Integrative analysis of risk burden, microbiome and metabolome in people at risk for multiple sclerosis

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Objective: We examined the relationship between multiple sclerosis (MS) susceptibility, diet, intestinal microbiome and serum metabolome in people at risk for MS.

Background:
Intestinal microbiome is a novel arena to investigate MS onset and potential prevention targets among high-risk individuals such as those with family history of MS.
Design/Methods: In a prospective cohort study of MS first-degree family members, we previously assessed each participant's MS risk based on validated genetic burden and environmental exposures ($GERS_{MS}$). Here, we conducted a cross-sectional study of 93 participants across the MS risk distribution. Each participant completed the food frequency questionnaire (FFQ), and donated stool and blood samples. From FFQ, we calculated fiber intake and a diet quality score. From stool, we generated the intestinal microbiome profiles (abundance of taxa, genes, functional modules) using shotgun whole metagenome sequencing. From serum, we measured the concentration of small molecules relevant to microbial activities on a targeted metabolome platform. We clustered co-abundant groups and performed multivariate linear modeling, adjusting for age, gender, body mass index.

Results: Among higher risk asymptomatic family members (according to $GERS_{MS}$), at the taxa level, we found loss of abundance in bacteria organisms that are implicated in promoting immune tolerance, including members of the Lachnospiraceae family that produce short-chain fatty acids (SCFAs). We found corroborative evidence when examining the bacteria gene and functional pathways. For example, $GERS_{MS}$ is inversely associated with bacterial genes involved in SCFA production, including butyrate-acetoacetate-CoA transferase subunit B, glutamate/gamma-aminobutyrate antiporter, and short chain enoyl CoA hydratase. Additional results will be presented.

Conclusions:
Asymptomatic individuals at higher risk for MS harbor intestinal microbiome profiles associated with decreased SCFA production. These findings are consistent with prior human microbiome studies in MS and other autoimmune diseases and highlight a possible protective role of SCFA in MS onset.