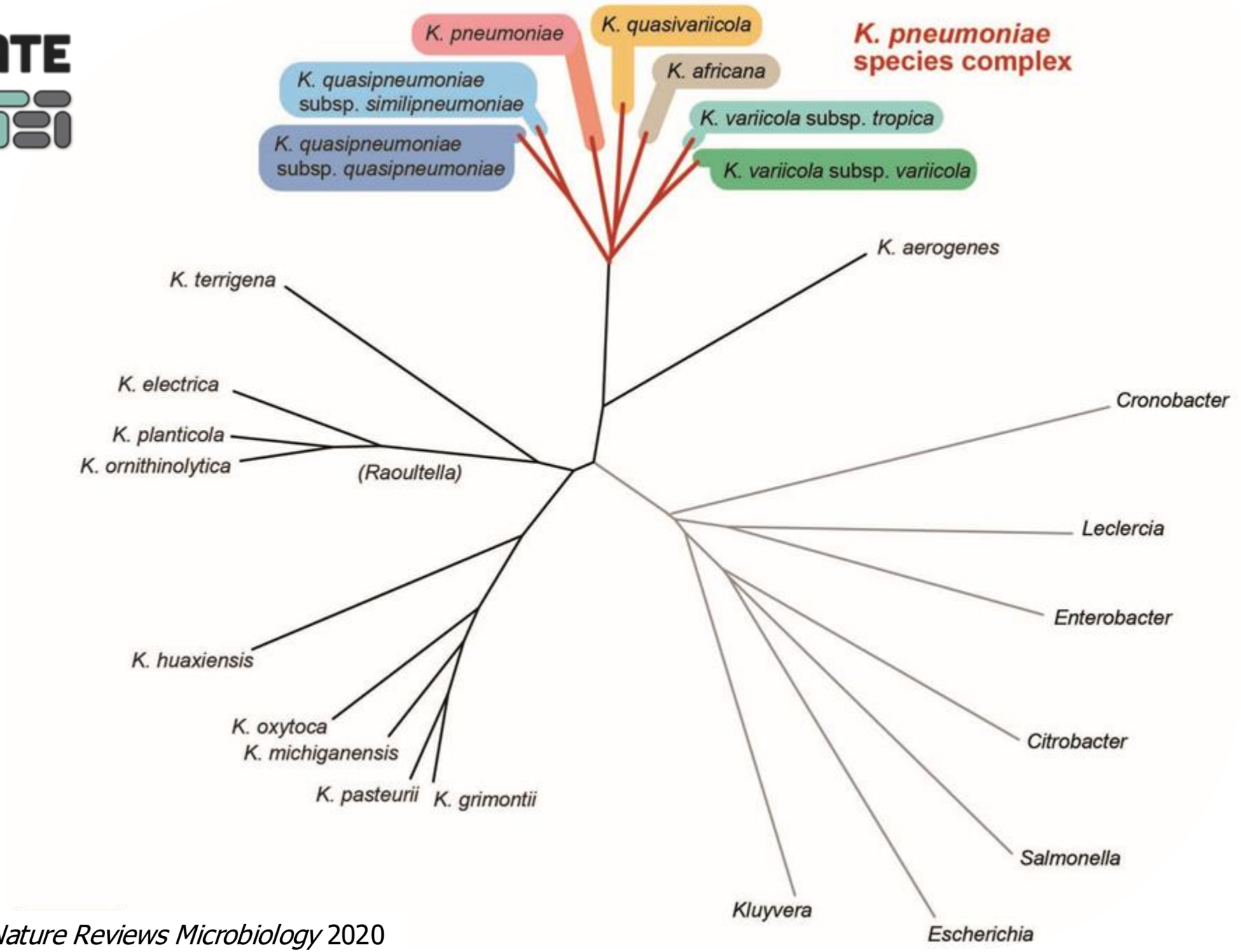
- Gram-negative bacterium of the Enterobacterales
- Colonises gut of humans and other animals
- Primarily opportunistic healthcare-associated infections
  - Especially in infants, elderly, immunocompromised
  - Pneumonia, urinary tract infection, wound infection, sepsis
  - Often multidrug resistant, can be challenging to treat

- In Europe: ESBL, carbapenemase-producing or colistin resistant *Kp* causes >90 thousand infections annually[1]
  - 25% of total DALYs associated with AMR infections
- Globally: Drug resistant *Kp* causes >735 thousand deaths annually[2]
  - >100 thousand neonatal sepsis deaths

1: Cassini et al, *Lancet Infect* Dis 2019. 2: GBD 2021 Antimicrobial Resistance Collaborators, Lancet 2024.

KLEBORATE

KlebNET-GSP



Wyres, Lam & Holt, *Nature Reviews Microbiology* 2020

Genomic features and strain diversity

KlebNET-GSP

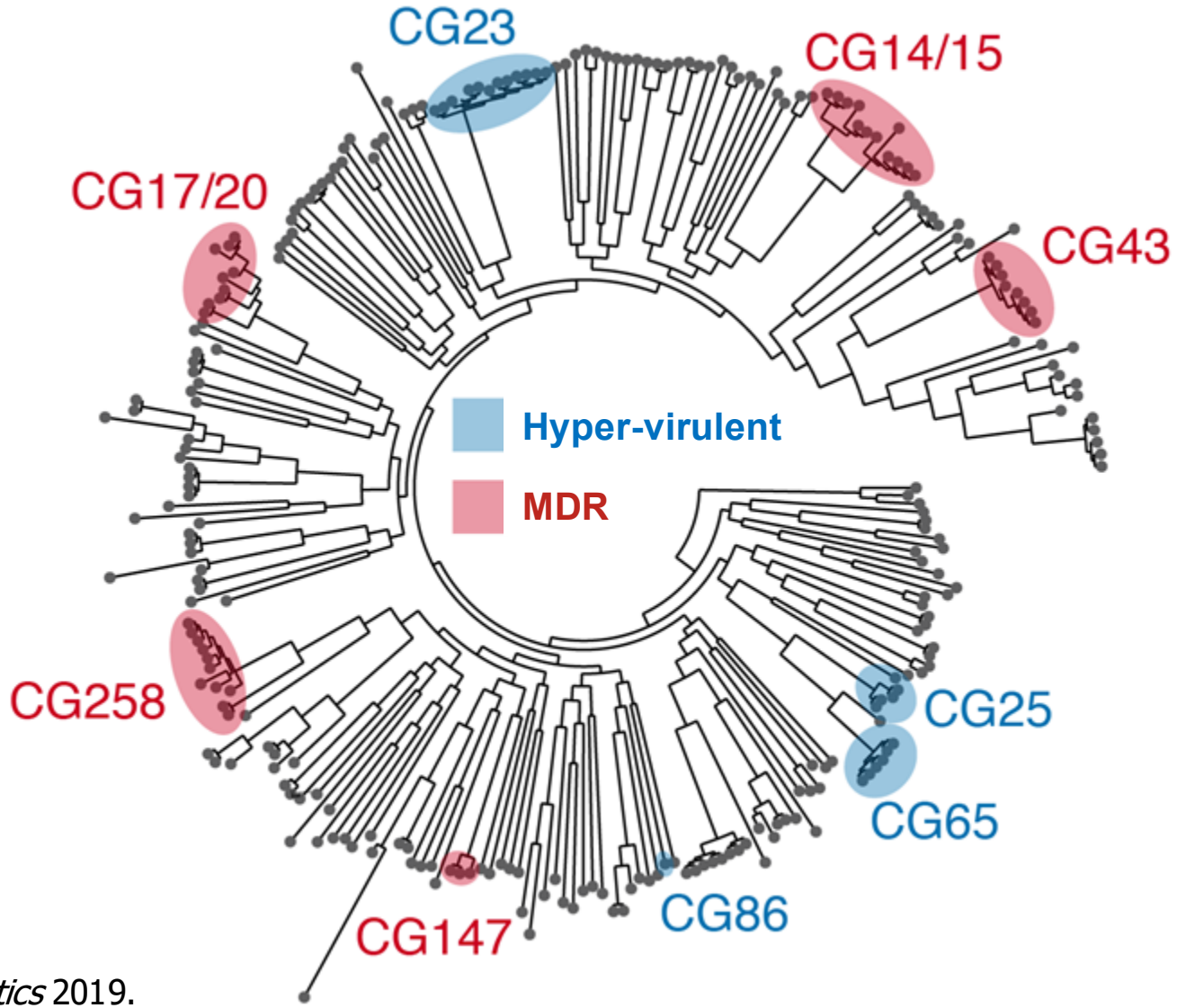
Approx. 5,500,000 base pair chromosome

0-10 plasmids per genome

Thousands of deep branching lineages or ‘clonal groups’, which differ in gene content

Diverse phylogenetic lineages

KlebNET-GSP



Population structure
Core-genome phylogeny
~0.5% divergence between lineages

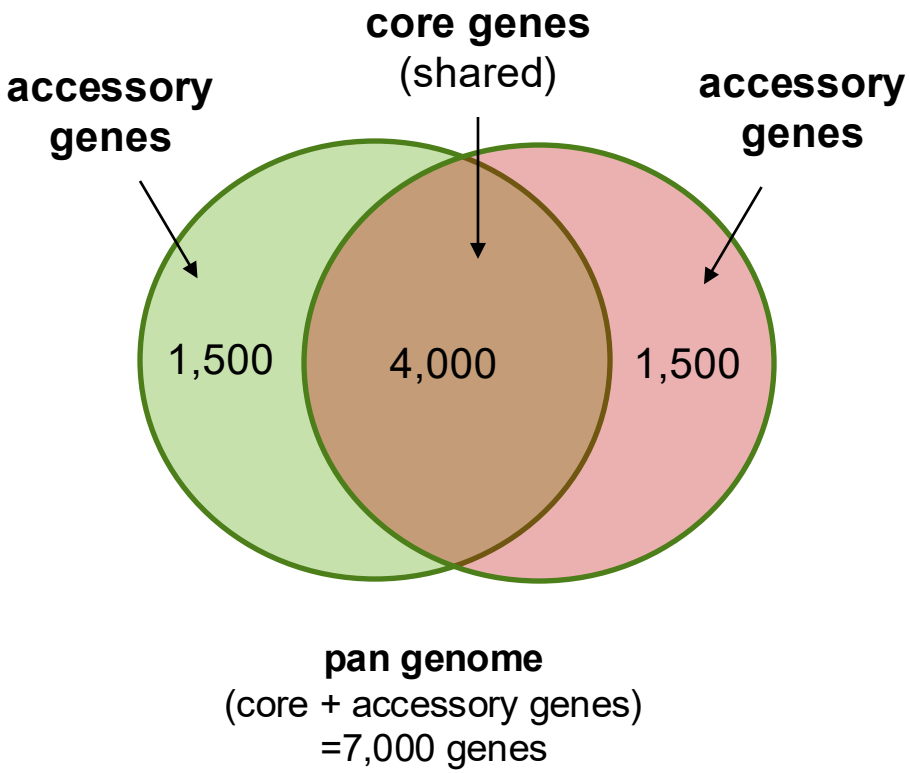
Clonal groups (CG)
see next lecture (Sylvain Brisse)

Wyres et al, *PLoS Genetics* 2019.

Variable gene content

KlebNET-GSP

Comparing 2 *Kp* genomes:

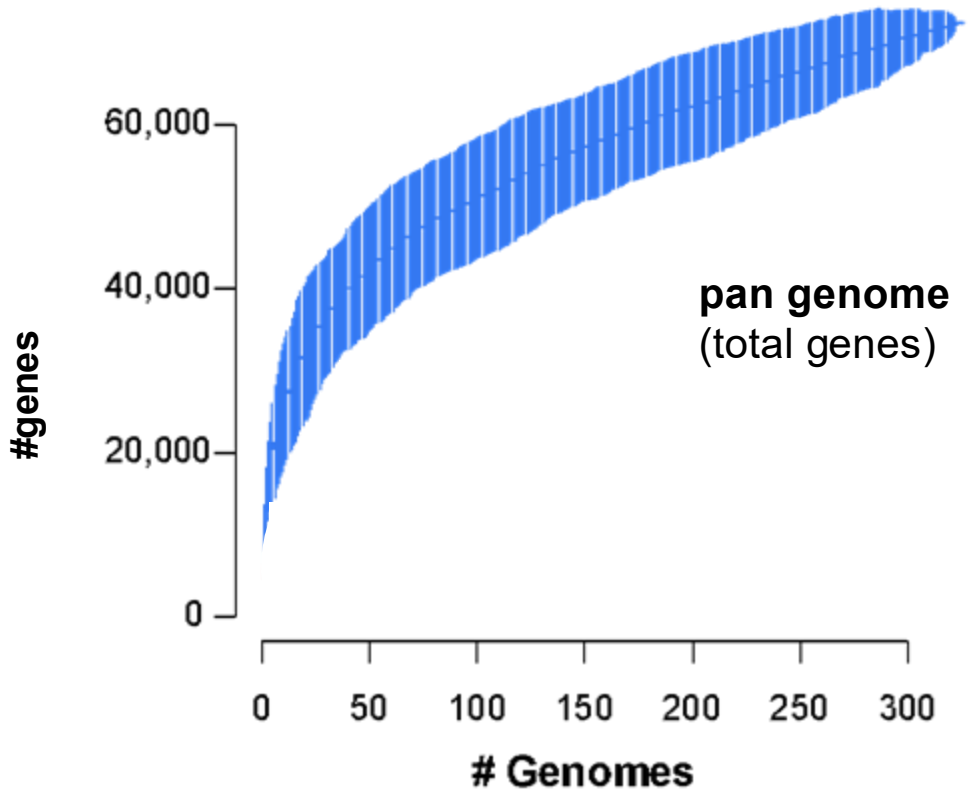


Holt et al, *PNAS* 2015
Wyres & Holt, *Trends Micro* 2016

Variable gene content

KlebNET-GSP

Comparing 300 *Kp* genomes:

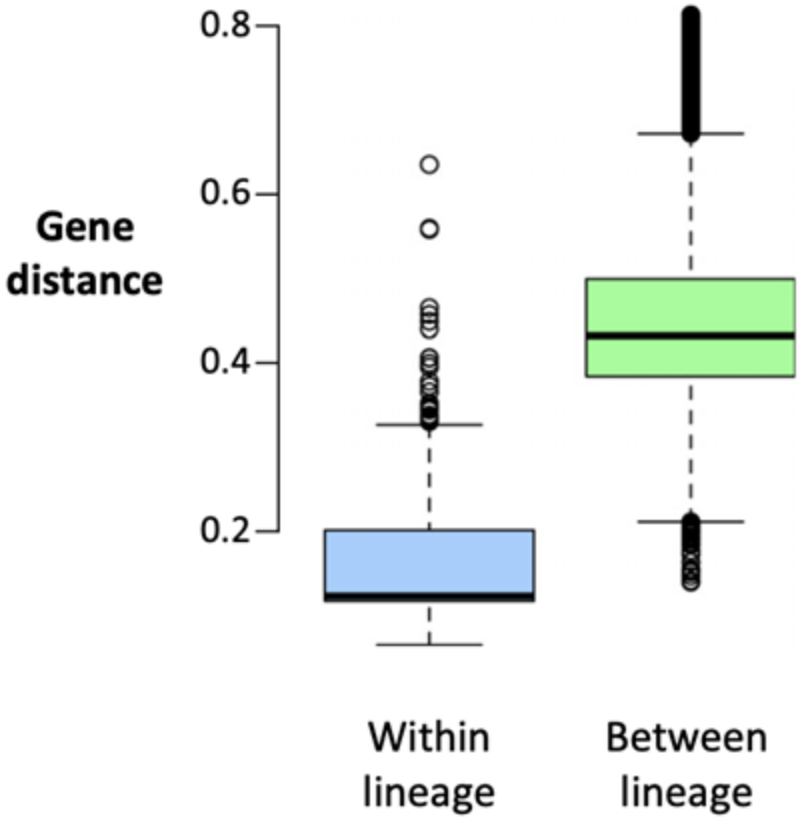


Holt et al, *PNAS* 2015
Wyres & Holt, *Trends Micro* 2016

Variable gene content

KlebNET-GSP

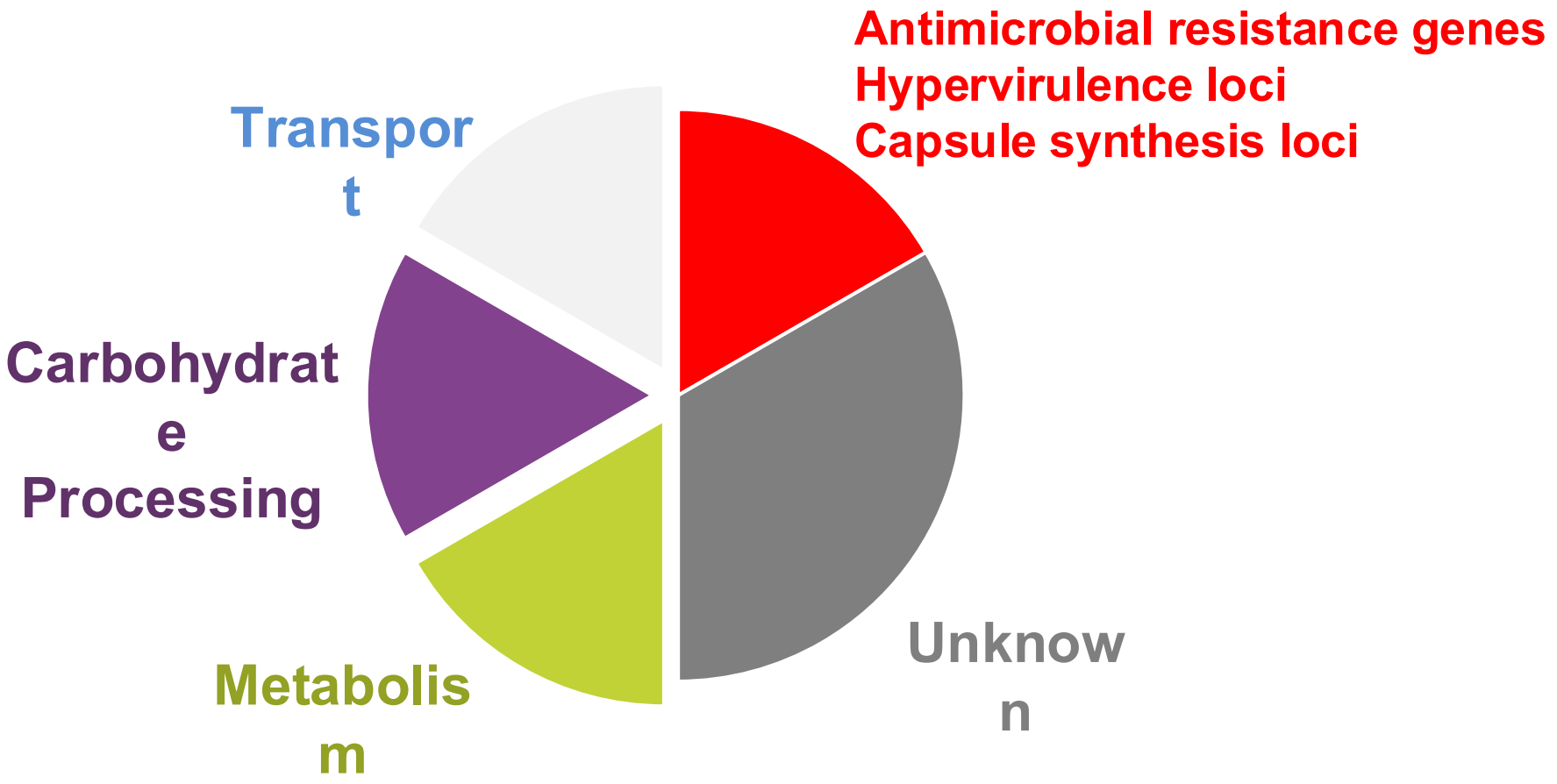
Comparing between *Kp* lineages:



Holt et al, *PNAS* 2015
Wyres & Holt, *Trends Micro* 2016

Accessory gene functions

KlebNET-GSP

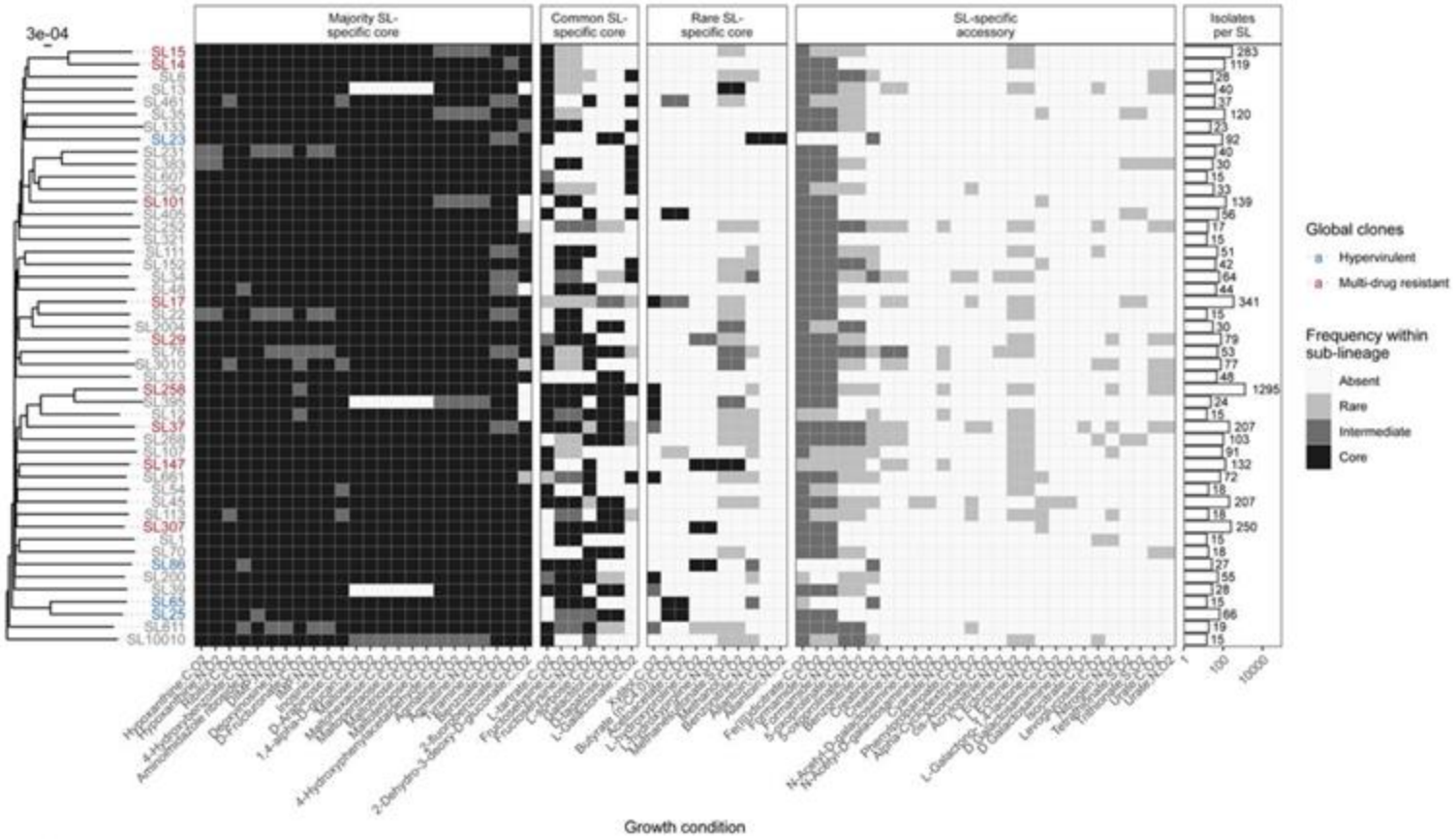


Holt et al, *PNAS* 2015.

Variation in metabolic genes & predicted phenotypes

KlebNET-GSP

A metabolic atlas of the *Klebsiella pneumoniae* species complex reveals lineage-specific metabolism that supports persistent co-existence of diverse lineages



Plot shows variation in substrate utilization per lineage, predicted from genomes using Bactabolize

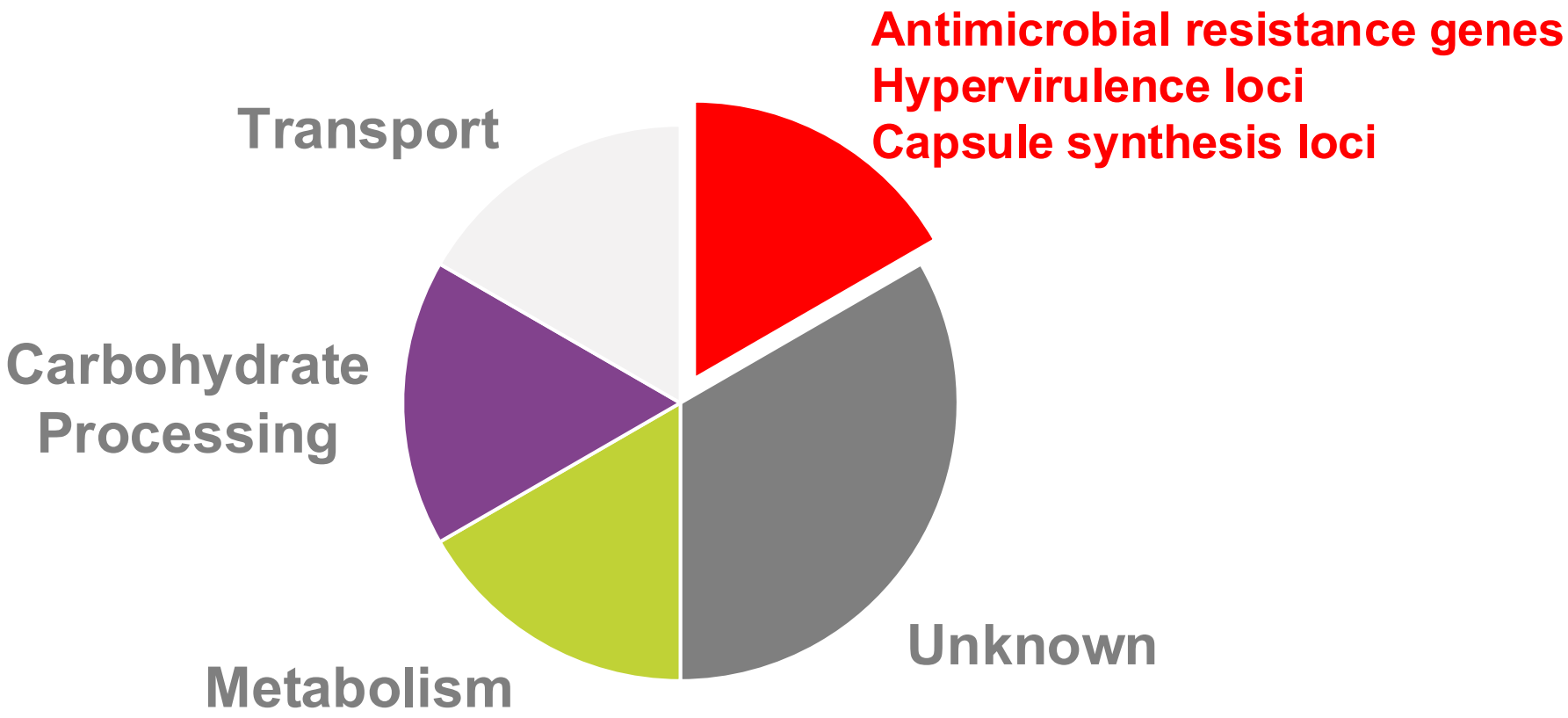
Bactabolize

A high-throughput genome-scale metabolic reconstruction and growth simulation pipeline.

Bactabolize tool: Vezina et al, *eLife* 2023
Population diversity: Vezina et al, *BioRxiv* 2024

Genes of known public health importance

KlebNET-GSP

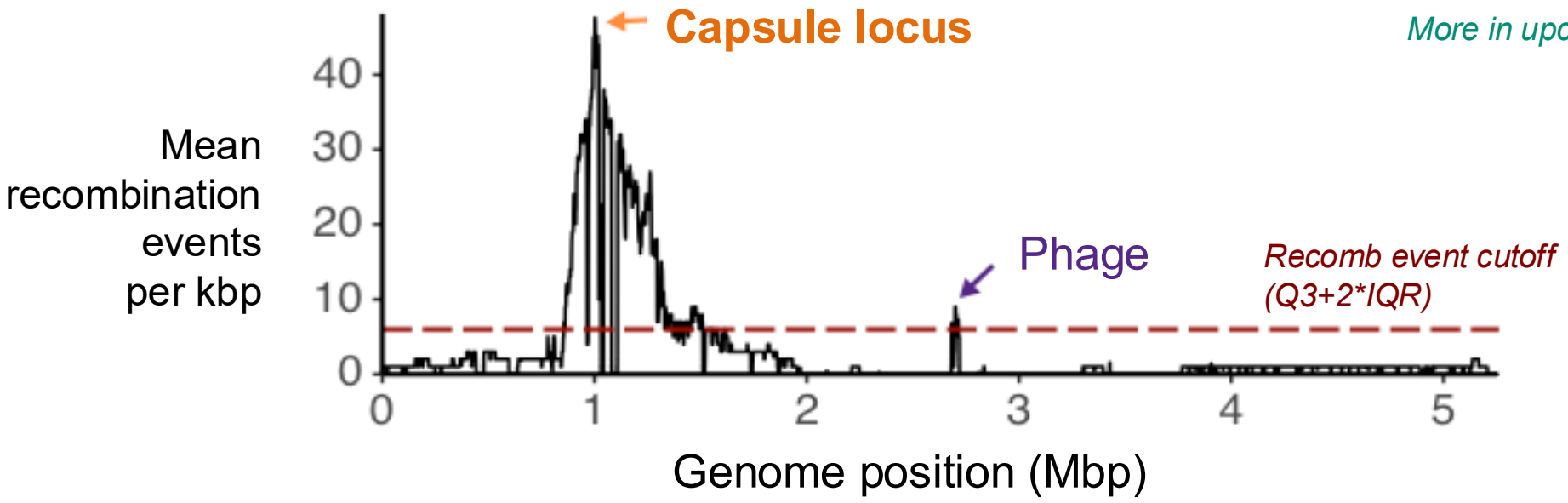


Holt et al, *PNAS* 2015.

Capsule (K) and O antigen synthesis loci

KlebNET-GSP

- >150 capsule (K) loci and 15 O loci defined in *Kp* [1]
- Capsule locus is a recombination hotspot in the *Kp* chromosome[2]



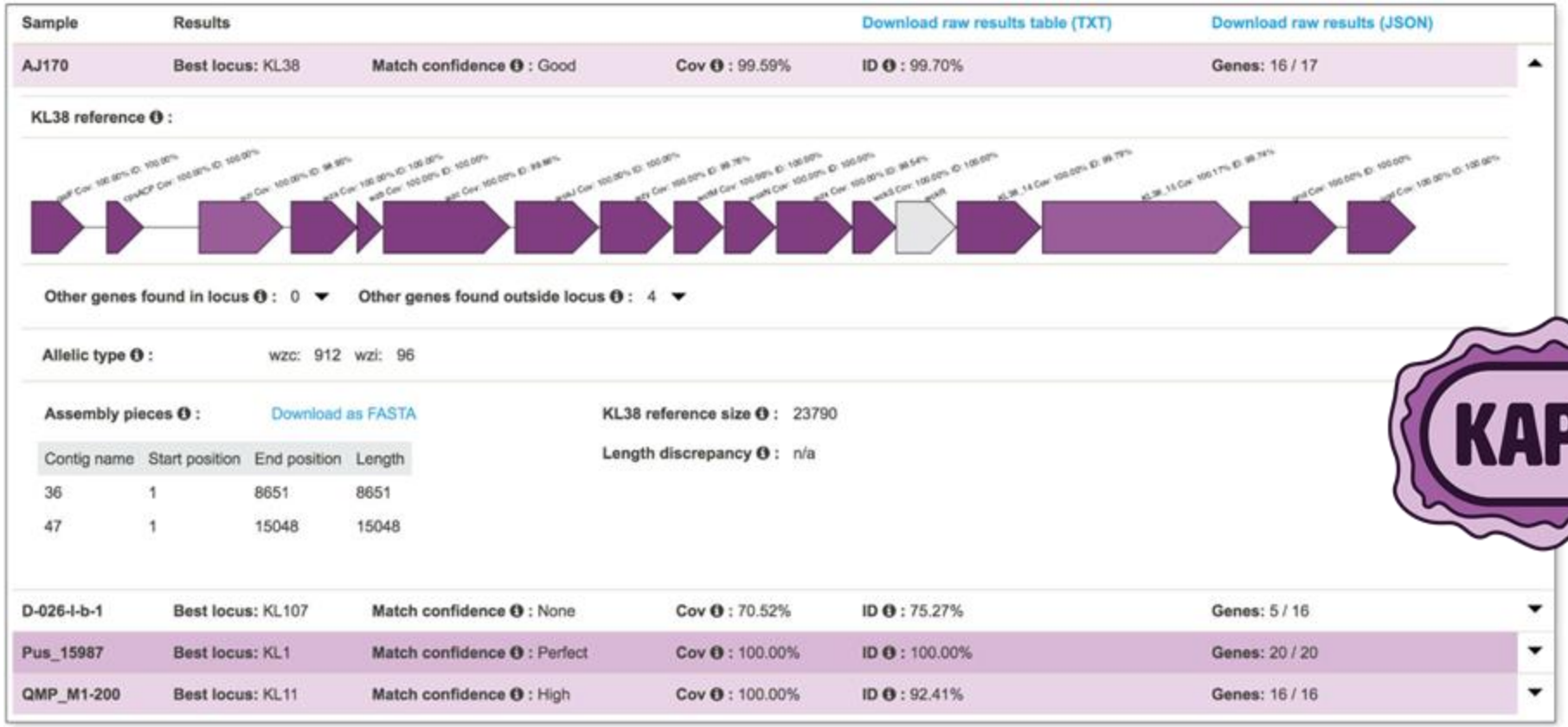
More in upcoming lecture from Kelly Wyres

1: Wyres et al, 2016 *Microbial Genomics*. 2: Wyres *et al,* 2019 *PLoS Genet.*

Capsule (K) and O locus typing

KlebNET-GSP

More in upcoming lecture from Tom Stanton

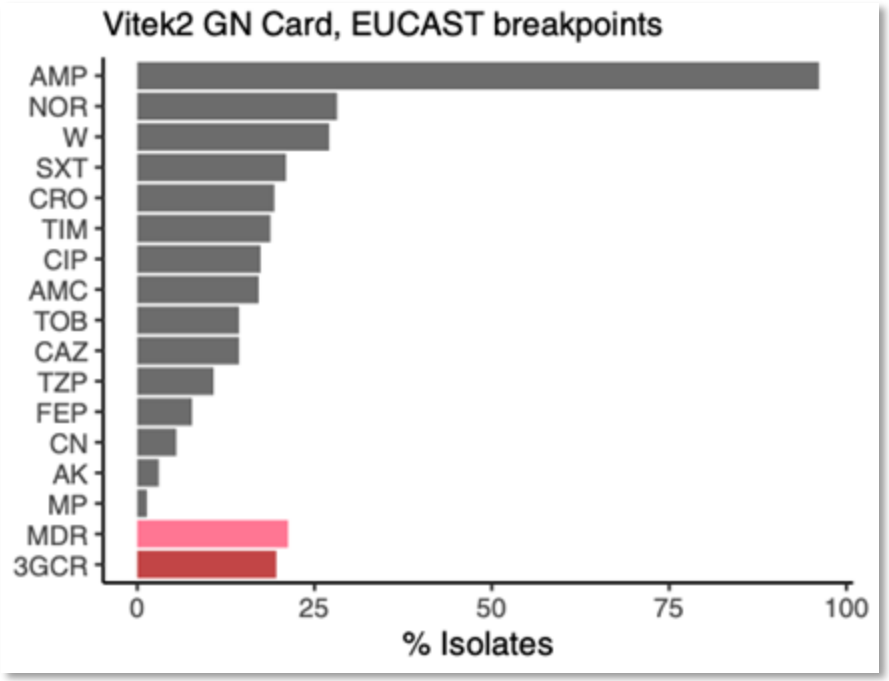


1: Wyres et al, 2016 *Microbial Genomics*. 2: Wick et al, 2018 *J Clin Microbiol.*

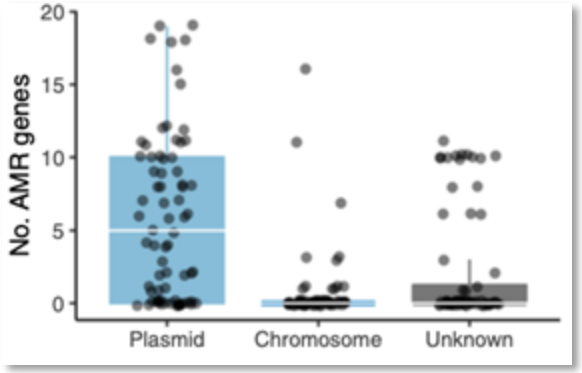
Antimicrobial resistance (AMR)

KlebNET-GSP

Snapshot of hospital *Kp* resistance
(all clinical isolates for 1 year)



Antimicrobial	Determinants (% of resistance explained)	Major error N (%)	Very major error N (%)
Ceftriaxone	$bla_{CTX\text{-}M\text{-}15}$ (71%), $bla_{CTX\text{-}M\text{-}14}$ (13%)	2 (0.8%)	5 (11%)
Meropenem	$bla_{IMP\text{-}4}$ (50%), $bla_{OXA\text{-}48}$ (50%)	1 (0.3%)	0 (0%)
Ciprofloxacin	*qnrB1* (61%), *qnrS1* (7%), GyrA-83 (32%), GyrA-87 (16%), ParC-80 (23%) *	15 (6.0%)	6 (14%)
Gentamicin	*aac(6')-Ib-cr* (79%), *rmtB* (15%), *aac3-IIa* (15%), *aac3-IId*	0 (0%)	1 (9%)
Tobramycin	(12%), *aadA2* (9%), *ant(2")-Ia* (9%), *aac(6')-Ib4* (6%)	1 (0.4%)	1 (3%)
Amikacin		§0 (0%)	§2 (29%)
Trimethoprim +Sulfamethoxazole	*dfrA14* (51%), *dfrA12* (6%); +*sul2* (89%), +*sul1* (29%)	2 (0.9%) 4 (1.7%)	14 (20%) 4 (7%)



Gorrie et al, *Nature Comms* 2022. (Alfred Hospital, Melbourne, Australia)

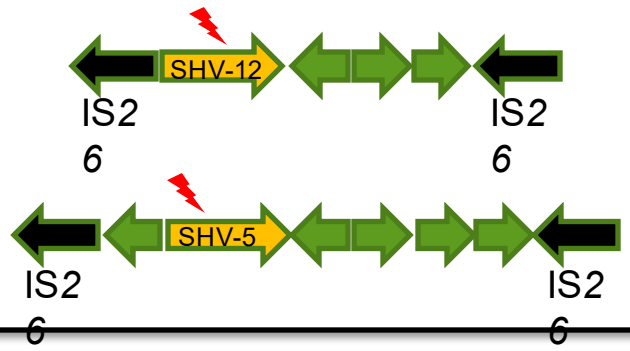
AMR-related core genes

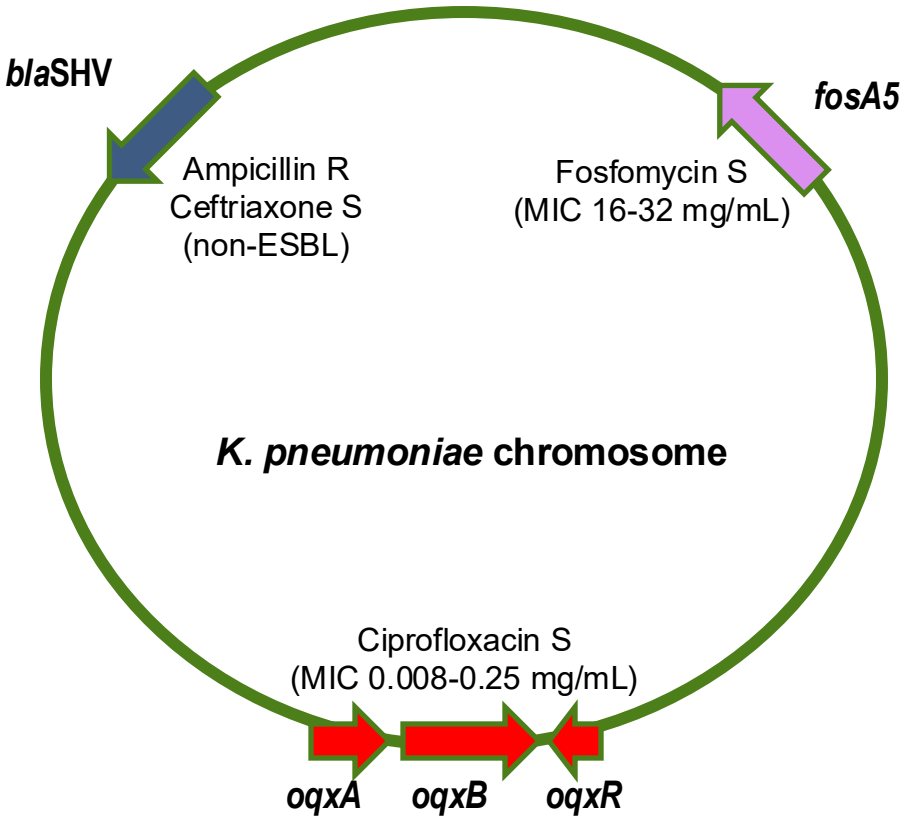
KlebNET-GSP

Protein identifier	Gene symbol	Sequence name	Element type	Class
FNMJAFEK_00618	fosA	FosA5 family fosfomycin resistance glutathione transferase	AMR	FOSFOMYCIN
FNMJAFEK_04094	blaSHV	class A broad-spectrum beta-lactamase SHV-1	AMR	BETA-LACTAM
FNMJAFEK_05097	oqxB19	multidrug efflux RND transporter permease subunit OqxB19	AMR	PHENICOL/QUINOLONE
FNMJAFEK_05098	oqxA	multidrug efflux RND transporter periplasmic adaptor subunit OqxA	AMR	PHENICOL/QUINOLONE

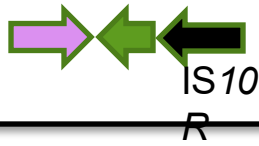
AMRFinderPlus output for wildtype *K. pneumoniae* (expected ampicillin resistance only)

Mobile *blaSHV*
ESBL, 3rd gen cephalosporin resistant

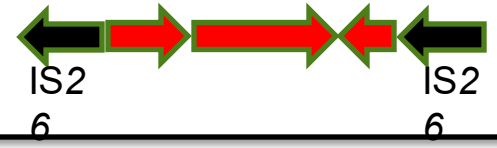




Mobile *fosA5*, *E. coli*
Fosfomycin MIC ≥1024 mg/mL



Mobile *oqxAB*, *E. coli*
Ciprofloxacin MIC 2-4x



Custom AMR dictionary in Kleborate

Commandline result:

Species	Klebsiella pneumoniae
MLST	ST113
K_locus	KL114
O_type	O3/O3a
Ybt	ybt 8; ICEKp3
AGly_acquired	-
Col_acquired	-
Fcyn_acquired	-
Flq_acquired	-
Gly_acquired	-
MLS_acquired	-
Phe_acquired	-
Rif_acquired	-
Sul_acquired	-
Tet_acquired	-
Tgc_acquired	-
Tmt_acquired	-
Bla_acquired	-
Bla_inhR_acquired	-
Bla_ESBL_acquired	-
Bla_ESBL_inhR_acquired	-
Bla_Carb_acquired	-
Bla_chr	SHV-1^
SHV_mutations	-
Omp_mutations	-
Col_mutations	-
Flq_mutations	-

See upcoming lecture from Margaret Lam

Antimicrobial resistance (AMR)

Sourced from Kleborate

Pathogenwatch

Drug/Class	Resistance Determinants
Aminoglycosides	None found
Carbapenems	None found
Cephalosporins (3rd gen.)	None found
Cephalosporins (3rd gen.) + β-lactamase inhibitors	None found
Colistin	None found
Fluoroquinolones	None found
Fosfomycin	None found
Penicillins	**SHV-1**
Penicillins + β-lactamase inhibitors	None found
Phenicols	None found
Sulfonamides	None found
Tetracycline	None found
Tigecycline	None found
Trimethoprim	None found

Detailed SHV typing in Kleborate

MICROBIAL GENOMICS

RESEARCH ARTICLE

Tsang *et al.*, *Microbial Genomics*

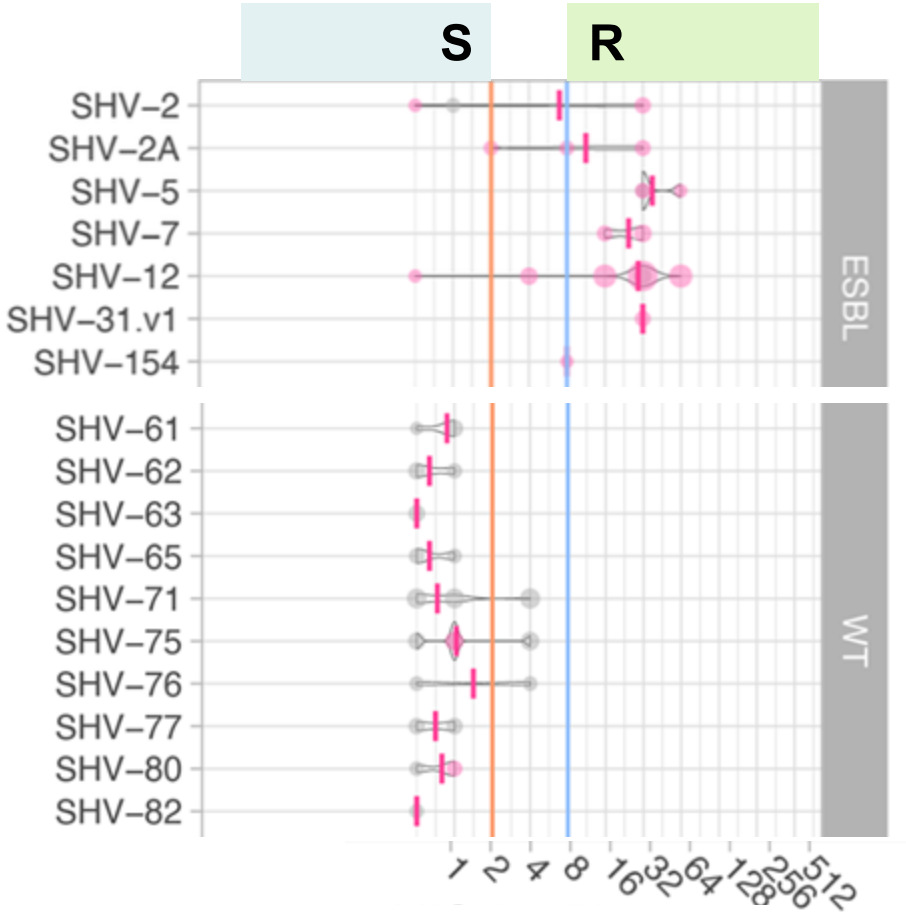
DOI 10.1099/mgen.0.001294

MICROBIOLOGY SOCIETY

OPEN DATA OPEN ACCESS

Diversity, functional classification and genotyping of SHV *β*-lactamases in *Klebsiella pneumoniae*

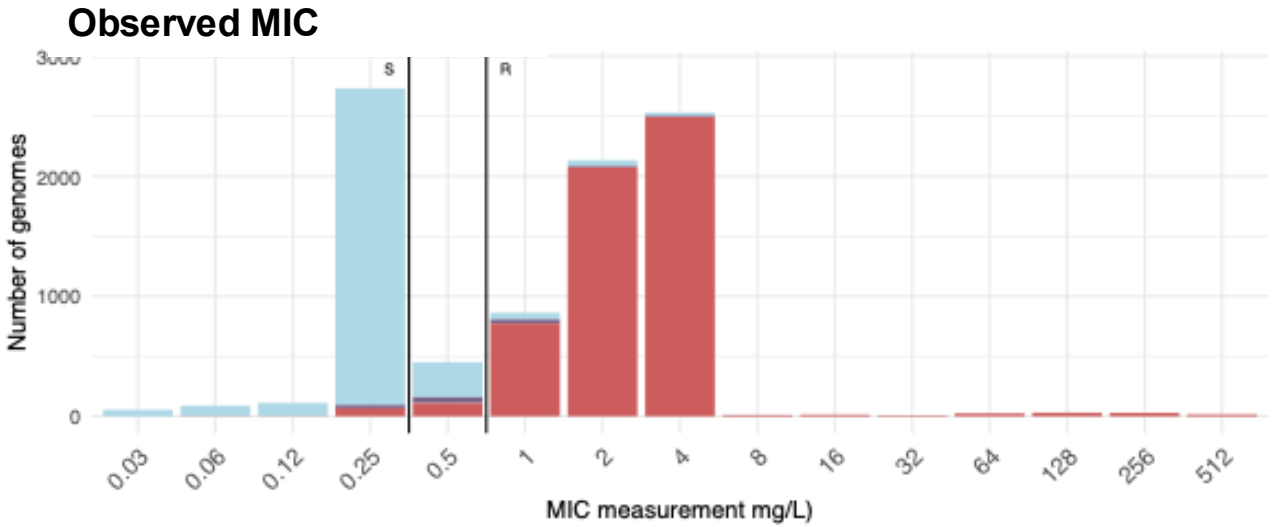
Kara K. Tsang[1], Margaret M. C. Lam[2], Ryan R. Wick[2,3], Kelly L. Wyres[2], Michael Bachman[4], Stephen Baker[5], Katherine Barry[6], Sylvain Brisse[7], Susana Campino[1], Alexandra Chiaverini[8], Daniela Maria Cirillo[9], Taane Clark[1], Jukka Corander[10], Marta Corbella[11], Alessandra Cornacchia[8], Aline Cuénod[12], Nicola D'Alterio[8], Federico Di Marco[9], Pilar Donado-Godoy[13], Adrian Egli[12], Refath Farzana[14], Edward J. Feil[15], Aasmund Fostervold[16], Claire L. Gorrie[3], Brekhna Hassan[17], Marit Andrea Klokkhammer Hetland[16], Le Nguyen Minh Hoa[18], Le Thi Hoi[19], Benjamin Howden[3], Odion O. Ikhimiukor[20], Adam W. J. Jenney[3], Håkon Kaspersen[21], Fahad Khokhar[5], Thongpan Leangapichart[21], Małgorzata Ligowska-Marzęta[22], Iren Høyland Löhr[16], Scott W. Long[23], Amy J. Mathers[6], Andrew G. McArthur[24], Geetha Nagaraj[25], Anderson O. Oaikhena[20], Iruka N. Okeke[20], João Perdigão[26], Hardik Parikh[6], My H. Pham[27], Francesco Pomilio[8], Niclas Raffelsberger[28], Andriniaina Rakotondrasoa[29], K. L. Ravi Kumar[25], Leah W. Roberts[30], Carla Rodrigues[7], Ørjan Samuelsen[31,32], Kirsty Sands[14], Davide Sassera[11,33], Helena Seth-Smith[12], Varun Shamanna[25], Norelle L. Sherry[3], Sonia Sia[34], Anton Spadar[1], Nicole Stoesser[35], Marianne Sunde[21], Arnfinn Sundsfjord[31,36], Pham Ngoc Thach[18], Nicholas R. Thomson[27], Harry A. Thorpe[10], M. Estée Torok[5], Van Dinh Trang[18], Nguyen Vu Trung[19], Jay Vornhagen[37], Timothy Walsh[14], Ben Warne[5], Hayley Wilson[38], Gerard D. Wright[24], Kathryn E. Holt[1,2,*] and KlebNET-GSP AMR Genotype-Phenotype Group

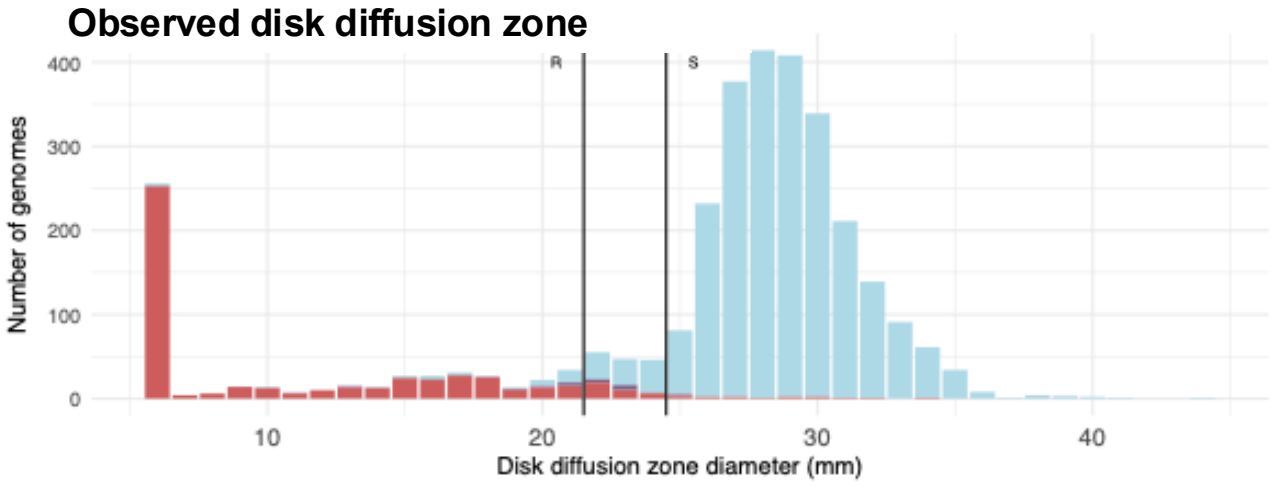


Ceftazidime MIC (mg/L)

13,000+ genomes with matched AMR phenotypes from 27 countries

Ciprofloxacin resistance prediction





Predicted phenotype

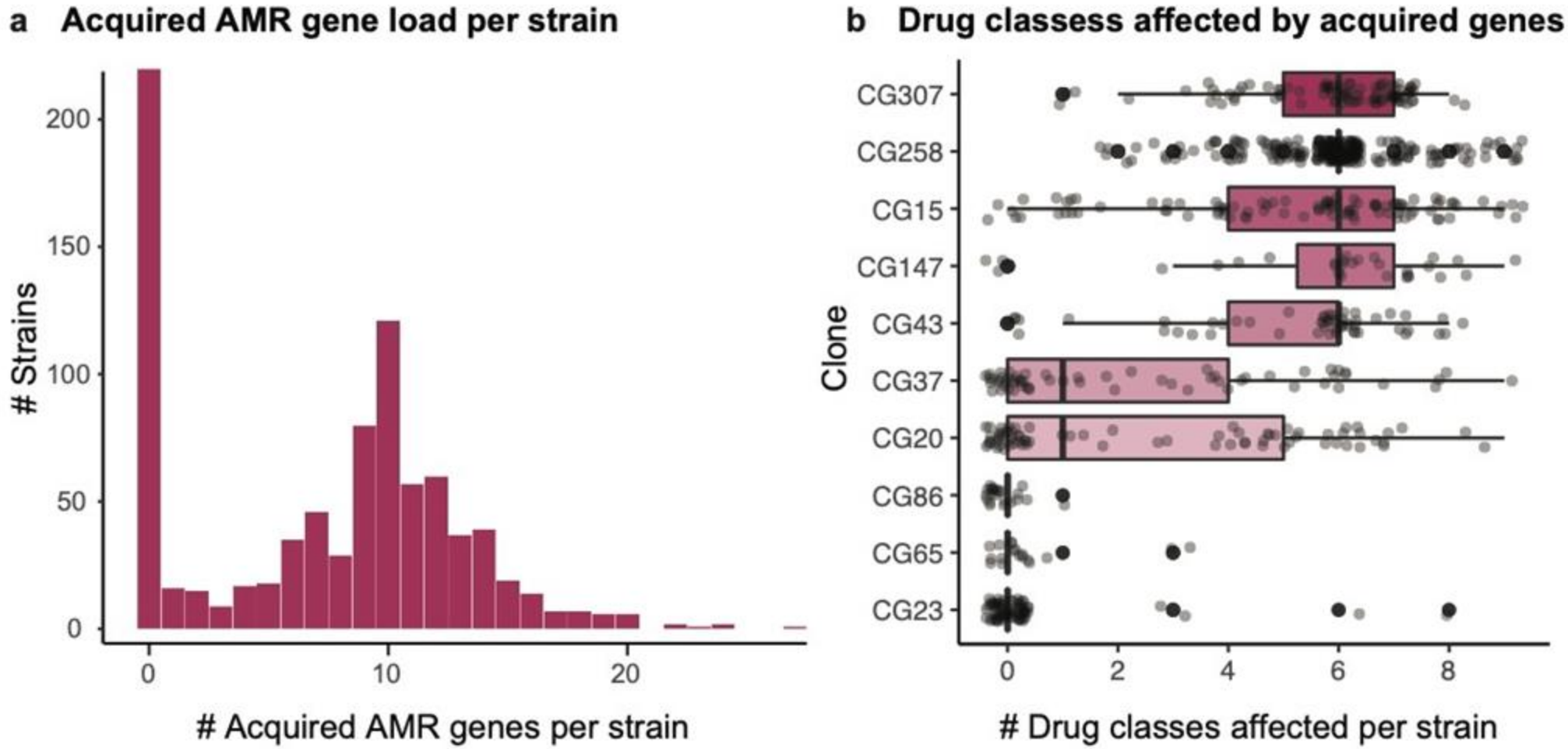
- S
- I
- R

(available in Kleborate v3.2.2+)

Tsang et al, BioRxiv, 2025

Acquired AMR genes

KlebNET-GSP



Wyres, Lam & Holt, *Nature Reviews Microbiology* 2020.

Klebsiella pneumoniae pathogenicity

KlebNET-GSP

Universal factors (core genes)

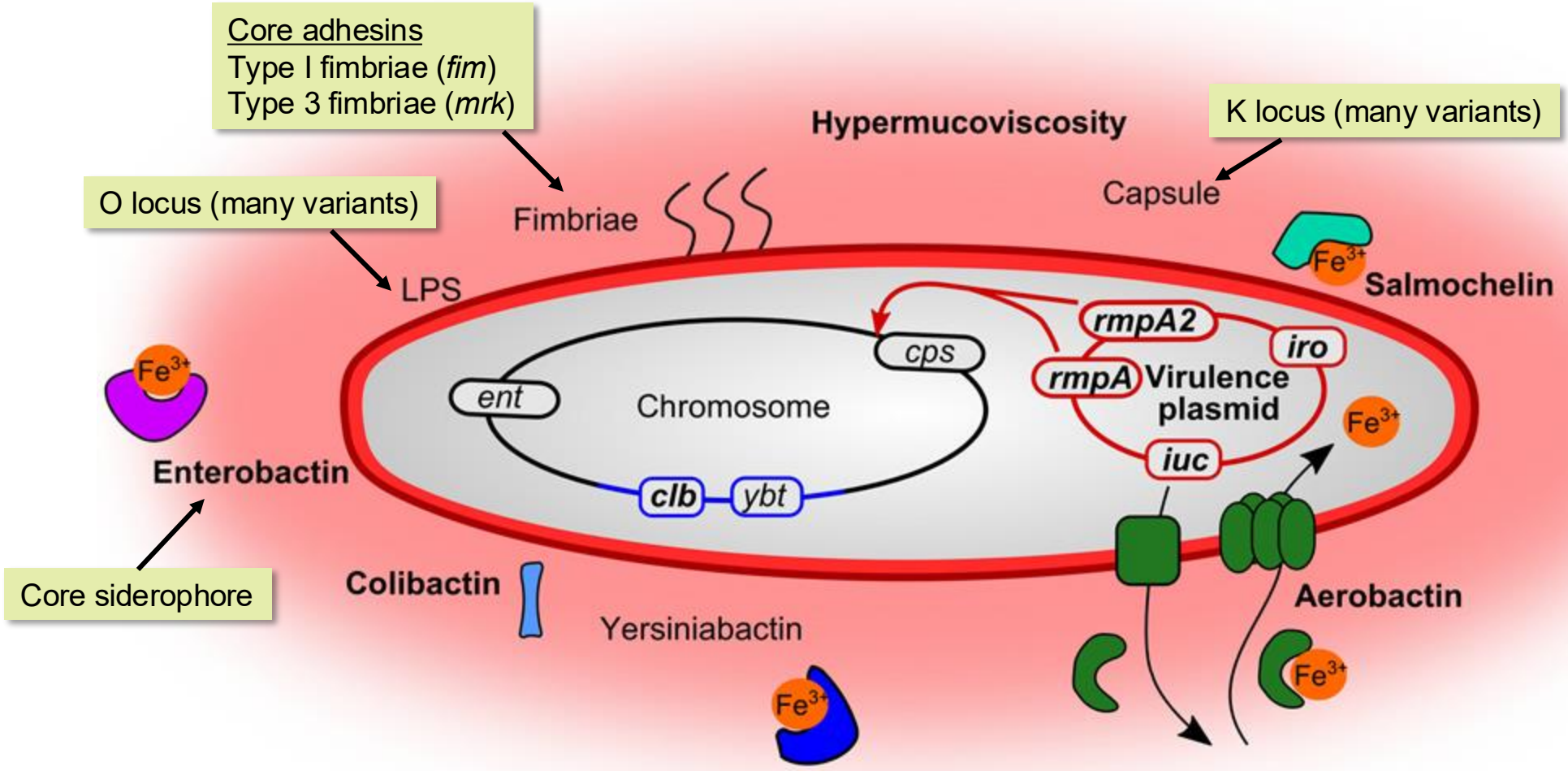
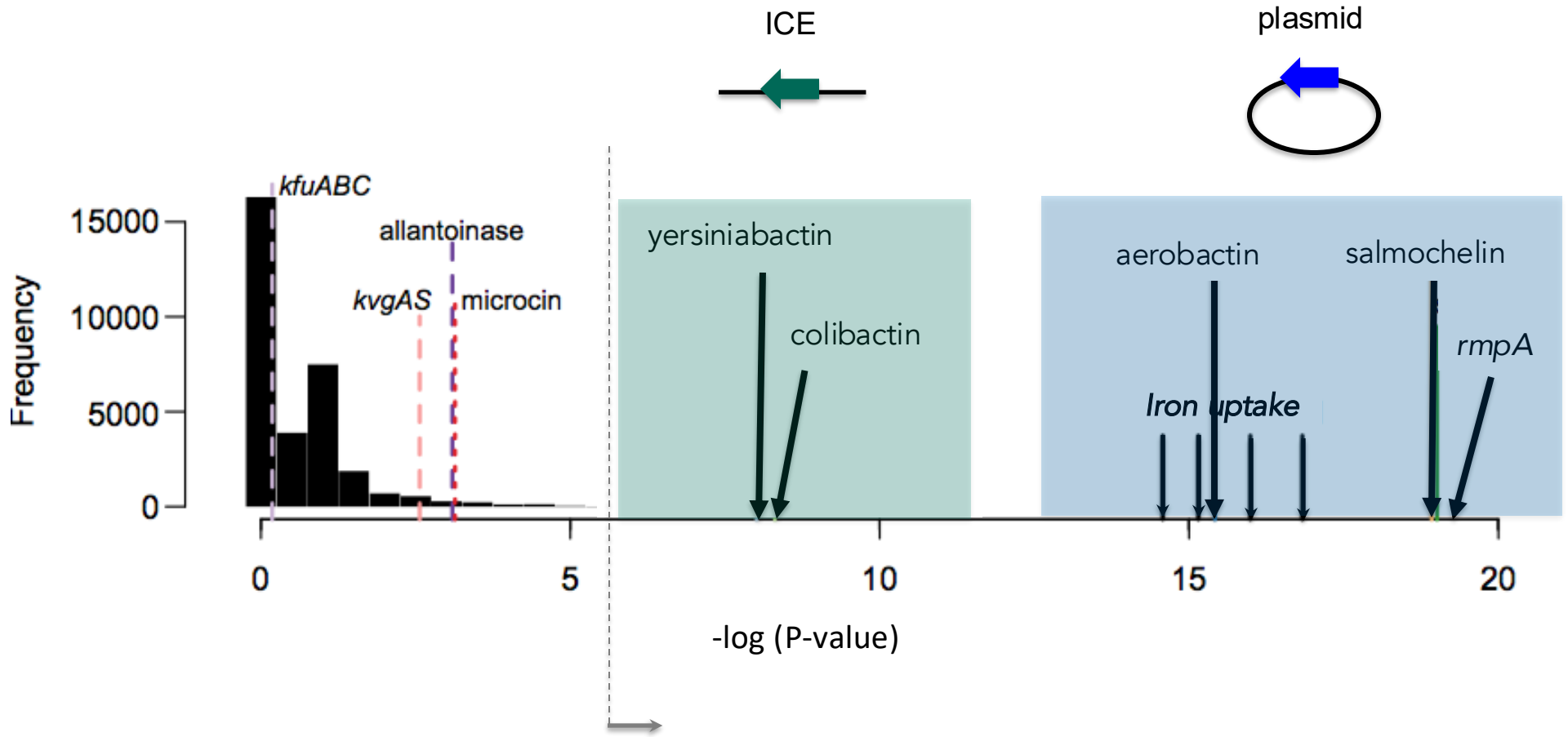


Image: © John Wiley and Sons, reproduced under license. Source: Choby et al, *J Intern Med* 2019.

Accessory genes associated with invasive infections

KlebNET-GSP



Genes significantly associated with invasive infection vs carriage

Holt et al, *PNAS* 2015.

Virulence factors (ICE*Kp*)

KlebNET-GSP

See upcoming lecture from Margaret Lam

Yersiniabactin (*ybt*)

- siderophore synthesis and receptor
- evades lipocalin-2 signalling, facilitating growth in tissue and immune evasion[1]

Colibactin (*clb* or *pks*)

- polyketide synthase
- produces genotoxin, which damages host cells (linked to GI/bowel cancer[2])
- promotes gut colonisation by killing microbiota[3]

1: Bachman et al, *mBio* 2012. 2: Kaur et al, *Microorganisms* 2023. 3: Tan et al, *ISME Journal* 2024.

Virulence factors (virulence plasmid)

KlebNET-GSP

See upcoming lecture from Margaret Lam

Aerobactin (*iuc*) & salmochelin (*iro*) loci

- siderophore
- facilitate growth in host niches[1]

rmp locus (*rmpADC*)

- confers capsule over-production and hypermucoidy[2]
- increases serum resistance[3]

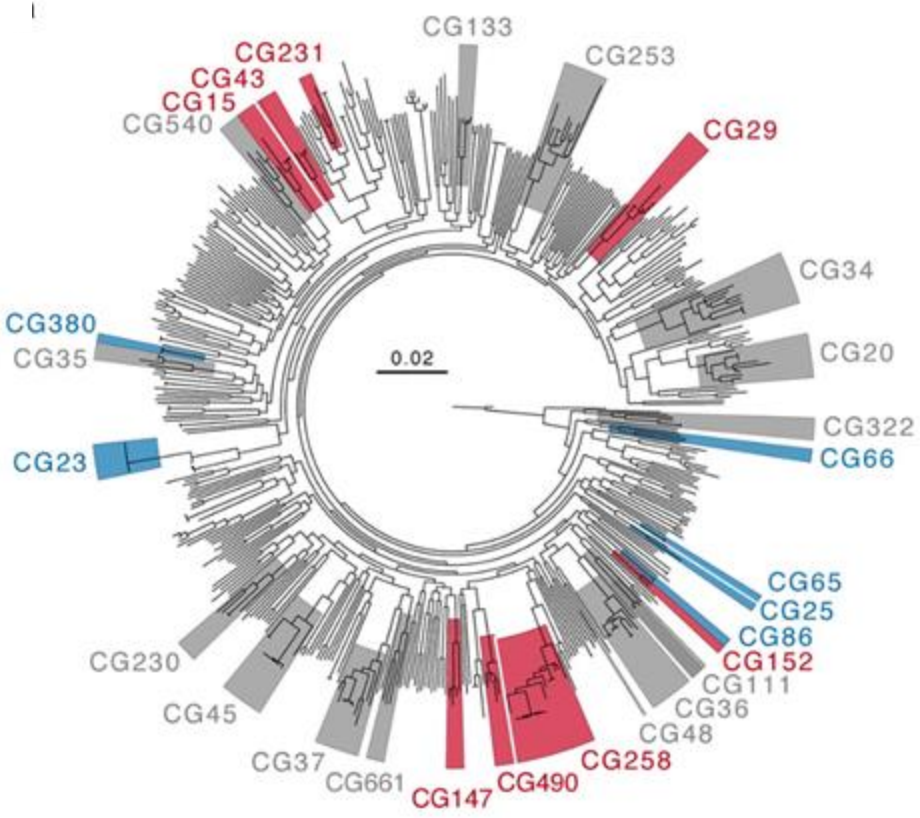
rmpA2 gene

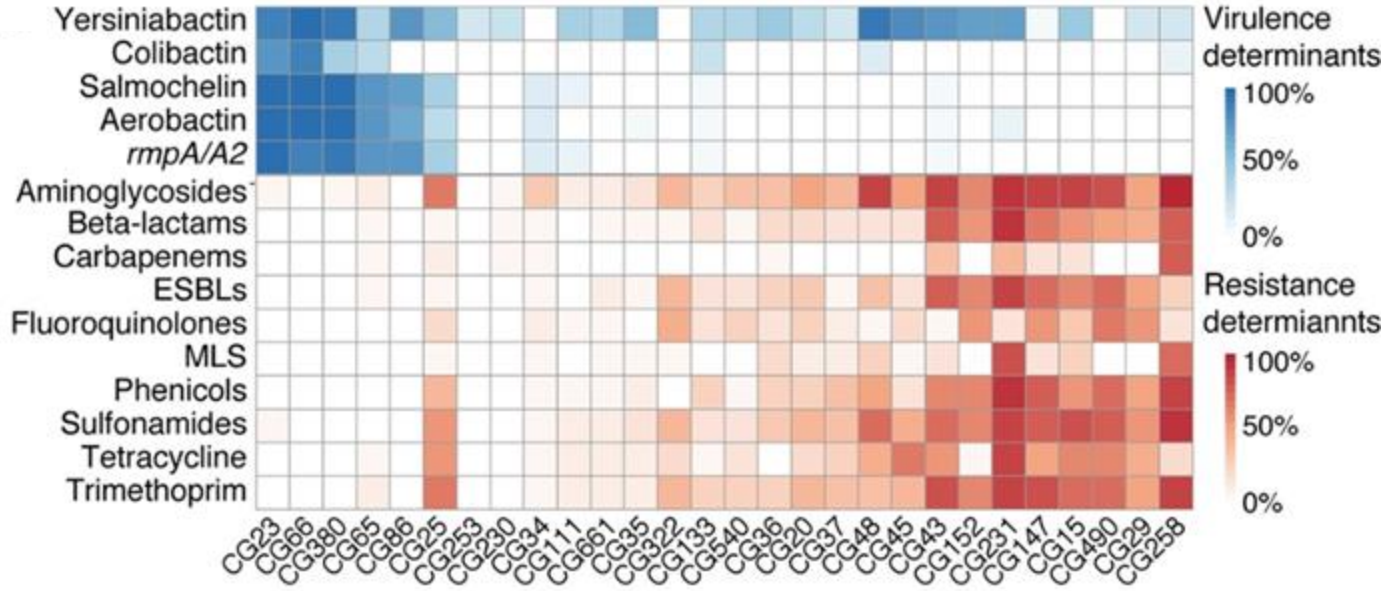
- homolog of *rmpA* in *rmp* locus, but not clear if function is the same
- typically (~90%) disrupted, so not clear if functional

1: Lim et al, *eBioMedicine* 2025. 2: Lam et al, *Genome Medicine* 2025. 3: Xu et al, *Virulence* 2021.

Distribution of AMR and virulence genes

KlebNET-GSP

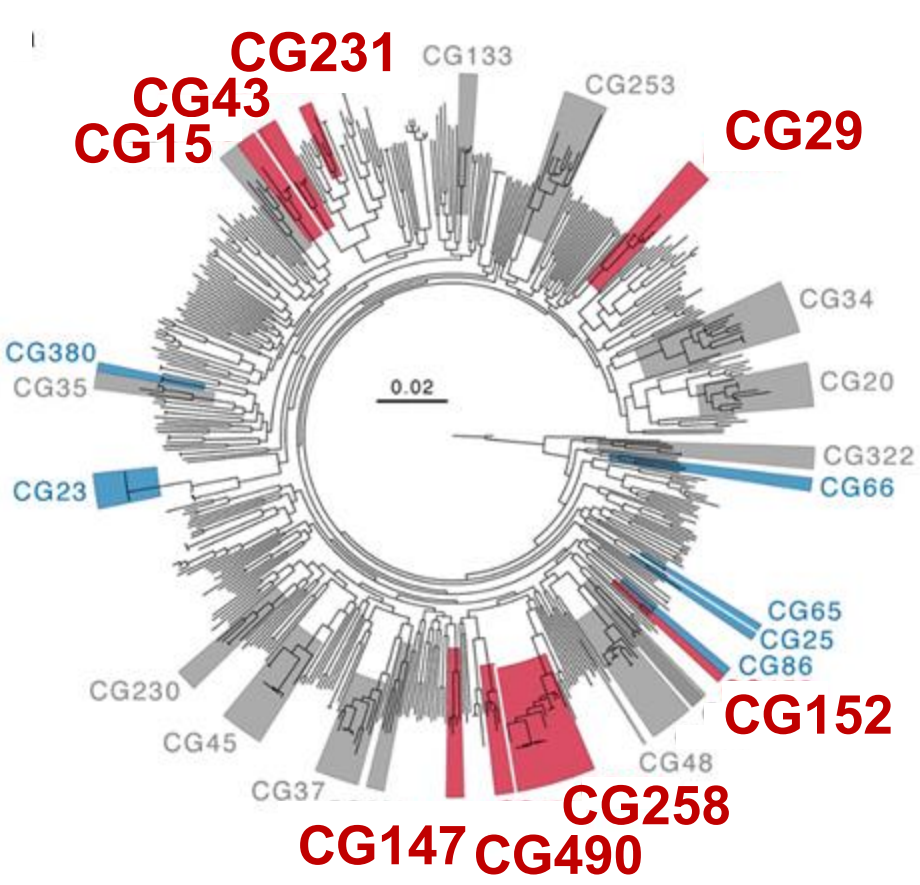


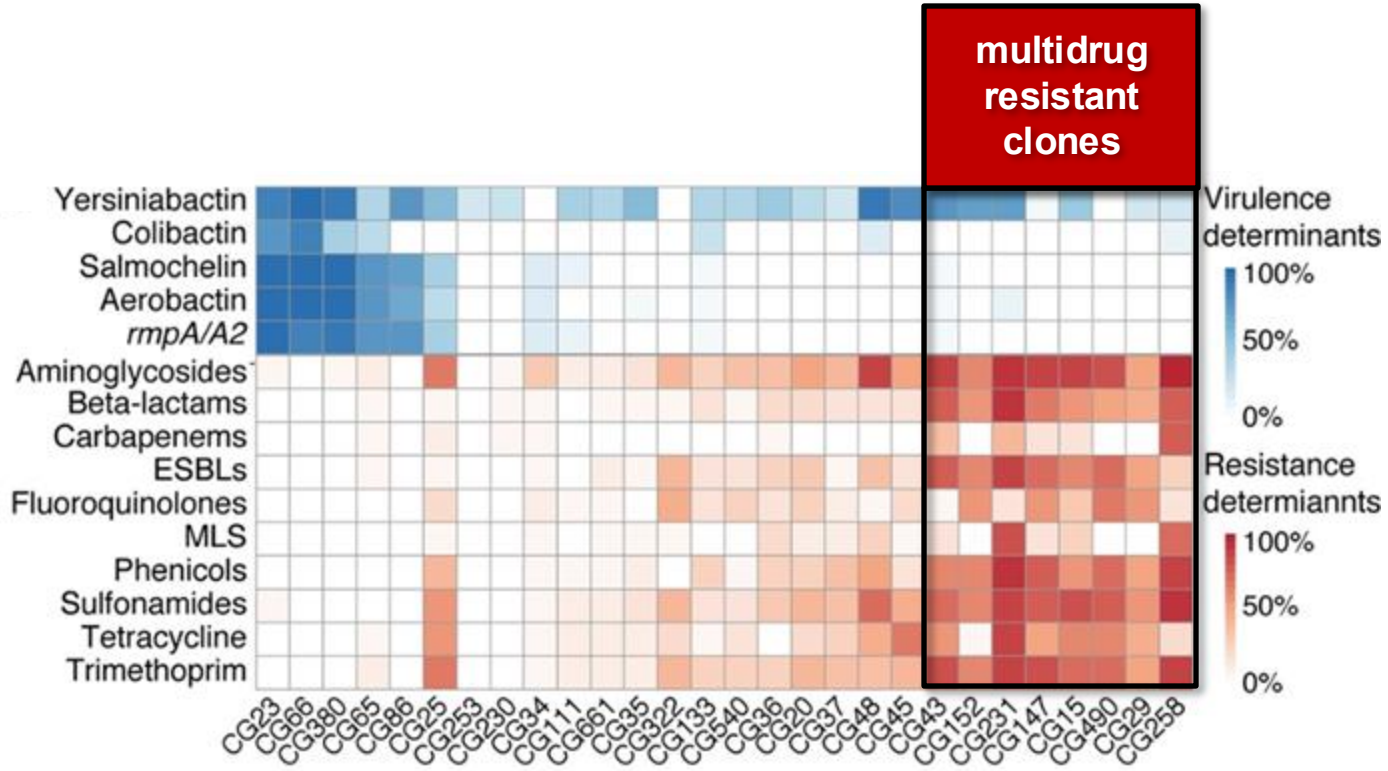


Wyres et al, *PLoS Genetics* 2019.

Distribution of AMR and virulence genes

KlebNET-GSP

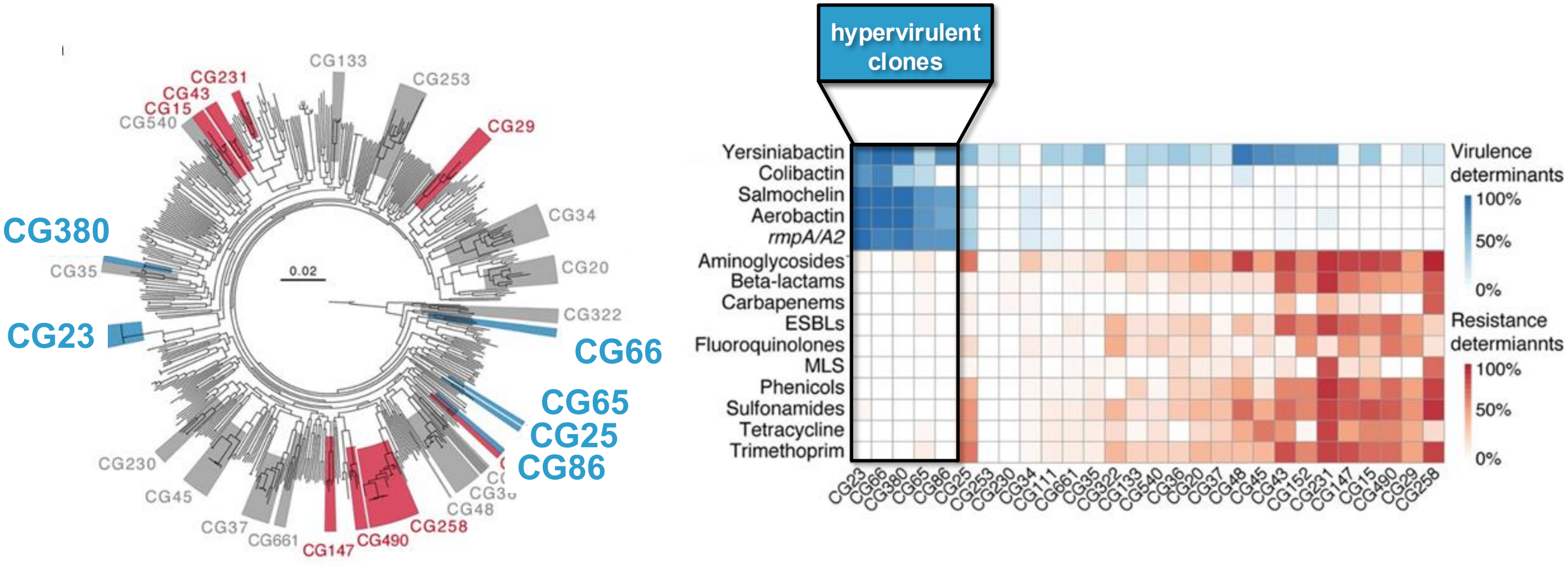




Wyres et al, *PLoS Genetics* 2019.

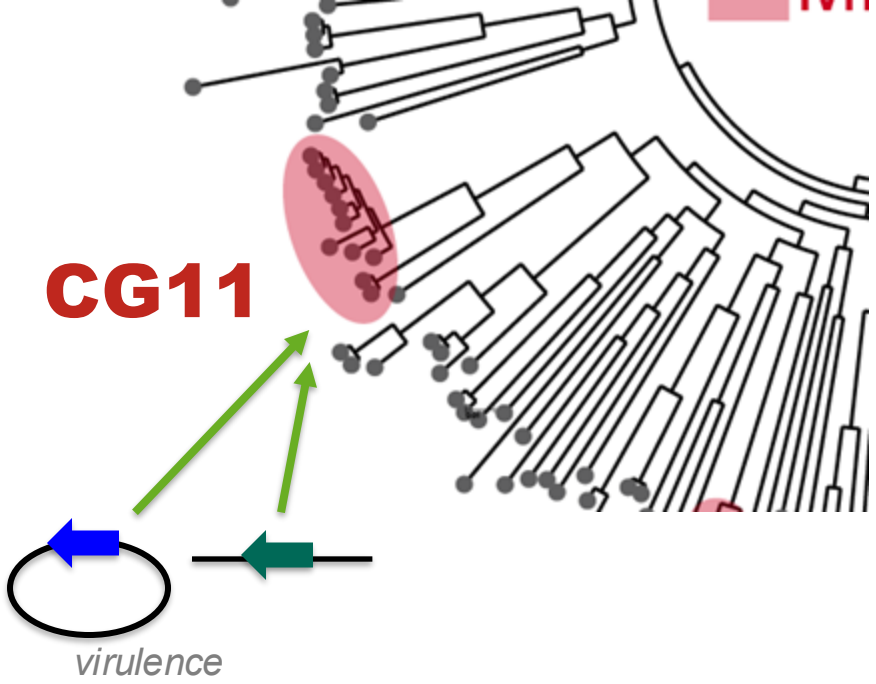
Distribution of AMR and virulence genes

KlebNET-GSP



Wyres et al, *PLoS Genetics* 2019.

Convergence of AMR and virulence



THE LANCET
Infectious Diseases

A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: a molecular epidemiological study

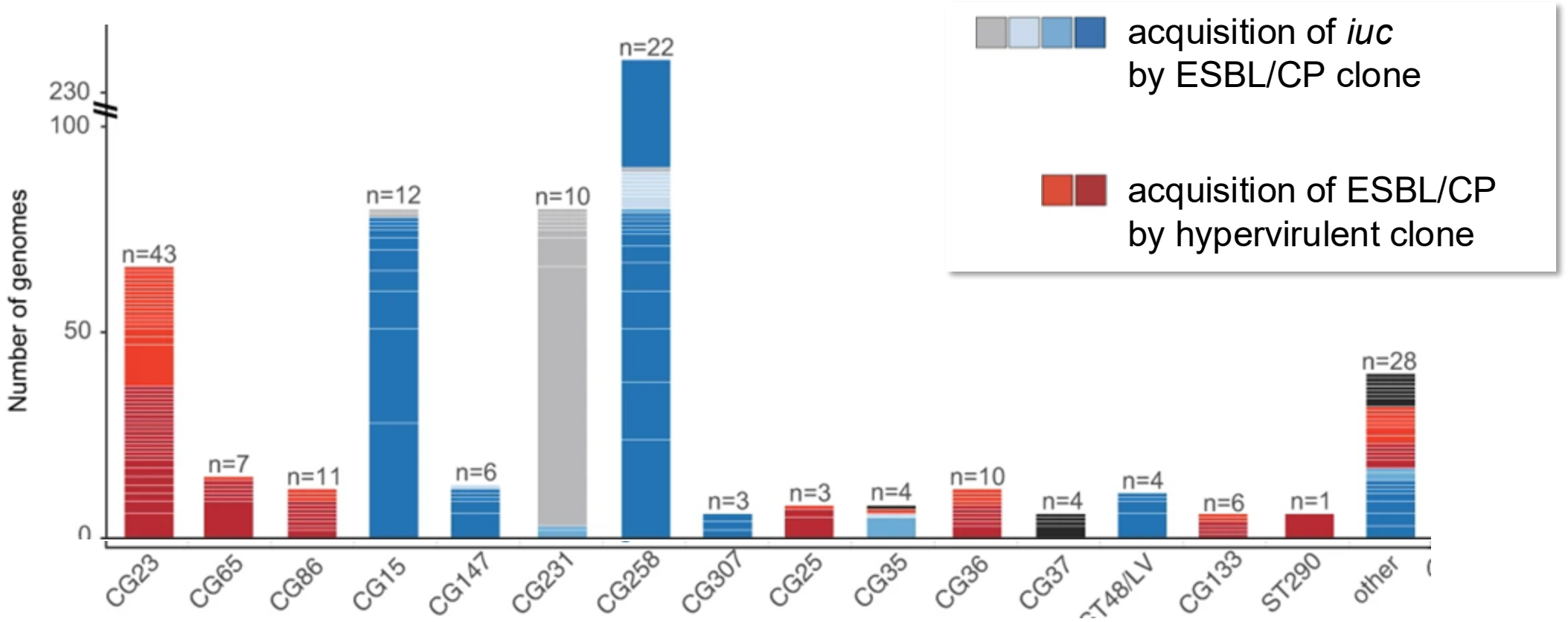
Danxia Gu, MS[†], Ning Dong, MS[†], Zhiwei Zheng, BS, Di Lin, MS, Man Huang, MD, Lihua Wang, MS, Edward Wai-Chi Chan, PhD, Lingbin Shu, MS, Jiang Yu, MS, Dr Rong Zhang, PhD, Dr Sheng Chen, PhD

Convergence of AMR and virulence

KlebNET-GSP

See upcoming lecture from Margaret Lam

Detected quite frequently now, but clinical significance not clear



Lam et al, *Nature Comms* 2021.

Convergence of AMR and hypervirulence?

KlebNET-GSP

See upcoming lecture from Margaret Lam

World Health Organization

Disease Outbreak News

Antimicrobial Resistance, Hypervirulent Klebsiella pneumoniae - Global situation

31 July 2024

THE LANCET
Microbe

Call for prudent use of the term hypervirulence in carbapenem-resistant *Klebsiella pneumoniae*

Yang, McNally & Zhong, 2025.

Convergence of AMR and hypervirulence?

KlebNET-GSP

Hypervirulent *Kp* infections are defined as

- tissue-invasive infections
- in otherwise healthy individuals from the community
- often involving infections in multiple body sites (metastasis)

Most typical presentation is pyogenic liver abscess, subsequently metastasising to the eye, lung, or central nervous system.

'Hypervirulent *Kp*' are strains associated with such infections, but there is no formal definition.

Choby et al, *J Intern Med* 2019.

Molecular markers of hypervirulence?

KlebNET-GSP

Hypervirulent *Kp* infections associated with a few clones, which possess ALL of:

- Specific K types (mostly K1, K2)
- Capsule over-production and hypermucoidy due to *rmp*
- Virulence plasmid including *iuc*, *iro*, *rmp*
- ICEKp including *ybt* (sometimes also *clb*)

Detection of **these clones (CG23, CG86, CG25, CG66, CG65, CG380)** is a strong indicator of hypervirulence, especially if you can confirm all or most of the markers are present.

As these factors are mobile, they appear in various combinations in other lineages…

- Which marker combinations indicate 'hypervirulent'?
- What clinical risk is associated with each marker, or combination?

Virulence markers associated with hypervirulence

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Gene	Marker of	Genetic context	Classifer accuracy, human cohorts	Odds ratio (95% CI), human cohorts	Hazard ratio (95% CI), mouse model
peg-344	putative transporter	VP	**0.97**	1,428.0 (163.4, 12,483.1)	51.7 (22.7, 118.1)
iroB	salmochelin	VP	**0.97**	892.3 (159.1, 5002.6)	59.2 (25.8, 135.5)
iucA	aerobactin	VP	**0.96**	464.7 (107.6, 2,007.2)	31.6 (15.8, 63.6)
rmpA	hypermucoidy (rmp)	VP	**0.96**	581.0 (114.0, 2,961.8)	41.0 (19.1, 88.2)
rmpA2	?hypermucoidy (rmp2)	VP	**0.95**	381.8 (92.4, 1,578.1)	31.2 (16.0, 60.7)
terB	tellurite resistance	VP	0.89	69.0 (26.3, 180.7)	14.3 (8.3, 24.8)
irp2	yersiniabactin	ICE*Kp*	0.79	13.9 (6.7, 28.7)	7.8 (4.7, 12.9)
string test	hypermucoidy	-	0.90	86.6 (31.8, 235.8)	15.5 (8.8, 27.2)

Comparing markers in isolates from two patient cohorts:

1) Hypervirulent infection: healthy, ambulatory patient with a clinical syndrome of tissue-invasive infection (e.g., hepatic and extrahepatic abscesses, necrotizing fasciitis, or endophthalmitis) [n=85, from USA and Taiwan]
2) Classical infection: randomly chosen, deidentified blood isolates [n=90, from USA, Canada, UK]

- All these markers were associated with hypervirulent infections
- 5 markers (*peg-344, iro, iuc, rmpA, rmpA2*) each with classification accuracy ≥95%
- …but these are all in strong genetic linkage on the virulence plasmid

Russo et al, *J Clin Microbiol* 2018.

Which markers are essential for hypervirulence?

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Isogenic mutants in 4 hypervirulent clinical isolates

ST23 / K1
ST86 / K2
ST1544 / K20
ST29 / K54

Subcutaneous challenge infection in mice

Hypervirulence lost if we delete:
- ✓ virulence plasmid
- ✓ *rmpA*
- ✓ *iucA* (2/4 strains only)

Hypervirulence retained if we delete:
- x *irp2* (yersiniabactin)
- x *clb* (colibactin)
- x *rmpA2* (truncated)

Russo et al, *eBioMedicine* 2024.

Marker combinations associated with hypervirulence

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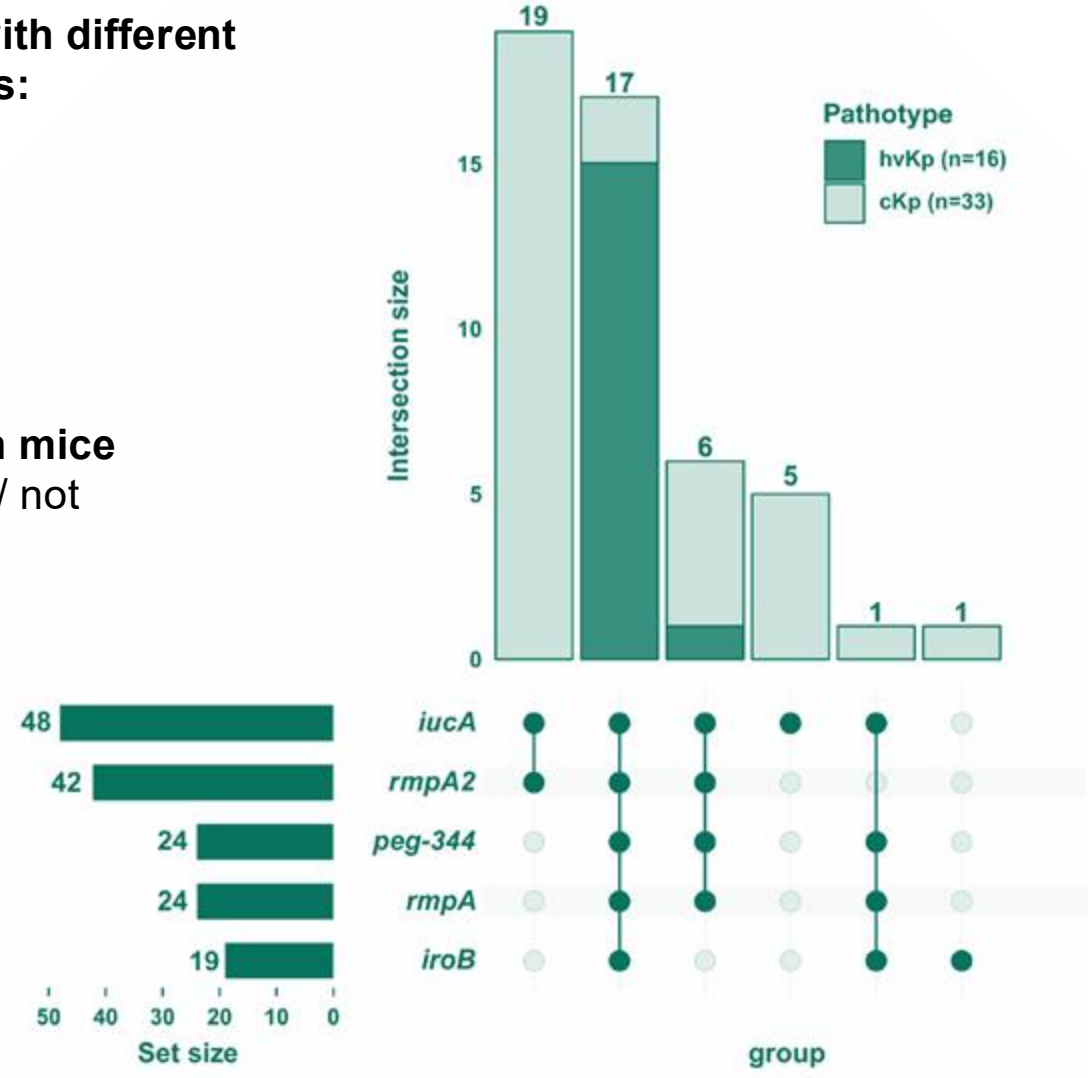
45 AMR clinical isolates with different combinations of 5 markers:

- *peg-344*
- *iroB*
- *iucA*
- *rmpA*
- *rmpA2*

Subcutaneous infection in mice

➢ classify as hypervirulent / not



✓ **All 5 markers (n=17):** hypervirulent

x ***iucA*/*rmpA2* alone (n=19):** not hypervirulent

? **other combinations:** insufficient samples

Russo et al, *mBio* 2024.

How to interpret virulence markers?

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Best indication of hypervirulence (including community onset and metastasis) is intact copies of loci:

- *rmp* AND *iuc* AND *iro*

***rmp* without *iuc/iro*? – not hypervirulent**

- Probably hypermucoid & hyperencapsulated, leading to enhanced serum resistance
- Not clear the effect on outcome, but unlikely to metastasise without siderophores

***iuc* or *iro* without *rmp*? (including *iuc/rmpA2* without *rmp*) – not hypervirulent**

- Reasonable to expect enhanced colonization potential and increased virulence, but not clear the overall effect on outcome

***ybt alone?* – not hypervirulent**

- Enhanced likelihood of healthcare associated pneumonia (and subsequent sepsis), but not hypervirulent (e.g. do not expect community acquired infection, metastasis, etc)

How to understand convergence?

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In the absence of a formal definition for hypervirulence, propose to define convergence of hypervirulence and resistance as:

- Presence of a complete virulence plasmid with intact *iuc*, *rmp*, and *iro* in a drug resistant strain

Presence of partial virulence plasmid with *iuc+rmpA2* in AMR clones is common, but these are likely not hypervirulent.

More clinical research is needed to understand whether such strains are associated with:

- increased clinical risk? (e.g. disease severity, metastasis, mortality)
- increased dissemination risk? (e.g. increased colonization efficiency, or transmission efficiency/R_0 in different patient groups)

How to understand convergence?

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Convergence of AMR and <u>hyper</u>virulence
- Known hypervirulent clone, with *iuc* + *iro* + *rmp*
- Clear link to clinical syndrome and confirmed in animal models

RISK: Severe invasive infection with limited treatment options

Convergence of AMR and virulence
- Presence of *iuc* but without *rmp*
- Only 10% blood isolates, majority isolated from UTI or screening

RISK: Clinical risk vs OXA-48+ *iuc*- strains not known, but dissemination of combined plasmid concerning

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Klebsiella pneumoniae
Genomic Surveillance Platform

klebnet.org

NEONET AFRICA

CARD

EnteroBase

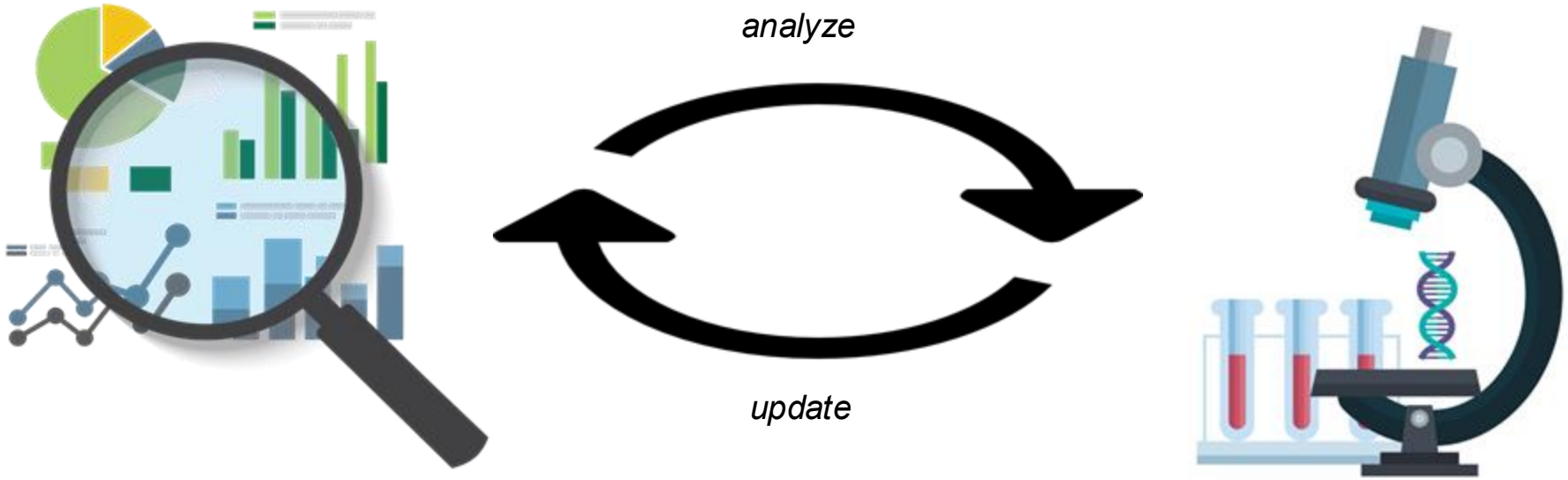
INSTITUT PASTEUR
BIGSdb-Pasteur

KLEBORATE

KAPTIVE

Pathogenwatch

Data sharing is essential to support the digital tools we all need for *Klebsiella* genomics



Tools + databases

Sequence + metadata

KlebNET AMR Geno-Pheno Consortium

Collating matched genotype and phenotype data from the *Kp* species complex isolated from diverse sources to test and improve tools for prediction of AMR from genomic data, including Kleborate and AMRrules.

- Partners include **ESGEM-AMR, CARD, NCBI Pathogens**, and **BLDB**.

KlebNET-GSP Epidemiology Consortium

Collating publicly available *Kp* species complex whole genome sequences with matched isolate source and sampling information, to support:

- **KlebNET Clone Reviews** – collaborative genomic epidemiology reviews of globally distributed clones (e.g multi-drug resistant or hypervirulent clones);
- **KlebNET Clone Risk Framework** – a systematic risk framework to support global genomic surveillance of *Kp*;
- **KlebNET Metadata Repository** – a comprehensive open-access repository of enhanced contextual meta-data, facilitating use and reuse of publicly available data by the global research community by enabling robust epidemiology and genomic meta-analyses.

klebnet.org

Other KlebNET resources

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Lab protocols for isolating, identifying and sequencing *Klebsiella*

Curated genome data collections

- Neonatal sepsis isolates
- Bacterial strains available in public reference collections

Data standards

- Metadata template
- QC standards for *K. pneumoniae* genome assemblies

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In summary

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List of learning points in this session:

- *Kp* population structured into lineages, characterised by differences in gene content drawn from large pan-genome
- Key genomic features relevant to clinical & public health are K/O loci, AMR variants, virulence markers
- Hypervirulent *Kp* lacks a formal definition, but seems to require both acquired siderophores (especially *iuc*) and hypermucoidy (*rmp*)
- Typing tools for all these loci are available from KlebNET, which also provides resources on QC, metadata, curated genome collections, and collaborative consortia to support further development of public health genomics tools

Further reading

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Specific further reading for this session

Population genomics of *Klebsiella pneumoniae*

Wyres, Lam & Holt, *Nature Reviews Microbiology*, 2020

PMID: 32055025

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