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Scientists find genes related to body mass

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Johns Hopkins scientists who specialize in unconventional hunts for genetic information outside nuclear DNA sequences have bagged a weighty quarry — 13 genes linked to human body mass. The experiments screened the so-called epigenome for key information that cells remember other than the DNA code itself and may have serious implications for preventing and treating obesity, the investigators say.

"Some of the genes we found are in regions of the genome previously suspected but not confirmed for a link to body mass index and obesity," says co-lead investigator Andrew Feinberg, M.D., M.P.H., King Fahd Professor of Molecular Medicine and director of the Center for Epigenetics at Johns Hopkins' Institute for Basic Biomedical Sciences. "Meanwhile, others were a surprise, such as one known to be associated with foraging behavior in hungry worms."

Starting with DNA samples extracted from Icelanders' white blood cells banked in 1991 and 2002 by scientists there as part of the AGES-Reykjavik study of individuals in the general population, the Hopkins team used a customized, genome-wide profiling method dubbed CHARM (comprehensive high-throughput arrays for relative methylation) to look for regions that were the most variable, all chemically marked by DNA methylation.

The DNA methylation analyses revealed epigenetic fingerprints, which, unique to each individual, remain stable over time and may be associated with various common traits including risks for common, complex diseases such as cancer and other conditions.

"Epigenetics has given us 13 exciting new leads to variability in body mass and obesity," says co-lead investigator M. Daniele Fallin, Ph.D., associate professor of epidemiology at the Johns Hopkins Bloomberg School of Public Health. "The team's success suggests a new epigenetic strategy for identifying those at risk for many common diseases, and for possible new prevention methods and therapies."

In a report on the new study published Sept. 15 in *Science Translational Medicine*, the researchers reveal 227 regions within the genome where there's a great deal of variation among individuals. While 41 (about one-third) of these regions, known as VMRs, changed within each person between the 1991 and 2002 DNA analyses, 119 remained stable over time, satisfying the definition of an epigenetic fingerprint, or signature, for each person.

Curious to know if these signatures were linked to obesity-related disease, the researchers analyzed them in relation to each person's body mass index — a measure of one's weight relative to height. BMI was chosen, Feinberg says, because a high BMI predicts risk for many common diseases in the general population.

The team used BMI data provided by Iceland's AGES-Reykjavik study, which archives detailed information over time about that isolated nation's population, including body compositions and metabolic regulations. "We found a high statistical significance between 13 of these VMRs and body mass index," Fallin says. "The level of methylation at these VMRs is, in fact, related to the person's weight."

The researchers focused their search on the epigenetic mark known as DNA methylation because this chemical change in DNA involves the addition of a methyl (a carbon-and-3-hydrogen atom) group, which, although not contained in the DNA sequence itself, controls when and how genes are turned on and off. Such "switches" signal cells in the body

that share the same DNA to assume different functions or forms.

Overall, the team measured DNA methylation levels of 4.5 million selected sites genome-wide in the Iceland DNA samples that were taken 11 years apart, from 74 individuals, ultimately tracking down an array of genes associated with body mass index.

"What we accomplished is a small proof-of-principle study that we think is just the tip of the iceberg in using epigenetics to expand our knowledge of new markers for many common diseases and opening the door for personalized epigenetic medicine," Feinberg says.

"BMI is just a starting point for us," agrees Rafael Irizarry, Ph.D., a professor of biostatistics and co-author of the report. "We want to use the same method to look for genes associated with autism, bipolar disease and variations in aging."

More information: *Science Translational Medicine*: stm.sciencemag.org/

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