Towards Aging Hidden Genetic Differences in Gut Bacteria may Hold Clues

Researchers investigated associations between gut microbial single-nucleotide variants (SNVs) and a broad range of human health phenotypes and environmental exposures using a phenome-wide association approach.



Study

Scientists at the University Medical Center Groningen in the Netherlands led the research, in collaboration with researchers from institutions in Italy, Tanzania, the United States, Romania and Germany.

The researchers analyzed whole-genome shotgun (WGS) metagenomic sequencing data from 11,831 fecal samples collected from 10,781 individuals across six independent cohorts. Five cohorts originated from the Netherlands, while the sixth was from Tanzania.

The datasets included the Dutch Microbiome Project (DMP), Lifelines-DEEP (LLD), 500-Functional Genomics Project (500FG), 300-Obesity (300OB), 1000 Inflammatory Bowel Disease Project (1000IBD), and 300-Tanzania Functional Genomics Project (300TZFG).

Gut microbial genotypes were characterized using GT-Pro, which identified SNVs across bacterial genomes. After quality filtering, the researchers identified approximately 12.8 million common microbial SNVs, narrowing the set to about 12.7 million across 433 bacterial species. The researchers also harmonized 244 host characteristics, comprising 157 intrinsic phenotypes and 87 environmental exposure factors.

A linear mixed model (LMM) was developed to account for within-species population genetic structure and minimize associations arising from differences in bacterial lineages. Age, sex, microbial species abundance, and clean sequencing read counts were included as covariates, where applicable.

For each species, the analysis included only samples inferred to be dominated by a single strain. Association analyses were performed independently across the six cohorts, followed by sample-size-weighted meta-analysis.

Linkage disequilibrium-based grouping and permutation testing were used to identify independent and well-supported associations. Protein structural analyses were then conducted to investigate the potential functional consequences of associated missense variants.

Findings

The analysis initially identified 12,761,497 common microbial SNVs and retained 12,706,564 across 433 bacterial species. These species collectively represented an average of 84.3% of the gut microbial community. Most variants (93.02%) occurred in protein-coding regions. Of the retained variants, 75.39% were synonymous, 17.45% were missense, and 0.18% affected start or stop codons. The remaining variants were located in non-protein-coding regions.

The phenome-wide association analysis initially detected 49,346 significant and well-supported associations involving 39,663 SNVs across 101 bacterial species and 69 host phenotypes or exposure factors. Further grouping based on linkage disequilibrium yielded 940 independent association signals. These included 810 associations with intrinsic characteristics and 130 with environmental exposures. Of the 49,346 significant associations, 85.76% were supported by two independent cohorts, while 14.24% were supported by three or more cohorts.

Of the 940 independent association signals, 65.74% showed no significant association with bacterial species abundance. This indicates that bacterial genetic differences can be associated with human characteristics even when the abundance of those bacterial species shows no significant relationship.

Among 533 species–phenotype relationships identified at the SNV level, 460 (86.30%) were detected exclusively through SNV-based analysis, rather than species-abundance or structural-variant analysis. Only five relationships showed associations across species abundance, SNVs, and structural variants.

Age demonstrated the highest number of associations, with 99 independent signals involving 8,117 SNVs across 42 bacterial species. A machine-learning model trained using microbial genetic information predicted chronological age and explained 12.8%–42.0% of age variation across independent test datasets.

One notable finding involved five missense SNVs in the sarA_2 gene of Faecalibacterium prausnitzii (lineage I). These variants were associated with host age and were located in a region encoding a protein involved in an oligopeptide transporter complex.

Individuals whose stool samples contained the age-associated bacterial allele were, on average, approximately 4.9 years older than those without it, a difference that does not establish that the variant influences aging. Structural analyses predicted that the affected protein region could bind glutathione as part of a transport complex. Glutathione is an antioxidant that protects cells against oxidative stress.

These findings raised the possibility that microbial genetic variation may influence glutathione transport within gut bacteria, but this function was not experimentally tested.

Further structural characterization examined 3,705 associated missense variants across 2,141 proteins. Of these, 752 variants were located in potentially important structural regions, including ligand-binding pockets and protein–protein interaction interfaces. Age-associated variants were also identified in proteins potentially involved in inflammatory regulation and oxidative stress responses.

Associations were also reported across cardiovascular, metabolic, hematological, dietary, and biochemical characteristics, including blood pressure, body mass index, cholesterol measurements, triglycerides, bile acids, and blood cell parameters. The researchers made the association results available through an online catalog to support further investigation.

Conclusion

The findings provide a comprehensive resource linking gut microbial genetic variation to human health characteristics and environmental exposures. The identification of 940 independent associations shows the value of examining microbial genetics alongside species abundance to understand host–microbiome relationships. Age-associated variants in Faecalibacterium prausnitzii (lineage I) were located in a protein region predicted to bind glutathione, suggesting a potential biological mechanism that requires experimental confirmation.

Because the cohort is predominantly European and lacks experimental functional validation, the generalizability and interpretation of the results are limited. The largest Dutch cohort contributed nearly three-quarters of the samples, potentially inflating cohort-specific effect estimates, while the smaller Tanzanian cohort limited the statistical power of cross-population replication.

Clarifying the mechanisms behind these associations will require additional research that includes other populations, molecular studies, and experiments. These observational findings do not establish whether microbial variants affect human health or reflect host and environmental conditions.

Source:

https://www.news-medical.net/news/20261105/Hidden-genetic-differences-in-gut-bacteria-may-hold-clues-to-aging.aspx