



Early gut microbial and metabolic dysregulation with subclinical cardiac alterations in a nonhuman primate model of Rett syndrome

Ting Zhang^{1,2,3#}, Xiaopeng Wang^{1,4#}, Peng Li^{1#}, Junyu Zhang^{1,4#}, Wenjie Sun^{1,3}, Zhen Zhang¹, Yan Zhuo^{1,3}, Wenting Guo^{1,3*}, Yongchang Chen^{1,2,3,4*}

¹State Key Laboratory of Primate Biomedical Research, Institute of Primate Translational Medicine, Kunming University of Science and Technology

²Faculty of Life Science and Technology, Kunming University of Science and Technology

³Yunnan Key Laboratory of Primate Biomedical Research, Kunming, China

⁴Southwest United Graduate School, Kunming, China

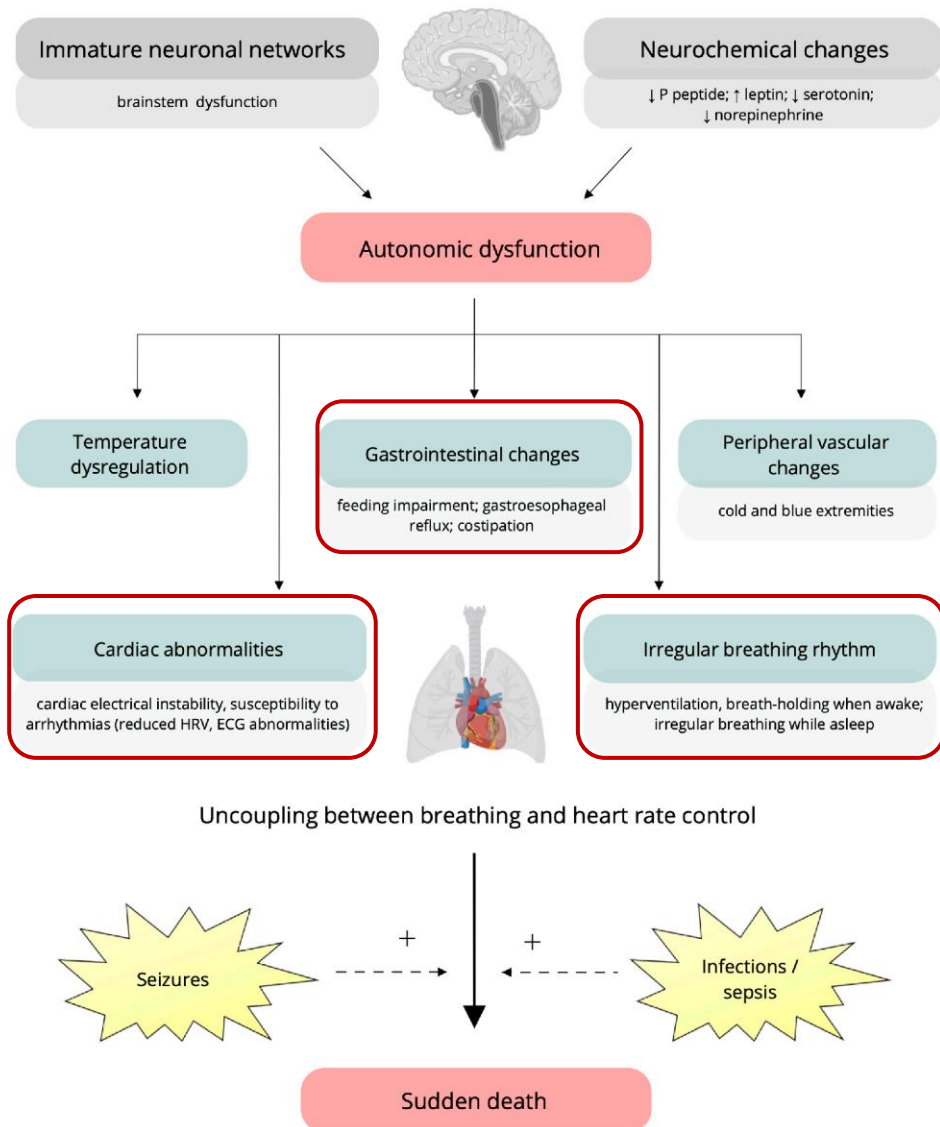


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Introduction

Rett syndrome



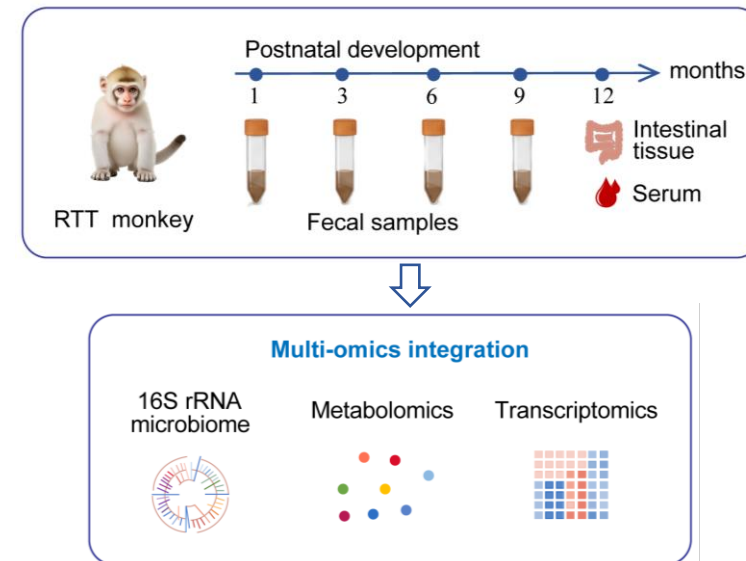
Cordani R et al , *Frontiers in Neuroscience*. 2023

Scientific Questions:

- Whether early RTT involves developmental imbalance and gut microbiota–metabolite dysregulation?
- Whether gut microbial dysbiosis associated with RTT-related phenotypic abnormalities?

Study Design and Objective:

Using a nonhuman primate RTT model, we integrated longitudinal multi-omics, histology, and ECG to characterize early systemic changes.





Early systemic and intestinal abnormalities in RTT monkeys

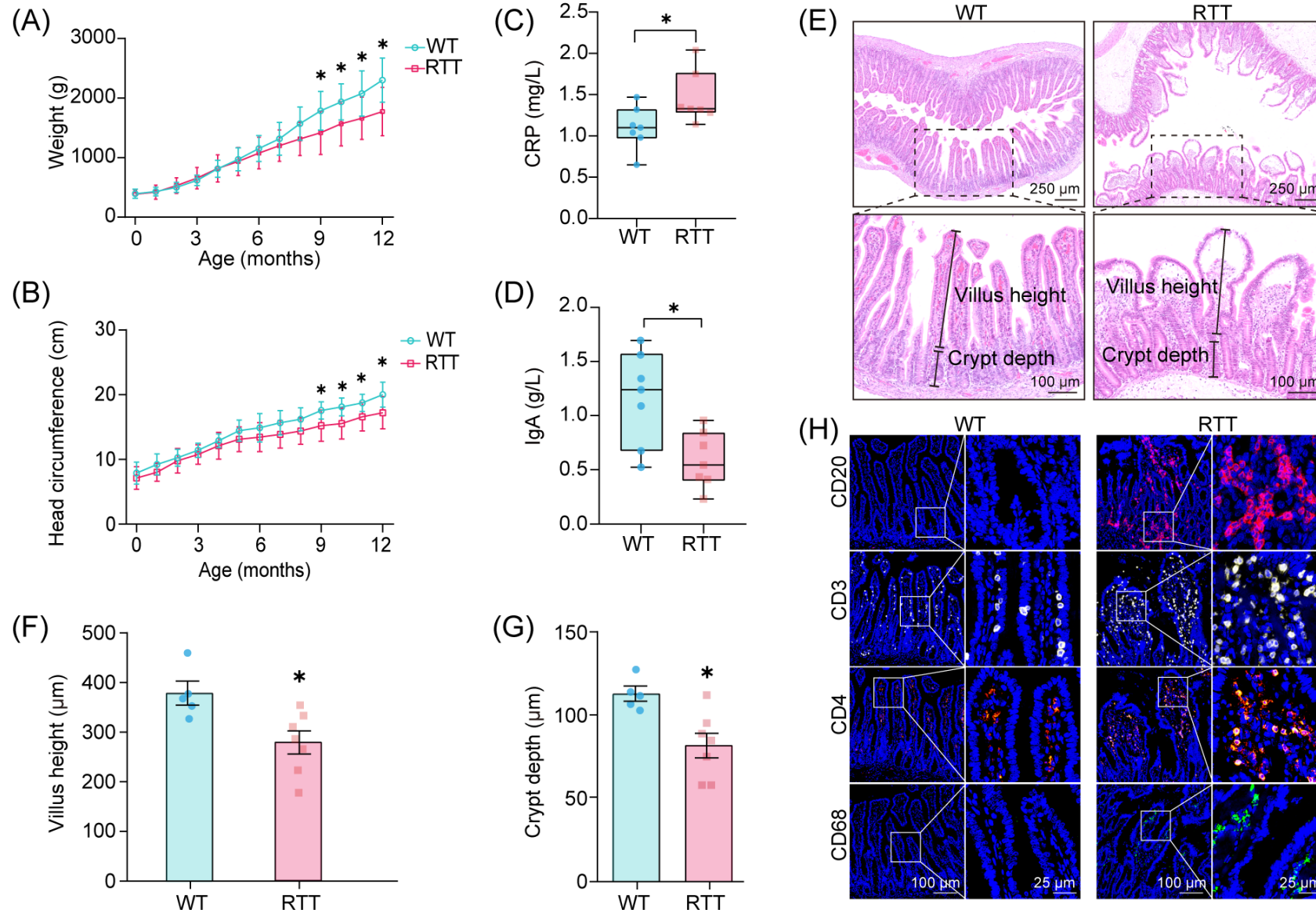
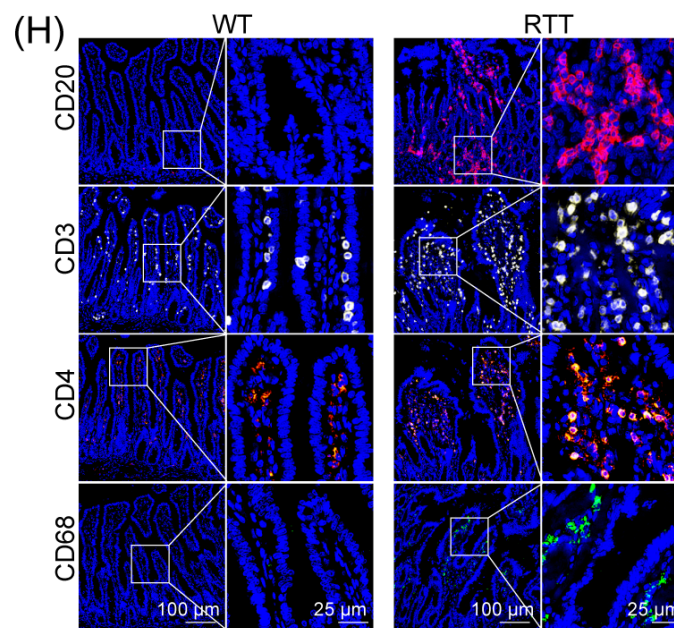


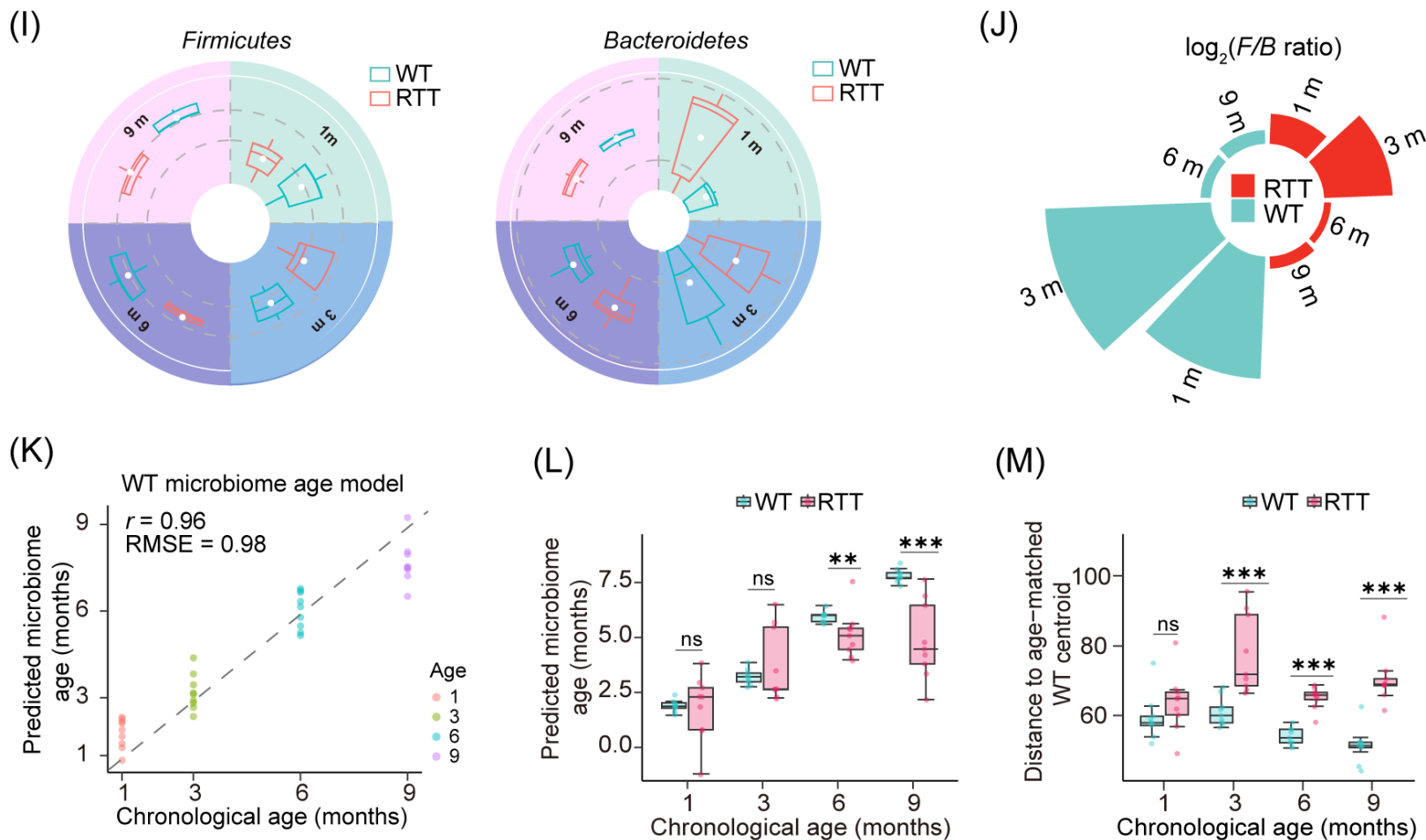
Figure 1. Early systemic, intestinal, and gut microbial abnormalities in RTT monkeys. (A–B) Growth retardation in RTT monkeys; (C–D) Abnormal CRP and IgA levels; (E–G) Intestinal villus damage; (H) Abnormal mucosal immune infiltration.



Early postnatal growth retardation and impaired intestinal mucosal and immune homeostasis in RTT monkeys.



Delayed microbiome maturation and age-mismatched dysbiosis



Reduced Firmicutes/Bacteroidetes (F/B) ratio in RTT monkeys.

Delayed gut microbiota maturation and age-discordant dysbiosis in RTT monkeys.

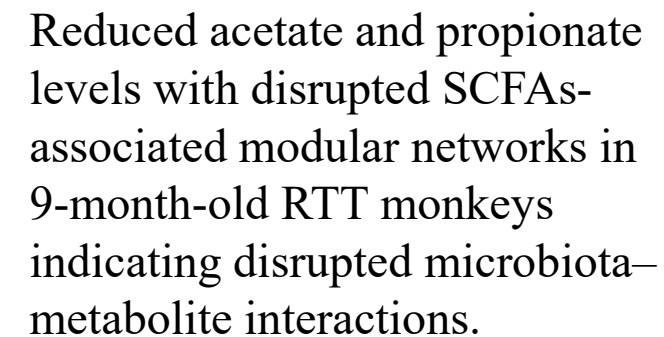
Figure 1. Early systemic, intestinal, and gut microbial abnormalities in RTT monkeys.

(I–J) Gut microbial dysbiosis and altered F/B ratio in RTT monkeys;

(K) WT-based microbiota age prediction model;

(L) Delayed microbiota maturation in RTT monkeys;

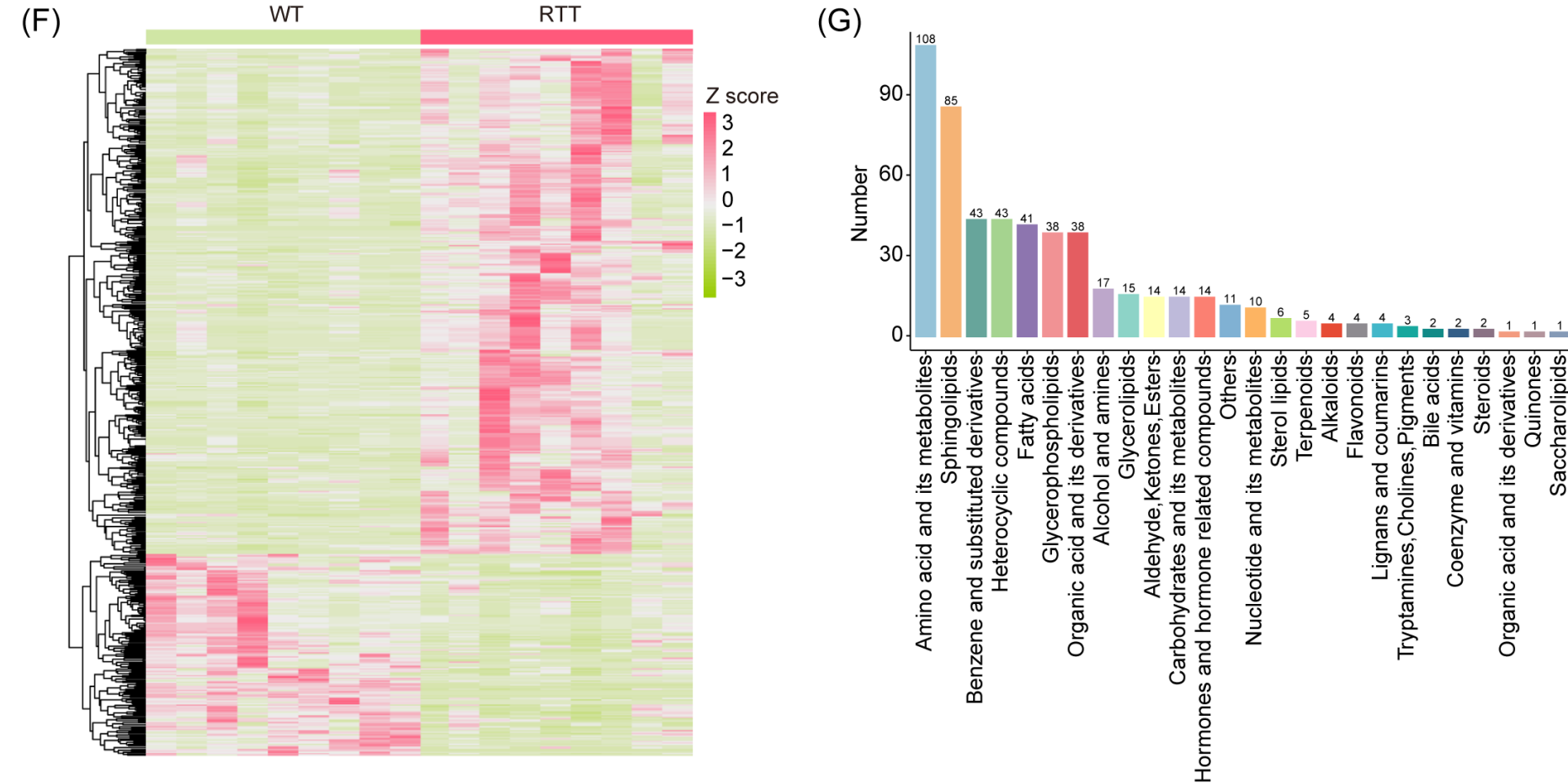
(M) Deviation from age-matched WT microbiota profiles.



(A–B) Reduced fecal acetate (AA) and propionate (PA) levels in RTT monkeys;
(C) Microbial co-abundance module clustering;
(D) Remodeling of SCFA-associated microbial networks;
(E) SCFA-associated module centered on Bifidobacterium.



SCFAs depletion and broader metabolic remodeling



Differential metabolites were mainly enriched in amino acid derivatives, sphingolipids, benzenoids, organic acids, and fatty acyls, suggesting disrupted energy and lipid metabolism in RTT monkeys.

Figure 2. SCFAs disruption, metabolomic remodeling, and subclinical cardiac alterations in RTT monkeys.

(F) Heatmap of differential fecal metabolites at 9 months;
(G) Distribution of differential metabolite classes.



Subclinical cardiac alterations with cautious interpretation of exploratory analyses

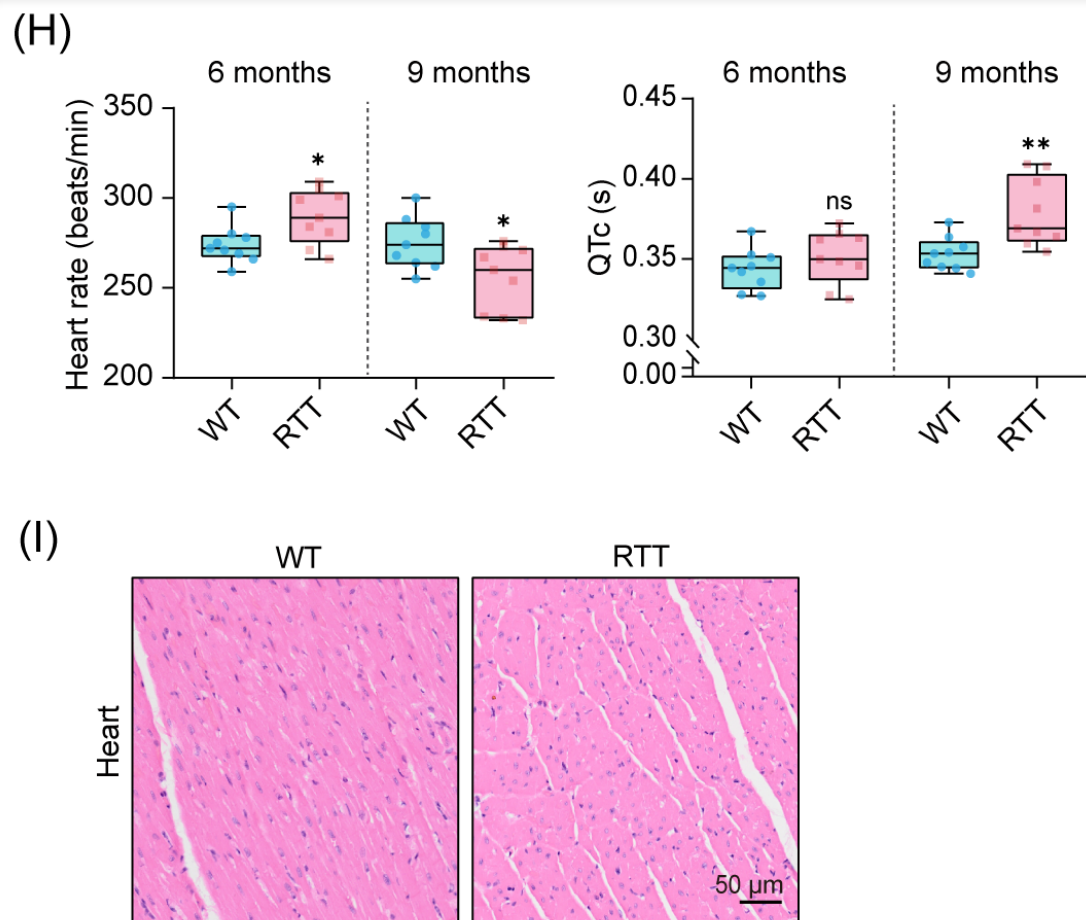


Figure 2. SCFAs disruption, metabolomic remodeling, and subclinical cardiac alterations in RTT monkeys.

(H) Subclinical ECG abnormalities in RTT monkeys;
(I) No obvious cardiac pathology in RTT monkeys.

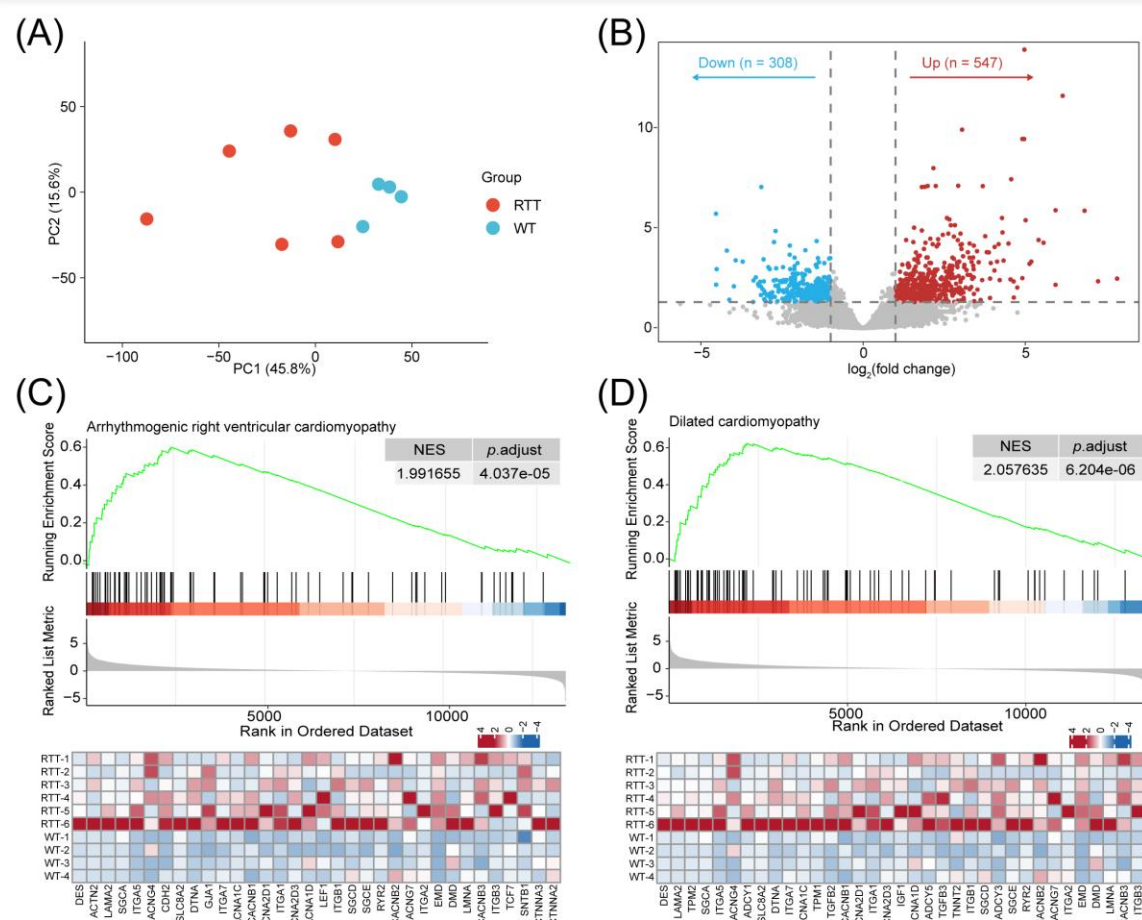


Figure S4. Intestinal transcriptomic alterations in RTT monkeys.

(A) PCA of intestinal transcriptomes;
(B) Differential gene expression analysis;
(C) ARVC-related pathway enrichment;
(D) DCM-related pathway enrichment.



Subclinical cardiac alterations with cautious interpretation of exploratory analyses

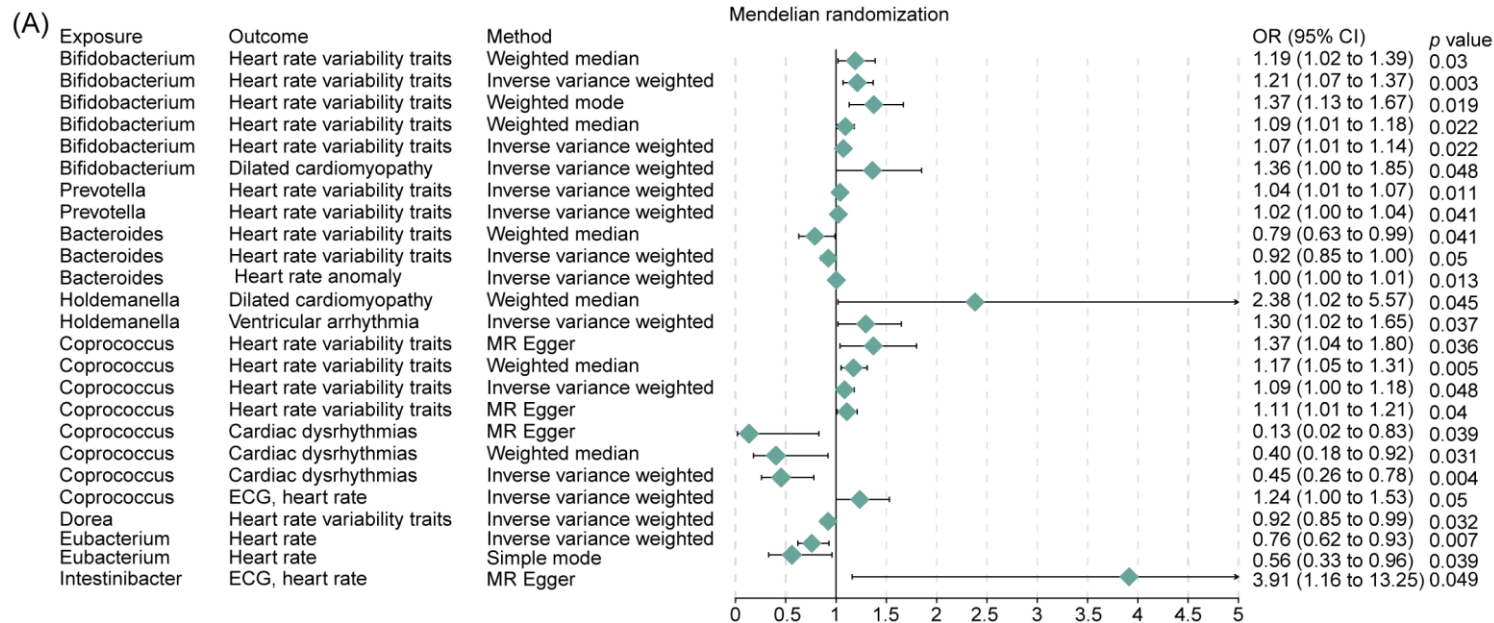
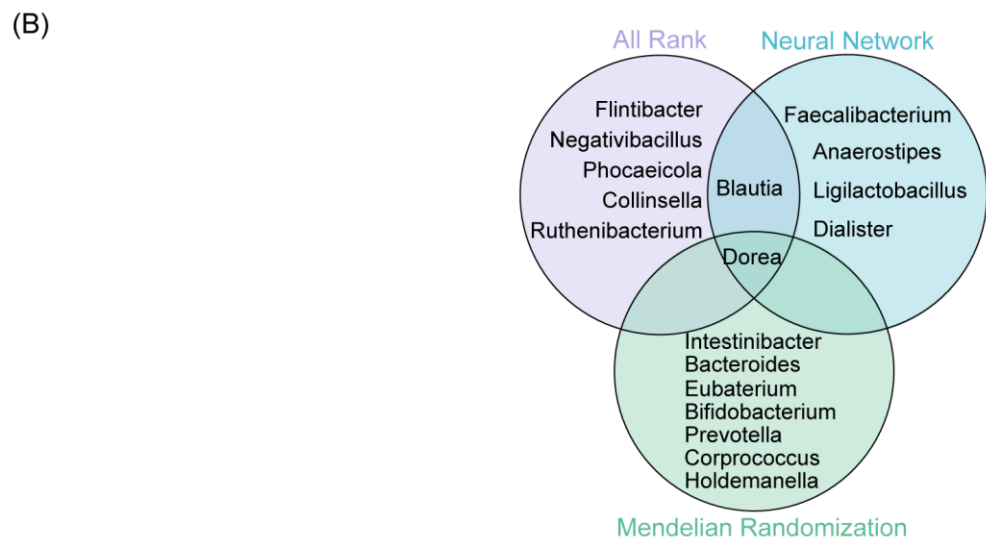


Figure S7. Exploratory microbiota–cardiovascular associations in RTT.

(A) MR analysis of RTT-associated genera and cardiovascular traits;

(B) Dorea identified as a shared key RTT-associated genus.



MR analysis suggested that RTT-associated genera may be linked to subclinical cardiac electrophysiological abnormalities. Dorea was consistently identified as a key genus; however, causal relationships remain to be validated.



Summary

- ❑ First systematic characterization of early gut microbiota alterations in an RTT monkey model, accompanied by growth retardation and intestinal immune abnormalities;
- ❑ Delayed microbiota maturation and age-discordant gut dysbiosis in RTT monkeys;
- ❑ Persistent SCFAs deficiency and disrupted microbe–metabolite networks associated with metabolic dysregulation;
- ❑ Gut microbial features potentially associated with subclinical cardiac electrophysiological abnormalities;
- ❑ Provides nonhuman primate evidence linking gut microbiota to RTT-related phenotypes and potential therapeutic targets.

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