# Gut Resistome Signatures Distinguish Cognitively Impaired Individuals from Controls

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## Introduction & Methodology

### Background

Growing evidence suggests that microbial dysbiosis in Alzheimer's disease (AD) is accompanied by functional changes in the resistome. Alterations in antimicrobial resistance genes (ARGs) may reflect a shift from a stable, commensal-associated microbial community toward a dysbiotic and inflammation-prone environment. Therefore, resistome analysis provides an important functional perspective for understanding microbiome alterations across Controls vs Cognitively impaired (CI) participants.

### Methodology

We analyzed the gut microbiome data of older adults from the MiaGB Consortium using whole-genome sequencing, comparing Controls (n=280) and CI (n=165) individuals. Participants were categorized based on the Montreal Cognitive Assessment (MoCA) assessments into Controls (Ctrl) amd CI groups according to their MoCA scores. The ARGs abundance were calculated using AMR++ software and taxonomy analysis of bacteria were done .

## Distinct resistome signatures in Control and CI participants

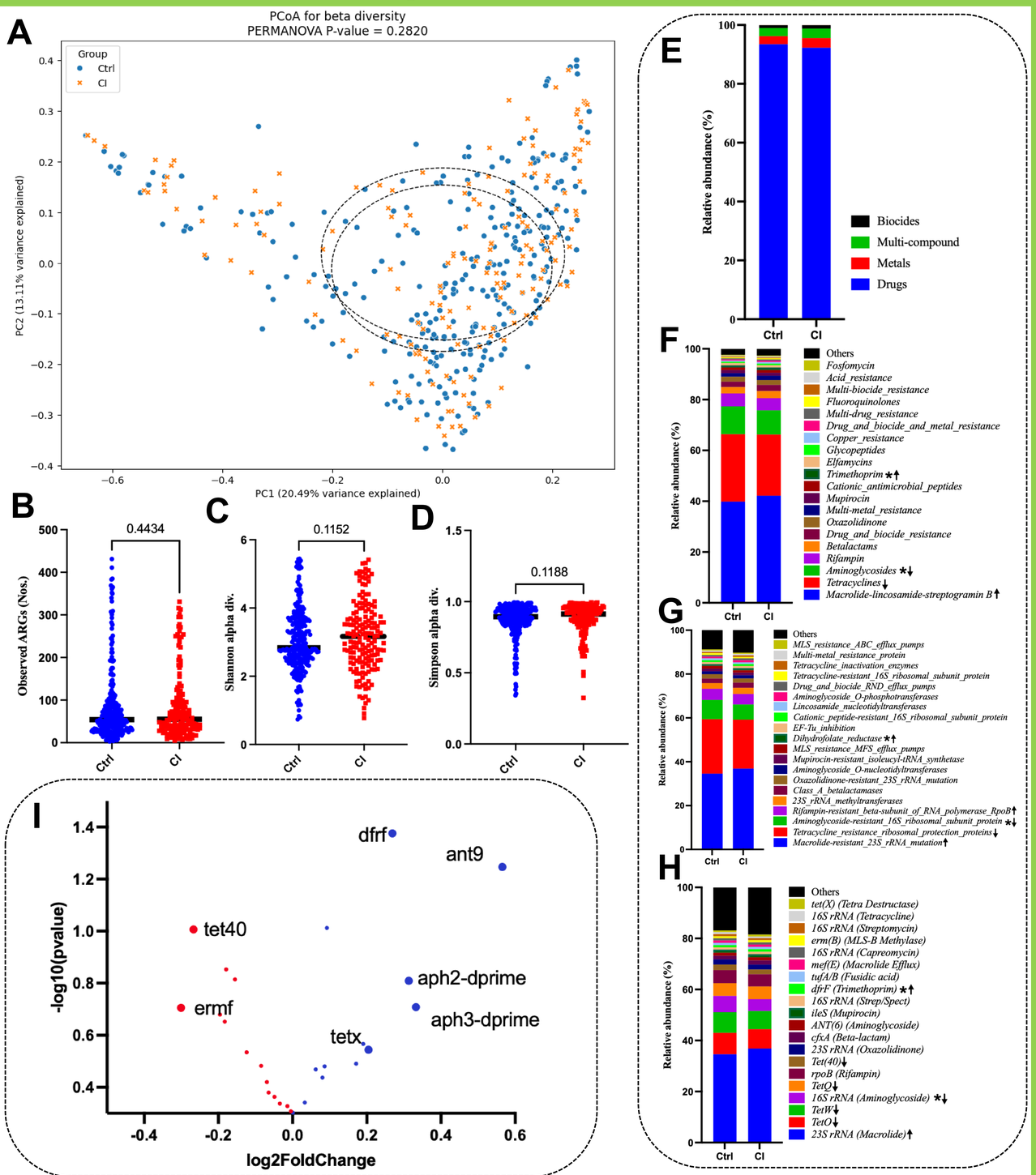


**Figure 1. Distinct resistome signature in Controls and Cognitively Impaired participants.** (A) Beta diversity, (B) ARGss, (C) Shannon diversity index, (D) Simpson diversity index, (E) Types of antibiotics categories, (F) Class, (G) Mechanism, (H) Genes and (I) Differential expression analysis of ARGs.
Abbreviations: ARGs: Antimicrobial resistance genes

## Correlation between ARGs and dominant bacterial species

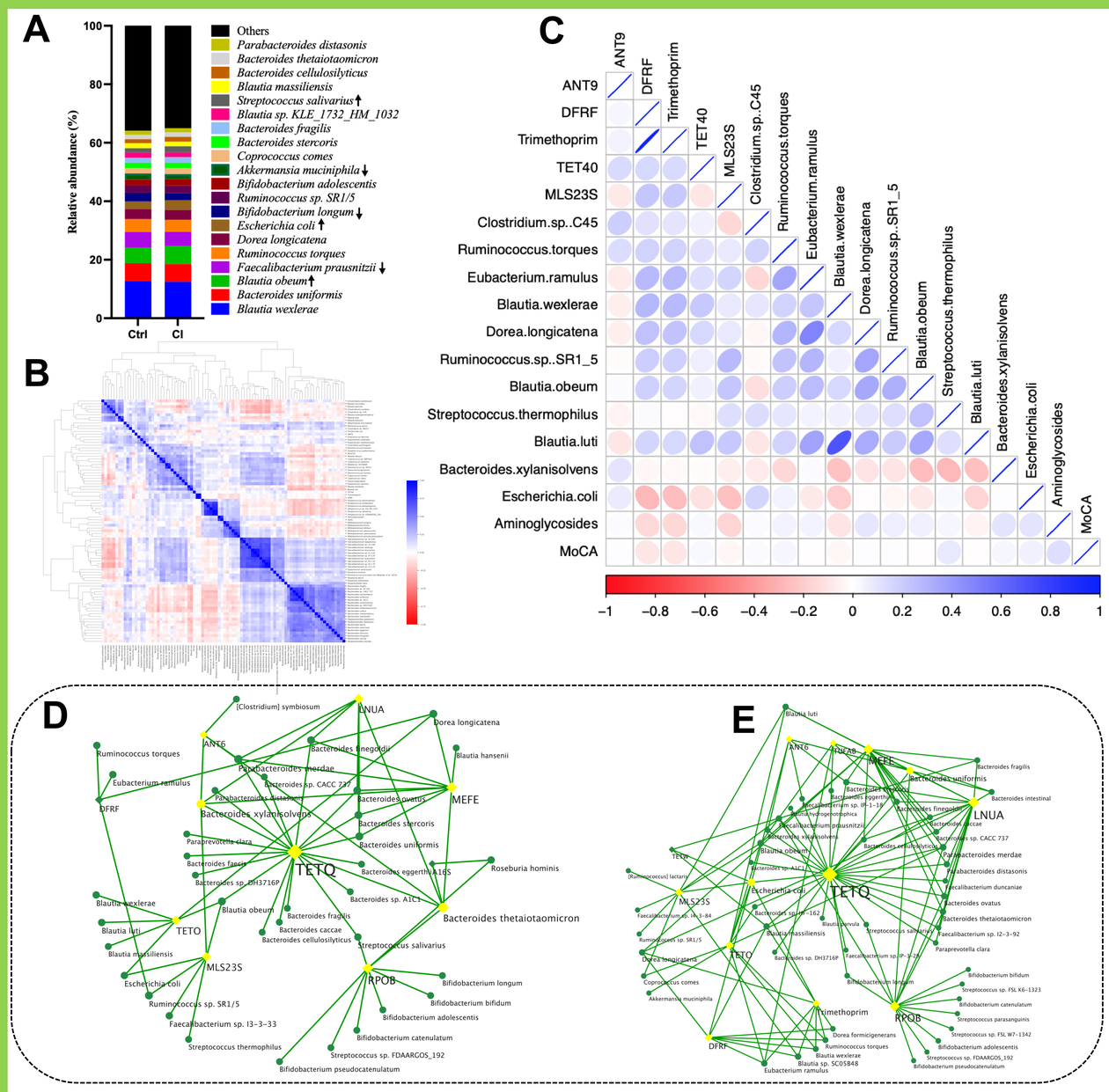


**Figure 2. Correlation between ARGs and top species to reveal their hosts.** (A) Top 20 species, (B) Hierarchical clustering of ARGs and all bacteria, (C) Spearman correlation (D) ARG-Bacteria network for Controls, and (E) ARG-Bacteria network for CI.

## Key findings

**Major ARG signatures in Controls and CI participants:**

- We observed distinct ARG patterns between Control and CI participants, suggesting resistome alterations in CI.ANT9, DFRF, Trimethoprim, and MLS23S were more strongly associated with CI participants. Their correlations with anaerobic and commensal bacteria may indicate dysbiotic ARG enrichment, mobile resistance gene transfer, and inflammation-associated resistome restructuring in CI.
- DFRF and Trimethoprim resistance genes showed positive correlations with *Eubacterium ramulus*, *Blautia wexlerae*, and *Dorea longicatena*, but negative associations with *Escherichia coli* and MoCA scores. This suggests possible mobile resistance gene propagation in CI.
- MLS23S showed positive associations with *Ruminococcus* and *Blautia* species, while showing negative associations with *Escherichia coli* and aminoglycoside resistance genes. This may indicate CI-specific ARG-bacteria network remodeling.
- Aminoglycoside resistance genes were higher in Controls and positively associated with *Escherichia coli*, *Streptococcus thermophilus*, and MoCA scores. This may reflect a more stable, commensal-associated resistome in Controls.
- TET40 was positively associated with *Blautia wexlerae* and *Blautia luti*, suggesting that its reduction in CI may reflect the loss of beneficial butyrate-producing commensals.

**Conclusion:**

Overall, the ARG analysis clearly suggests that Control and CI participants have distinct resistome profiles. The enrichment of mobile resistance genes in CI may indicate dysbiosis, ARG mobility, and inflammation-associated resistome disruption, while Controls appear to maintain a more stable and commensal-associated resistome.

## Acknowledgement

USF Health
Florida Health
NIH National Institutes of Health