Integrative host-microbiome modelling uncovers the implication of oral-gut translocation in advanced cirrhosis

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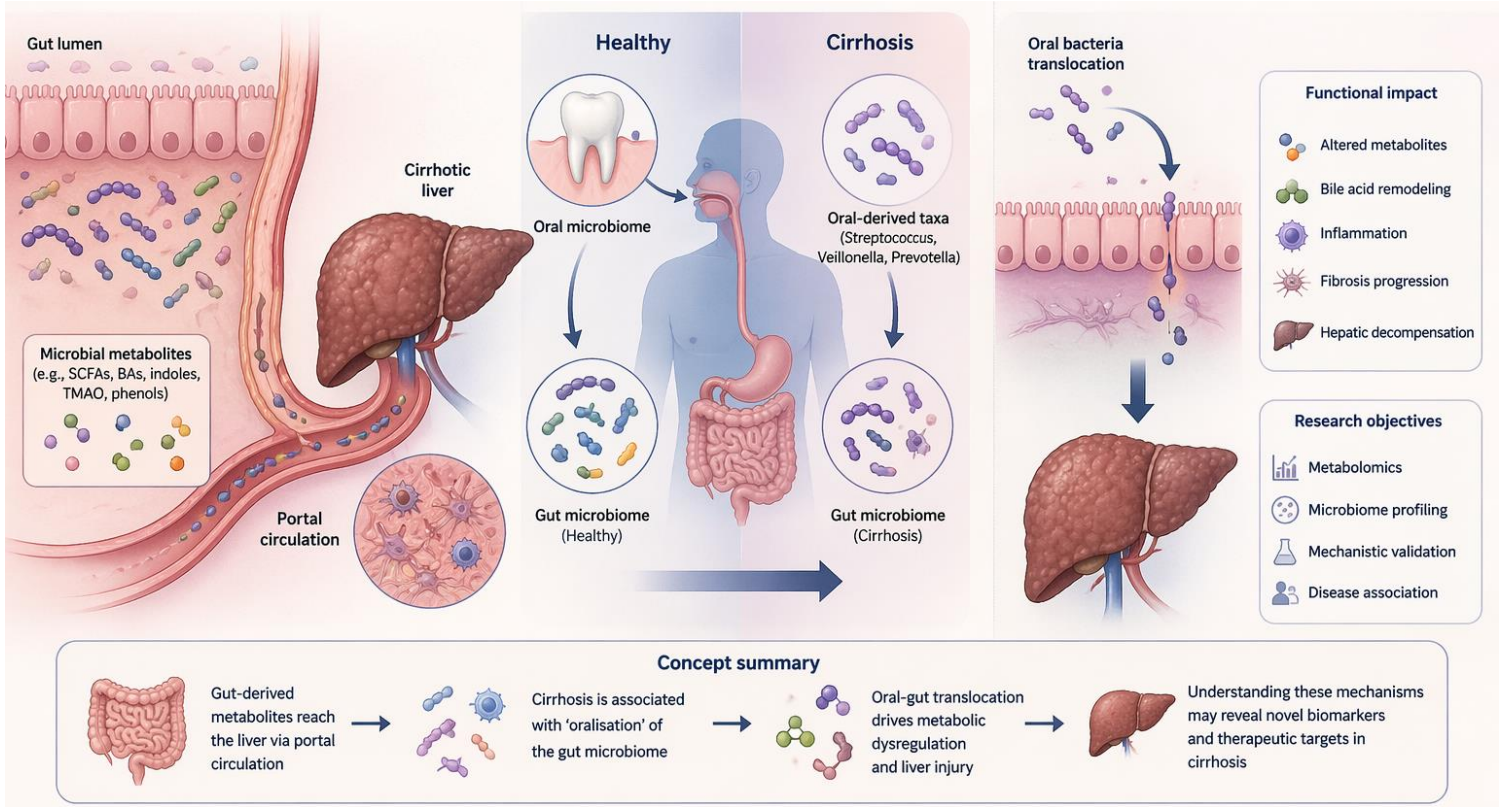
Introduction



Gut-Liver Axis

The liver is directly exposed to gut-derived metabolites via the portal circulation, making it highly sensitive to microbiome metabolic shifts in cirrhosis.

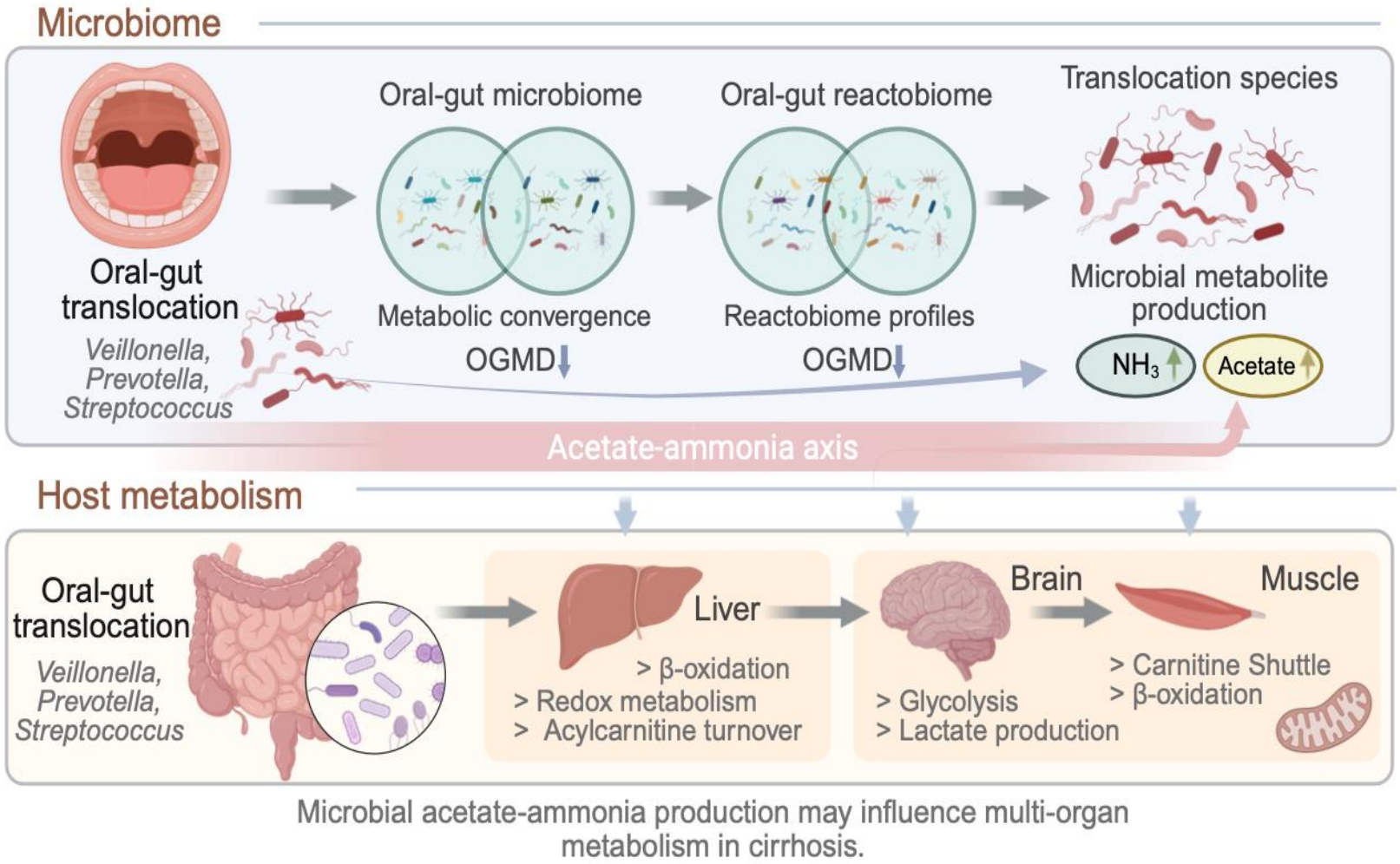
Oral-Gut Translocation

Oral bacteria (*Streptococcus, Veillonella, Prevotella*) are found in the gut of cirrhosis patients — 'oralisation' of the gut microbiome during disease progression.

Knowledge Gap & Objective

The metabolic consequences of these cross-site microbial invasions remain largely unexplored. We investigate the functional impact of oral-gut translocation on metabolism and hepatic disease.

Highlights



Microbial acetate-ammonia production may influence multi-organ metabolism in cirrhosis.

01 Reactobiome-based profiling reveals progressive oral-gut metabolic convergence (↓ OGMD) with increasing cirrhosis severity

02 16 translocation-associated species (tMSPs) are enriched in low-OGMD patients and predicted to have elevated ammonia and acetate production

03 Community GSMM confirms ecosystem-level amplification of NH_3 in low-OGMD microbiomes; validated in an independent cohort with blood metabolomics

04 Host metabolic modelling predicts multi-organ metabolic stress (liver, brain, muscle) driven by microbial ammonia-acetate burden

Results 1: Oral-Gut Functional Convergence with Disease Severity

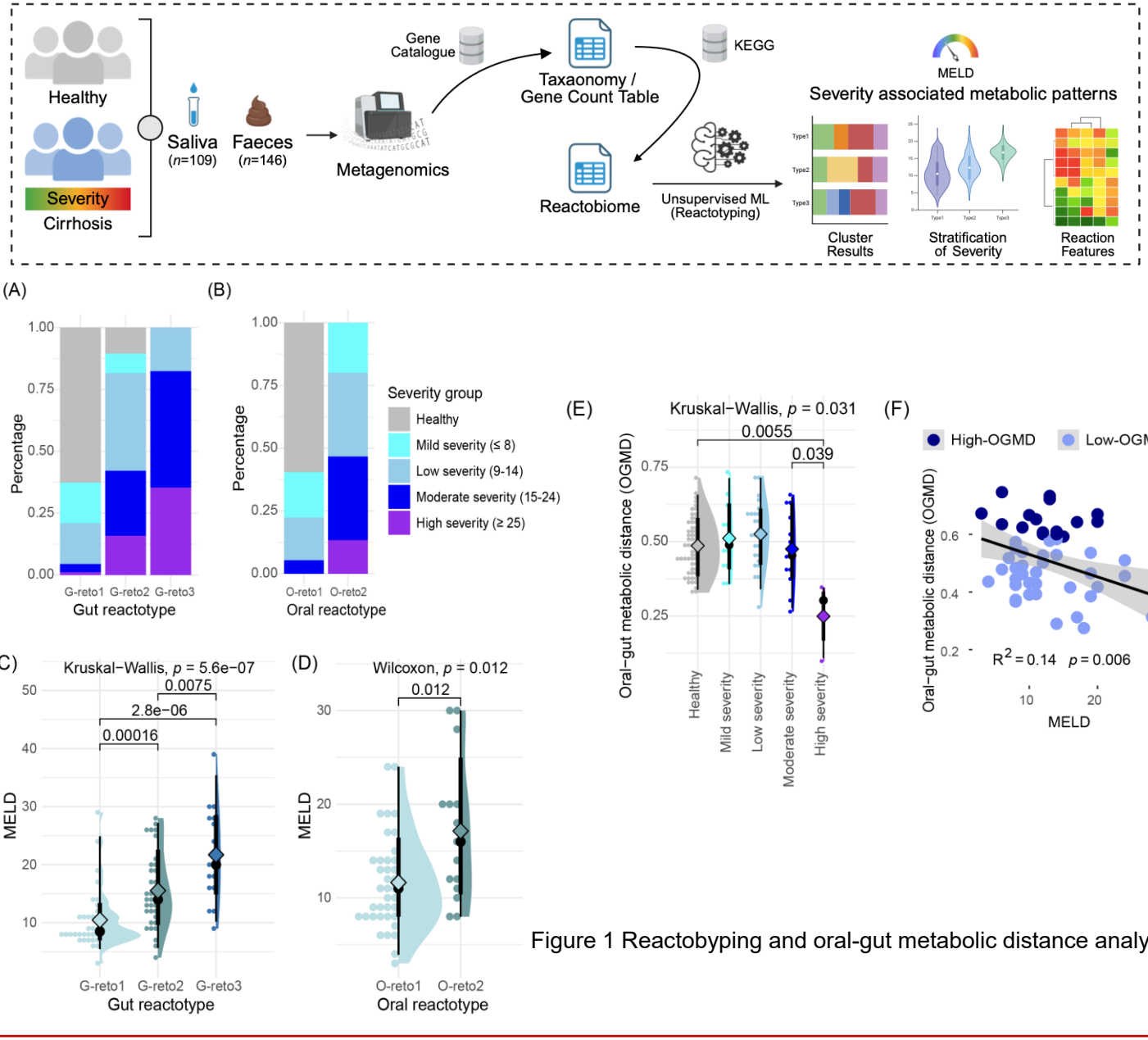


Figure 1 Reactobyping and oral-gut metabolic distance analysis

Paired Oral-Gut Samples + Reactobiome

Dataset: paired oral & faecal metagenomics. Reactobiome: the collective metabolic reaction repertoire encoded by the microbiome genes — captures functional capacity, not just taxonomy.

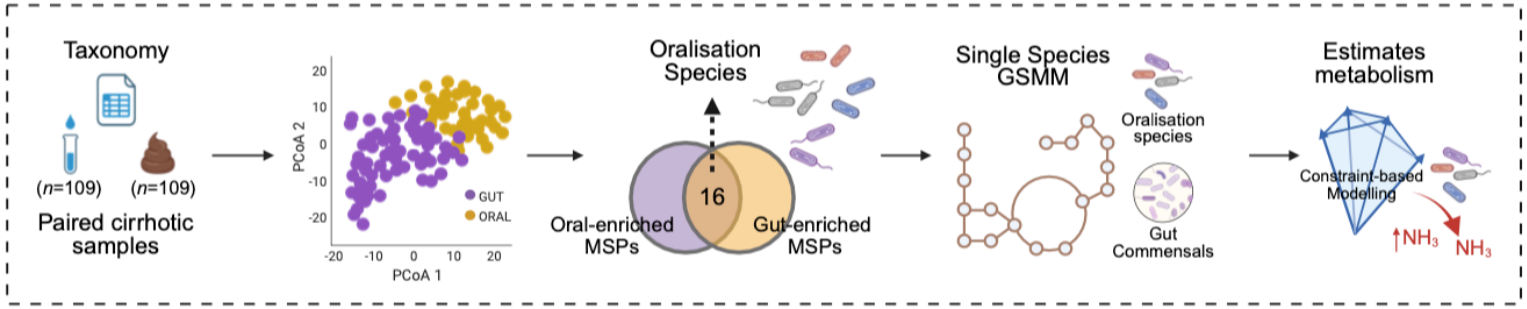
Reactotypes Stratify Severity (Unsupervised)

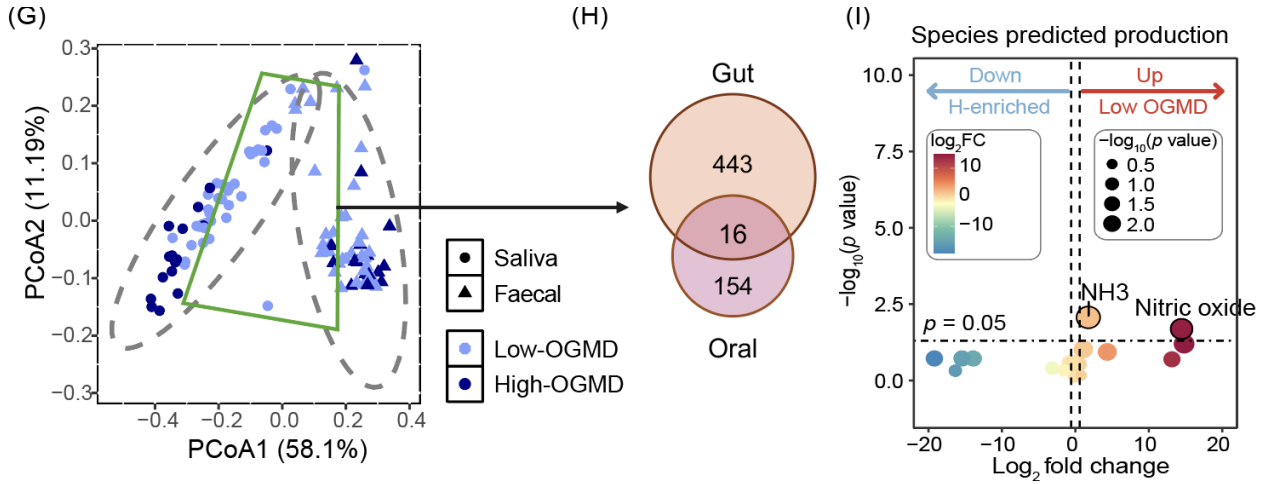
Three gut reactotypes (G-reto1–3) and two oral reactotypes (O-reto1–2) identified by unsupervised clustering. Both track MELD score severity gradient, independently of age and BMI.

OGMD Decreases with Severity → Functional Convergence

OGMD (Bray-Curtis dissimilarity oral vs. gut reactobiome) shows stepwise decrease with severity (p = 0.031). Negative correlation with MELD (R^2 = 0.14, p = 0.006). Patients split at 75th percentile → High/Low OGMD groups.

Results 2: Translocation Species Predict Elevated Ammonia & NO Production





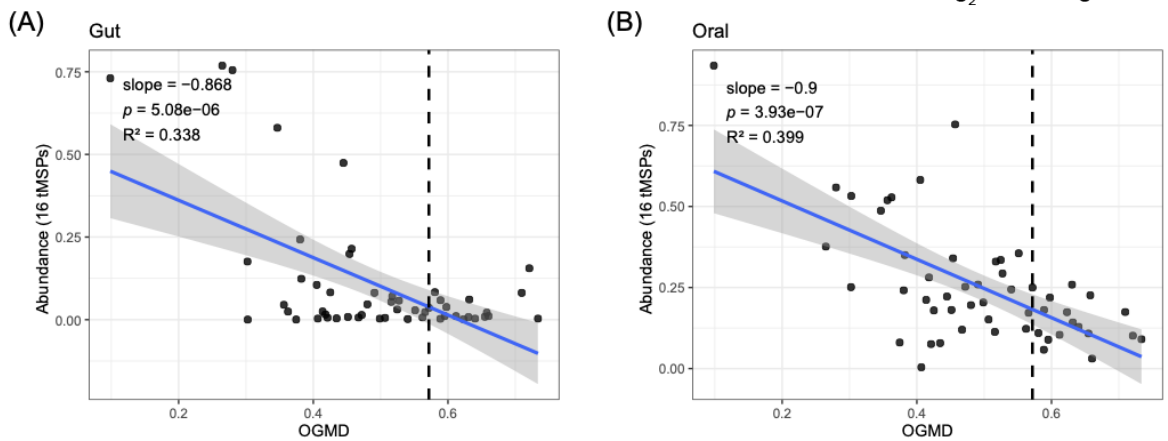


Figure 1 tMSP identification and GSMM simulations

tMSPs: 16 Translocation-Associated Species

tMSPs: species more abundant in low-OGMD patients in both oral and gut microbiomes. Abundance significantly negatively correlated with OGMD — the more convergent, the more tMSPs.

GSMM: Significantly Higher NH_3 and NO Production

Genome-Scale Metabolic Models (GSMMs) used for in silico flux balance analysis (FBA). Compared to 26 healthy gut commensals: tMSPs show significantly higher predicted ammonia and nitric oxide production (Wilcoxon, $p < 0.05$).

Results 3: Ammonia Production Across Diets, Co-production of Acetate & *Veillonella* as Hub Species

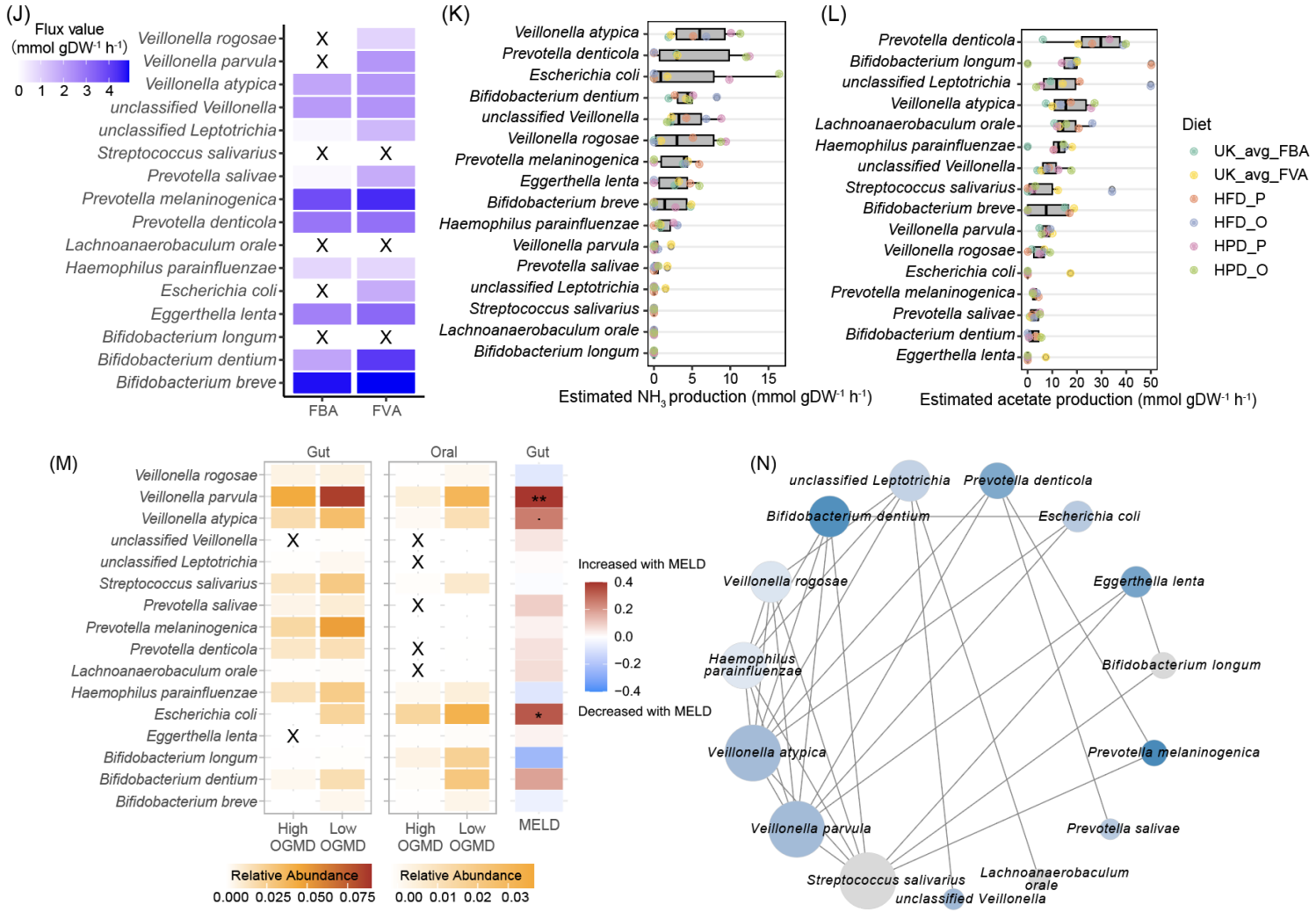


Figure 1 tMSP GSMM simulation and abundance analysis

NH_3 Production: Robust Across 13/16 tMSPs & Multiple Diets

FVA confirms NH_3 production feasibility in 13 out of 16 tMSPs. Consistent NH_3 production estimated across UK average, high-fibre, high-protein, omnivorous, and plant-based diets.

Acetate Co-production & Clinical Relevance

Five tMSPs (including *Prevotella denticola*, *Veillonella atypica*) co-produce NH_3 and acetate. In alcoholic cirrhosis, circulating acetate reprograms the gut microbiome and may exacerbate hyperammonaemia, amplifying systemic metabolic burden.

Veillonella as Network Hubs Correlated with MELD

V. parvula and *V. atypica* gut abundance correlates positively with MELD (FDR<0.1). Co-abundance network: these two *Veillonella* spp. have highest degree — central hubs — and high predicted NH_3 production.

Results 4: Community Metabolic Modelling — Ecosystem-Level Amplification of Ammonia

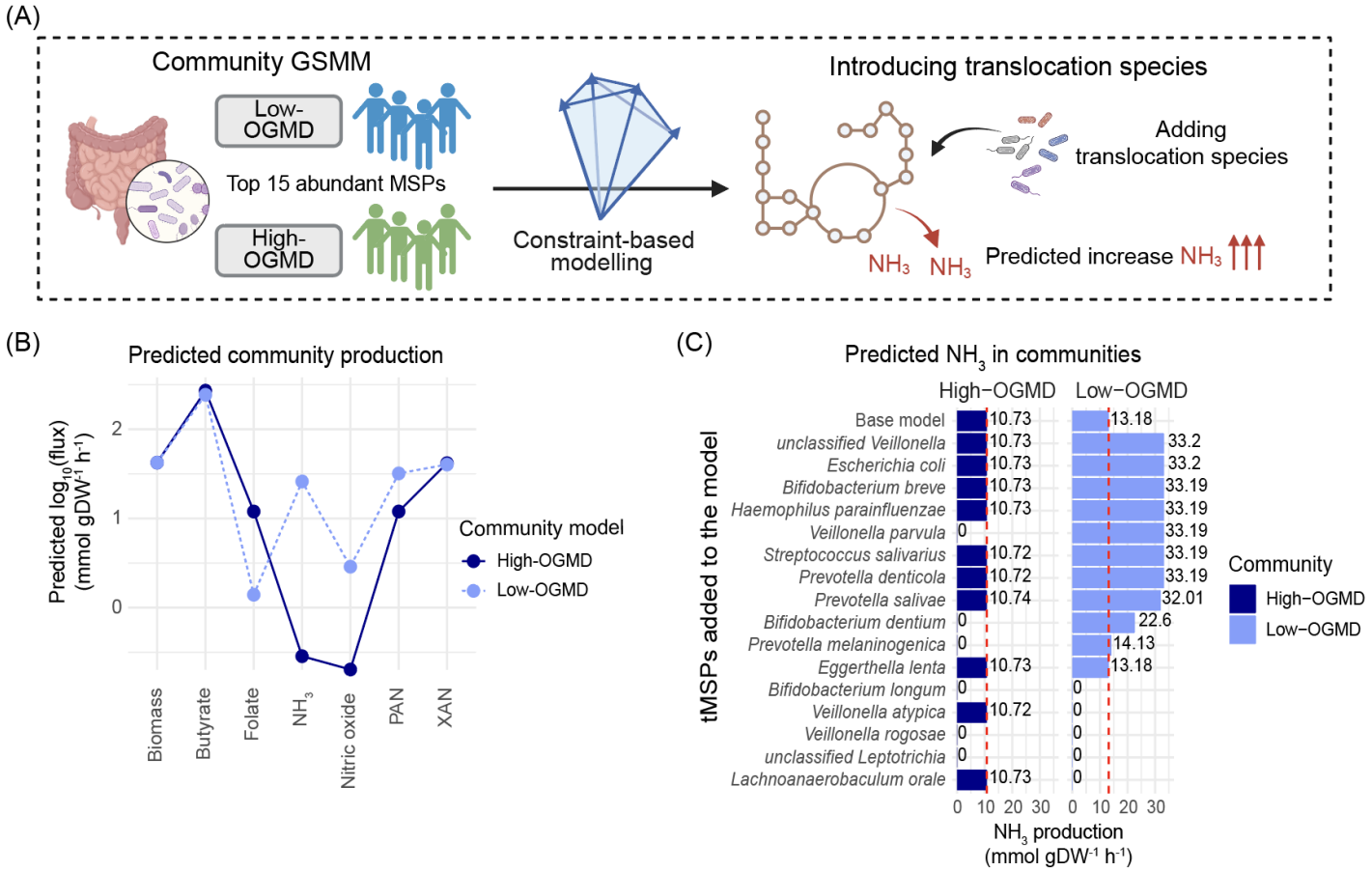


Figure 2 Community GSMM reconstruction and modelling

Community GSMM Construction

Patient-representative community GSMMs built from the top 15 most abundant species per OGMD group. Low-OGMD community includes 5 tMSPs among dominant members; high-OGMD community includes only 1.

Low-OGMD Community: Higher NH_3 & NO, Lower Folate

Under identical nutrient constraints, comparable biomass is achieved. However, low-OGMD community produces elevated ammonia and nitric oxide with reduced folate — a shift toward nitrogen-centred metabolic activity.

Perturbation Analysis: Metabolic Sensitivity to tMSPs

Introducing individual tMSPs into baseline community models: 10/16 tMSPs increase NH_3 in the low-OGMD community; minimal effect in high-OGMD community. Advanced-dysbiosis microbiomes are more susceptible to metabolic perturbation by invading taxa.

Results 5: Independent Validation & Multi-Organ Host Metabolic Modelling

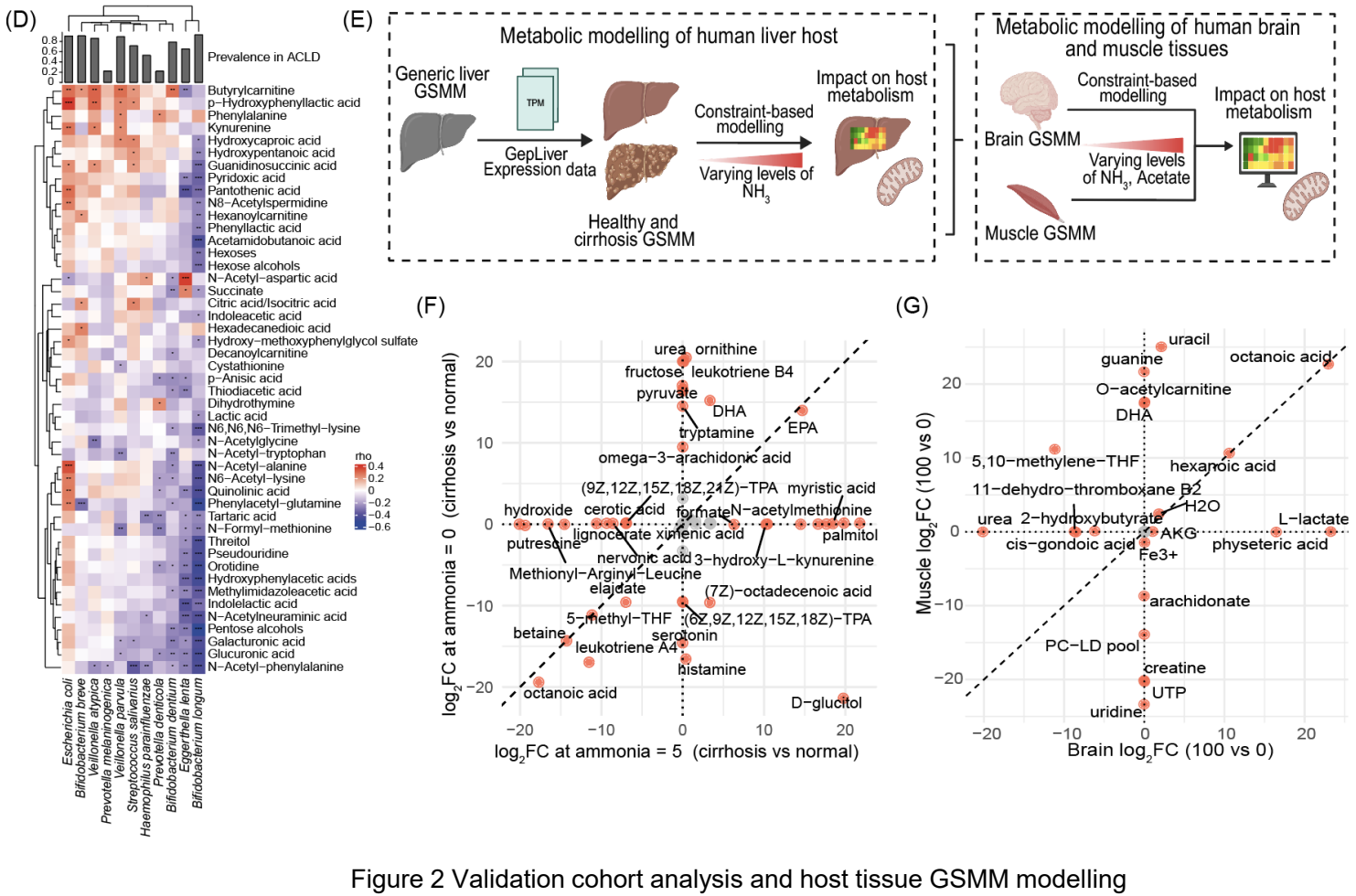


Figure 2 Validation cohort analysis and host tissue GSMM modelling

Validation Cohort: Oral tMSPs Detected

11/16 tMSPs detected in independent cohort. *V. parvula* and *V. atypica* show high prevalence. tMSP abundance co-associates with metabolomic signatures of altered nitrogen and mitochondrial metabolism.

Portal Metabolomics: Evidence of Systemic NH_3 Burden

V. atypica significantly correlated with guanidinosuccinic acid (marker of ammonia overload). Provides independent support for predicted metabolic activity of tMSPs.

Liver GSMM: Enhanced Fatty-Acid Oxidation & Redox Stress

Cirrhotic liver model under increasing NH_3 uptake shows marked upregulation of FA activation, β-oxidation, oxidative phosphorylation, and ROS detoxification — indicating intensified energetic and redox demands.

Brain & Muscle GSMMs: Systemic Consequences

Under elevated NH_3 and acetate: brain model: ↑ lactate production; muscle model: ↑ 2-hydroxybutyrate and O-acetylcarnitine. Both tissues show increased carnitine shuttle flux — systemic energetic stress and redox burden.

Summary

- Reactobiome profiling reveals progressive oral-gut functional convergence with cirrhosis severity, independent of age or BMI.
- 16 tMSPs are associated with higher oral-gut functional convergence in advanced cirrhosis; GSMM predicts significantly elevated NH_3 and acetate production across dietary contexts.
- *V. parvula* and *V. atypica* are hub species interact among tMSPs, correlated with MELD, and with predicted ammonia production.
- Community modelling confirms NH_3 amplification in low-OGMD microbiomes; consistent with portal metabolomics in independent cohort for its systemic impact.
- Host modelling (liver, brain, muscle) predicts multi-organ metabolic stress, with predicted increased β-oxidation, ROS detox, lactate — a potential microbiome-driven systemic burden.

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