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Genome-wide recombination drives diversification of epidemic strains of *Acinetobacter baumannii*

Evan S. Snitkin^a, Adrian M. Zelazny^b, Clemente I. Montero^b, Frida Stock^b, Lilia Mijares^{a,b}, NISC Comparative Sequence Program^{c,1}, Patrick R. Murray^{b,2,3}, and Julie A. Segre^{a,2}

Course 27104:

The Scientific Communication of Comparative Genomics

Malene I. Jacobsen (s102586)

Linda R. Jensen (s071929)

Monica V. Hermann (s061692)

Isa K. Kirk (s072914)



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^aEpithelial Biology Section, Genetics and Molecular Biology Branch, National Human Genome Research Institute, Bethesda, MD 20892; ^bDepartment of Laboratory Medicine, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, MD 20892; and ^cNational Institutes of Health Intramural Sequencing Center, National Institutes of Health, Rockville, MD 20852

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Acinetobacter baumannii is an emerging human pathogen and a significant cause of nosocomial infections among hospital patients worldwide. The enormous increase in multidrug resistance among hospital isolates and the recent emergence of pan-drug-resistant strains underscores the urgency to understand how *A. baumannii* evolves in hospital environments. To this end, we undertook a genomic study of a polyclonal outbreak of multidrug-resistant *A. baumannii* at the research-based National Institutes of Health Clinical Center. Comparing the complete genome sequences of the three dominant outbreak strain types enabled us to conclude that, despite all belonging to the same epidemic lineage, the three strains diverged before their arrival at the National Institutes of Health. The simultaneous presence of three divergent strains from this lineage supports its increasing prevalence in in-

ternational hospitals and suggests an ongoing adaptation to the hospital environment. Further genomic comparisons uncovered that much of the diversification that occurred since the divergence of the three outbreak strains was mediated by homologous recombination across 20% of their genomes. Inspection of recombinant regions revealed that several regions were associated with either the loss or swapping out of genes encoding proteins that are exposed to the cell surface or that synthesize cell-surface molecules. Extending our analysis to a larger set of international clinical isolates revealed a previously unappreciated ability of *A. baumannii* to vary surface molecules through horizontal gene transfer, with subsequent intraspecies dissemination by homologous recombination. These findings have immediate implications in surveillance, prevention, and treatment of *A. baumannii* infections.

Introduction: *Acinetobacter baumannii*

- Human pathogen
- Hospital environment
 - Immunocompromised patients
- Multidrug resistant (MDR)
 - Resistant to desiccation and facilitating spread
 - Prolonged infection



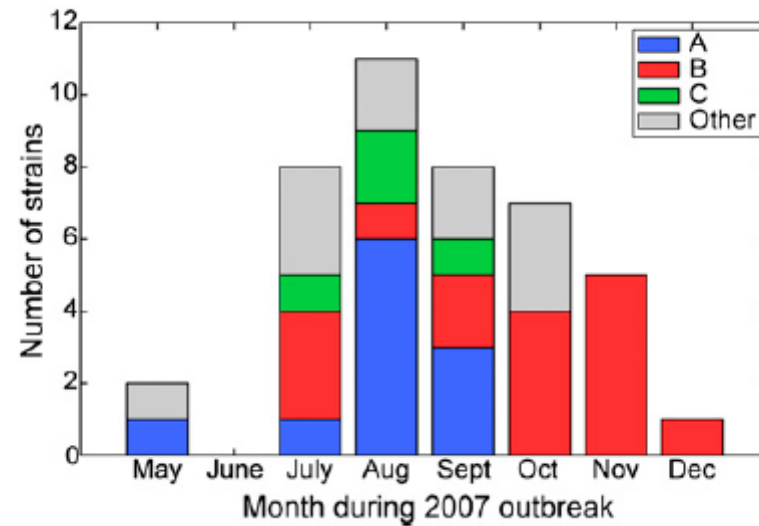
www.acinetobacterbaumannii.org/ (12/09/11)

Introduction: The study

- From other studies
 - Lineages: EC I, II, and III
- This study
 - Whole genome sequencing of clinical isolates
 - One outbreak
 - 29 MDR *A. baumannii* from 45 patients

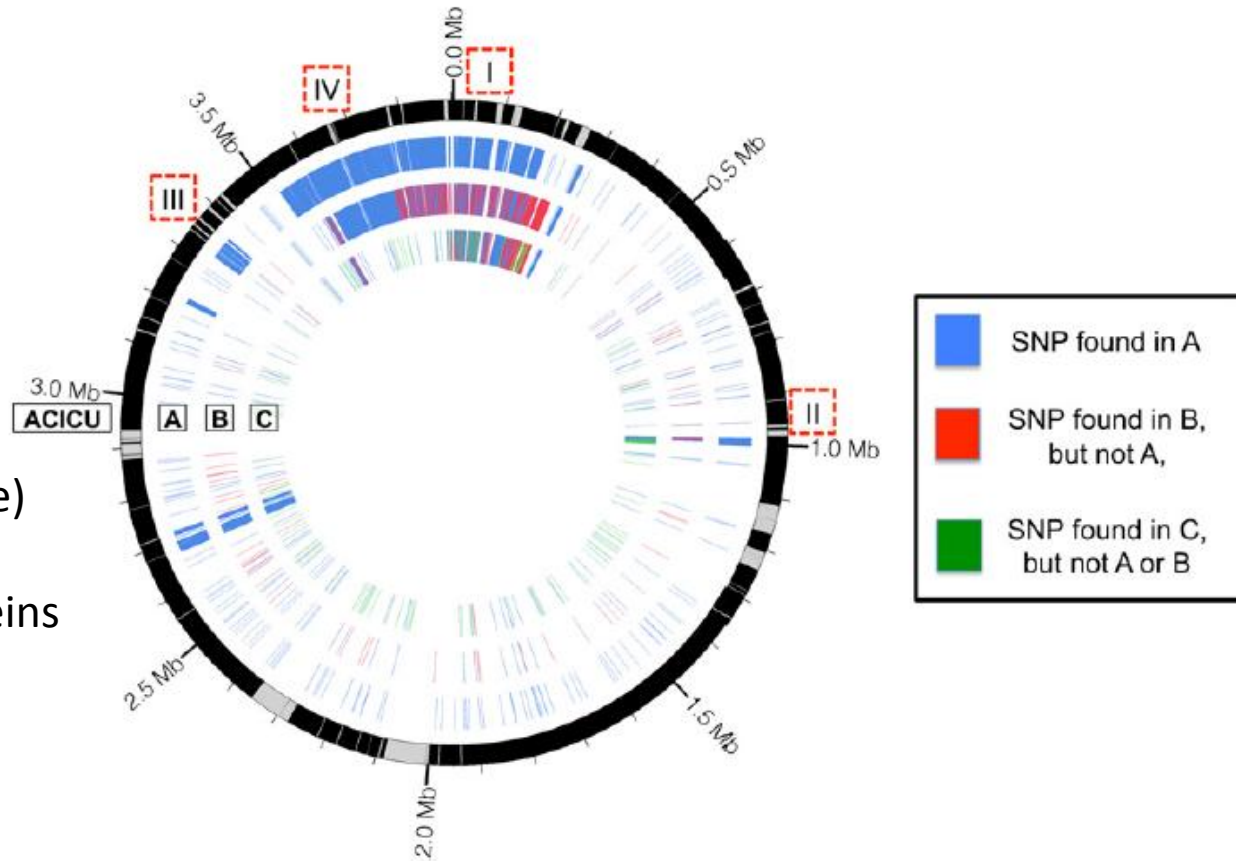
Results

- 3 pulsotypes (A, B & C)
- ECII
- Consequence:
 - Rapid divergence
 - Increased prevalence



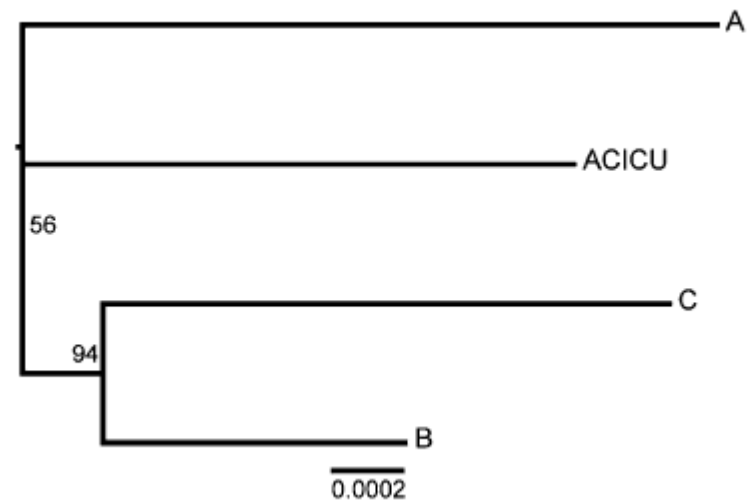
Recombination events facilitate swapping of genes

- Region I
 - O-antigen
- Region II
 - Iron acquisition
- Region III
 - LPS (glycosyltransferase)
- Region IV
 - Outer membrane proteins
 - Efflux pumps

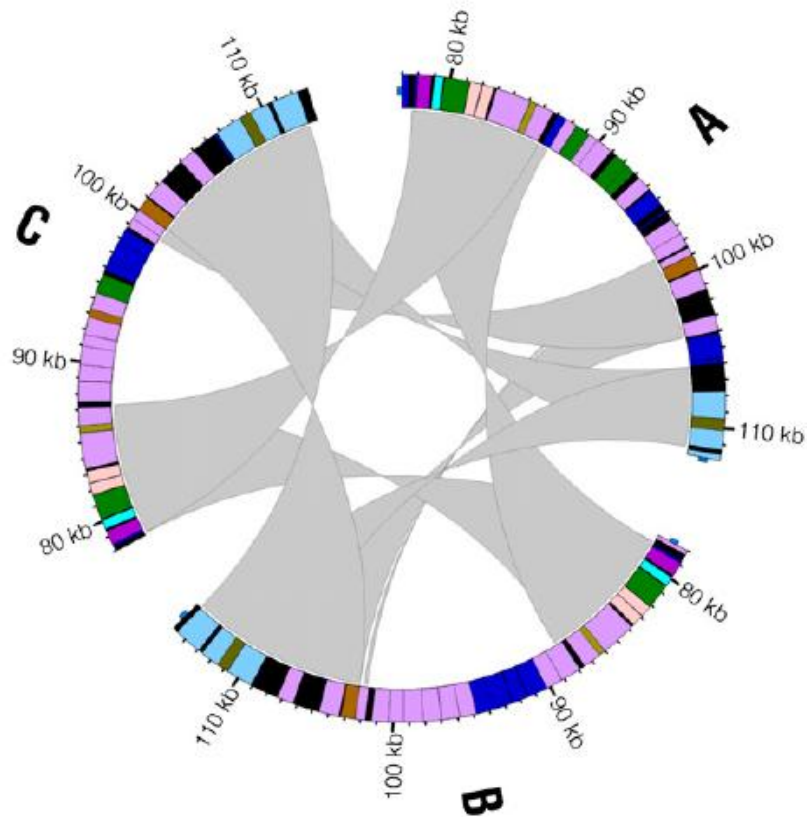


Dispersed presence across distant *A. baumannii* lineages

- Acicu reference strain
- B and C is derived from the same parental strain and came from the same patient
- A's is independent of B and C



Variable gene content in the O-antigen biosynthetic clusters



- Amino acid transport and metabolism (E)
- Carbohydrate transport and metabolism (G)
- Cell cycle control, cell division, chromosome partitioning (D)
- Cell motility (N)
- Cell wall/membrane/envelope biogenesis (M)
- Chromatin structure and dynamics (B)
- Coenzyme transport and metabolism (H)
- Cytoskeleton (Z)
- Defense mechanisms (V)
- Energy production and conversion (C)
- Extracellular structures (W)
- Function unknown (S)
- General function prediction only (R)
- Inorganic ion transport and metabolism (P)
- Intracellular trafficking, secretion, and vesicular transport (U)
- Lipid transport and metabolism (I)
- Nuclear structure (Y)
- Nucleotide transport and metabolism (F)
- Posttranslational modification, protein turnover, chaperones (O)
- RNA processing and modification (A)
- Replication, recombination and repair (L)
- Secondary metabolites biosynthesis, transport and catabolism (Q)
- Signal transduction mechanisms (T)
- Transcription (K)
- Translation, ribosomal structure and biogenesis (J)

Alignment of regions to other sequenced *Acinetobacter* genomes



	EC I Strains			EC II Strains				1951 Strain	WRARMC Strains	Louse Strain	sp. 13TU Strain
	AB0057	AB307-0294	AYE	A	B	C	ACICU	ATCC 17978	AB900	SDF	RUH2624
A O-antigen cluster											
B O-antigen cluster											
C O-antigen cluster											
A iron uptake											
A glycosyltransferases											
B glycosyltransferases											
B MDR pumps											
C MDR pumps											

Summary

- Different origin of the strains
- Genetic diversity as a result of homologous recombination
- 4 regions that shows swapping between genes
- Non MDR strain can serve as potential reservoirs for antigenic variations

Perspectives

- Change as a result of selective pressure?
- Drug targeting
- New screening methods

Critics

- Insight into origin of polyclonal outbreak
- Understanding of how epidemic lineages evolve
- Illustrative figures for visualization of gene clusters

Critics

- Use more strains
- Make phylogenetic relationship with more strains to get a better consensus tree
- Only one outbreak
- Include more and earlier isolated strains from different hospitals
- Including other parameters;
 - Antibiotic treatment
 - Cleaning
 - Interactions between involved individuals
 - Statistics