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Experts discover gene variants that protect a lucky few primates against obesity from a high fat diet

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A team of researchers from Baylor College of Medicine, the Oregon National Primate Research Center, and the University of Colorado may have discovered the answer to why a lucky few primates are resistant to obesity. In a paper that appears online in the journal *Scientific Reports*, researchers found two gene variants associated with a group of primates that maintained a healthy weight while consuming a high-fat diet that mimics many American diets.

While human studies have looked for genes that render susceptibility to obesity, this team of pregnancy experts were curious about the exception to that rule – genes that may protect against obesity, particularly in moms.

"Working as a team of investigators across three institutions, we have spent a decade building a highly relevant non-human primate model of maternal high-fat diet feeding," said Dr. Kjersti Aagaard, associate professor of obstetrics and gynecology at Baylor and the corresponding author of the study. "While our goal has been to describe the impact of a maternal high-fat diet on the offspring, over time we noticed that approximately one-third of our adult female primates did not become obese despite of consuming a high-fat diet for up to seven years."

This resistance to obesity in the face of a 36 percent fat diet was of interest to the researchers as it has been similarly observed in humans

that a subset of the population appears to remain lean despite the high amount of fat in their diets.

"This work could not have occurred without two key ingredients," said Aagaard, who is also a specialist in obstetrics and gynecology and maternal-fetal medicine at Texas Children's Pavilion for Women. "First, decades of dedication to primate studies and meaningful collaborative work with Drs. Grove, Friedman, and Sullivan, from Oregon Health and Science University, University of Colorado Anschutz Medical Campus and the University of Portland."

"Second, we used an innovative experimental approach called 'exon-hybrid capture'. At the start of these studies, we reasoned that variants in genes that control metabolism could be at least partly responsible for some of the weight stability in the face of the high fat diet in our dams. Our strategy was to apply this not-often-used gene-search approach that would allow us to capture new and known variants in presumptive lipid and obesity regulating genes in human, chimpanzee, orangutan and rhesus macaque full-gene encyclopedias to identify common genetic variants. We then laid these down on a microchip, bound our experimental animal DNA, and looked for changes and variants that were always present in lean, high-fat-diet-resistant animals and never present in the obese animals."

Using these tools and methods, researchers identified two genes involved in lipid metabolism that were associated with obesity resistance in female primate models. One gene, APOB, had two single variants of interest. The other gene, PLA2G4A, had one variant that also was associated with lean body type. Together, APOB and PLA2G4A act on several traits that together render the primates resistant to obesity when fed a high-fat diet. Some of these traits included levels of serum cholesterol, low-density lipoprotein and insulin, as well as direct estimates of central obesity (DEXA scans) and weight gain.

"In modeled gene interactions, we found a significant effect of APOB variants on both the leptin to body weight ratio (leptin is known as the satiety hormone), as well as total fat and free fatty acids," said Aagaard. "Taking into account our primate studies and the available evidence in human population studies, we speculate that APOB may be a key determinant of high-fat-diet-induced obesity."

The second gene, PLA2G4A, is important in phospholipid metabolism and involved in inflammation. Other groups have found that a variant of PLA2G4A is implicated in regulating the levels of plasma triglycerides in a human clinical trial. "In our female macaques, PLA2G4A variants had an additive impact on lowering serum triglycerides," said Aagaard.

"Based on our results and recent evidence in humans, we think that interactions between diet and genes likely affect both maternal health and the future health of the offspring," said Freidman. "The association between maternal weight gain and genetic variation in these two genes discovered here may affect the next generation. Some of the effects may derive directly from the action of maternal and paternal genes on the offspring, while others may indirectly affect the fetus by perturbing the in-utero metabolic environment, particularly with respect to lipid metabolism. The biological pathways and processes underlying how these two genes—and perhaps others—may affect the obesity risk of the next generation when exposed to a high-fat diet remain to be determined."

Other researchers that contributed to this work include, Elinor L. Sullivan of the University of Portland, Diana Takahashi, Karalee Baquero, Peter Blundell, Antonio E. Frias, and Kevin L. Grove all from Oregon Health and Science University, Carrie E. McCurdy from the University of Oregon, Sarah Comstock of Corban University, Stephanie Wesolowski and Jacob E. Friedman both from the

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