A Pleiotropic Missense Variant in SLC39A8 Is Associated With Crohn's Disease and Human Gut Microbiome Composition

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BACKGROUND & AIMS: Genome-wide association studies have identified 200 inflammatory bowel disease (IBD) loci, but the genetic architecture of Crohn's disease (CD) and ulcerative colitis remain incompletely defined. Here, we aimed to identify novel associations between IBD and functional genetic variants using the Illumina ExomeChip (San Diego, CA). METHODS: Genotyping was performed in 10,523 IBD cases and 5726 non-IBD controls. There were 91,713 functional single-nucleotide polymorphism loci in coding regions analyzed. A novel identified association was replicated further in 2 independent cohorts. We further examined the association of the identified single-nucleotide polymorphism with microbiota from 338 mucosal lavage samples in the Mucosal Luminal Interface cohort measured using 16S sequencing. RESULTS: We identified an association between CD and a missense variant encoding alanine or threonine at position 391 in the zinc transporter solute carrier family 39, member 8 protein (SLC39A8 alanine 391 threonine, rs13107325) and replicated the association with CD in 2 replication cohorts (combined meta-analysis P = 5.55 x 10(-13)). This variant has been associated previously with distinct phenotypes including obesity, lipid levels, blood pressure, and schizophrenia. We subsequently determined that the CD risk allele was associated with altered colonic mucosal microbiome composition in both healthy controls (P = .009) and CD cases (P = .0009). Moreover, microbes depleted in healthy carriers strongly overlap with those reduced in CD patients (P = 9.24 x 10(-16)) and overweight individuals (P = 6.73 x 10(-16)). CONCLUSIONS: Our results suggest that an SLC39A8-dependent shift in the gut microbiome could explain its pleiotropic effects on multiple complex diseases including CD.
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