Saliva exonerated: Gene previously linked to obesity is unrelated, says new study

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This is an image of a weight scale. Credit: CDC/Debora Cartagena

A gene previously suspected of wielding the single greatest genetic influence on human obesity actually has nothing to do with body weight, according to a new study led by researchers at Harvard Medical School and Boston Children's Hospital.

The work not only overturns a major finding about the genetics of

obesity but also provides the first effective ways to analyze "particularly ornery and confusing" parts of the genome, such as the locus of this gene, said the study's co-senior author, Steven McCarroll, assistant professor of genetics at HMS.

The techniques described in the paper, published June 22 in *Nature Genetics*, should help scientists clarify whether genes in similarly complex regions are associated with disease, the authors said.

Sticky science

The gene AMY1 encodes an enzyme that helps humans convert starch into sugar. Though other enzymes also perform this function, AMY1 begins this process in the saliva. It's what makes crackers taste sweet once they've been in the mouth long enough. People have different numbers of copies of the AMY1 gene and different amounts of the enzyme.

"There's been some speculation that because this enzyme helps get nutrients out of our food, it could be linked to obesity," said Christina Usher, a graduate student in the McCarroll lab and first author on the paper.

Co-senior author Joel Hirschhorn, the Concordia Professor of Pediatrics at Boston Children's and professor of genetics at HMS, studies genetic variants that influence obesity. A few years ago he became interested in whether AMY1 was one of them.

He analyzed genome-wide association data collected by the GIANT Consortium and found no association between AMY1 and body mass index, a measure of a person's weight relative to their height. But because that region of the genome was so complicated, with AMY1 varying so widely (from two to 14 or more copies per person), he wasn't

sure his data told the whole story.

He approached McCarroll to see if they could team up to answer the question.

"We have expertise in obesity genetics, and Steve's group has expertise in this kind of complex variation," said Hirschhorn.

Trial and error

Hirschhorn put the problem on hold while the McCarroll lab worked on developing tools that could make sense of the region containing AMY1.

"This part of the genome was past the frontier of what genetics and molecular biology could do," said McCarroll.

That didn't stop scientists from trying. In 2014, an unrelated international group reported in *Nature Genetics* that AMY1 did have a link to obesity—and a substantial one at that. People with fewer than four copies of AMY1, the researchers found, had about an eightfold higher risk of obesity than people with more than nine copies. AMY1 appeared to be protective.

They believed that Hirschhorn's study hadn't uncovered the link because it was designed to analyze simple variants called SNPs, and AMY1 was too complex.

Meanwhile, McCarroll's team had developed molecular and mathematical strategies for studying complex variation like that of AMY1—and wanted to take a second look at the other group's results.

Seeking simplicity

Using the recently developed molecular techniques, Usher obtained copy number measurements of AMY1 and its surrounding genomic structures in unprecedented detail. Then she developed a statistical framework to find underlying patterns that explained the data.

At first, the region looked "insanely complicated," said McCarroll. But Usher found that the wide range of variation had a simpler explanation: There were nine common forms of AMY1, and most people had some combination of two of them.

The new techniques allowed McCarroll and Hirschhorn's team to probe AMY1's biological significance with greater accuracy than had been possible before. And when they ran their analyses on the genomes of about 4,500 Europeans with a range of body mass indexes, AMY1 had no association with higher or lower body mass index.

"This form of complex variation, while fascinating, is almost certainly not the large influence on obesity that scientists thought it was," said McCarroll.

A maturing field

Although identifying genes associated with disease is crucial for prevention and treatment, ruling out genes is important, too, the authors emphasized. Learning which genes are worth following up on helps prevent scientists from wasting years of work and other resources on leads that don't pan out.

As tools like theirs become available to understand complex variants, McCarroll and Hirschhorn believe questions such as those surrounding AMY1 will be more easily answered.

"There are hundreds of loci in the human genome with this kind of

complexity. They have been like black holes in our knowledge of the human genome," said McCarroll. "I think this is the beginning of a playbook for making sense of those regions."

"If AMY1 had been a simple variant, it would have been really surprising to see opposite results like this," said Hirschhorn. "We've established best practices for identifying and confirming simple variants, but complex variants are not at that stage yet. This is a younger field having its birth pangs."

More information: Structural forms of the human amylase locus and their relationships to SNPs, haplotypes and obesity, *Nature Genetics*, DOI: 10.1038/ng.3340

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