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HERITABILITY

The family roots of obesity

Scores of genes are implicated in obesity, but they cannot account for a family's predisposition to obesity. Are there other ways parents can influence their children?

BY CASSANDRA WILLYARD

Stephen O'Rahilly and Sadaf Farooqi, genetics researchers at the University of Cambridge, UK, have been on the hunt for the genes that drive obesity for more than 15 years. One of their first big breaks came in 1997, when two severely obese cousins from Pakistan were referred to them for a clinical assessment. The eight-year-old girl weighed 86 kg — as much as a tall man — and the two-year-old boy tipped the scales at 29 kg. No matter how much these children ate, they never felt full.

A quick blood test pointed Farooqi and O'Rahilly to the problem: both children lacked leptin, a hormone that regulates appetite. The scientists found that the cousins had a mutation in the gene responsible for leptin production — called *ob* for 'obese' — which had only recently been identified in mice[1]. The cousins provided the first irrefutable evidence that our genes can lead us to pile on the pounds. Researchers have since implicated dozens more genes.

"Obesity is one of the strongest genetically influenced traits that we have," says O'Rahilly. Classic twin studies in the 1980s and 1990s, which relied on pairs of identical and fraternal twins, suggest that 40–70% of variation in body size is due to genetic factors[2].

Although rare genetic mutations in the leptin gene and elsewhere in the genome can cause extreme obesity, most cases seem to be

influenced by several more common genetic variants that have much subtler effects on weight. Over the past two decades, researchers have begun to zero in on some of these genes. "We have developed a very large and growing body of data on genes and variants that either cause obesity or likely increase the risk of obesity," says Claude Bouchard, an obesity researcher at the Pennington Biomedical Research Center in Baton Rouge, Louisiana. But the picture is far from complete. While some research groups work to uncover other genes that could help explain the wide variability in body weight, others are beginning to investigate whether epigenetics can account for the heritability of obesity.

GWAS REVOLUTION

No research technique has helped to link more genes to obesity than genome-wide association studies (GWAS). Researchers previously had to make educated guesses about which genes might be involved, and then examine a few variants within that gene to see whether any could be tied to obesity. But in 2005, when researchers published the first GWAS, "everything changed", says Ruth Loos, a genetics expert at Mount Sinai Hospital in New York.

Using GWAS let researchers compare the genomes of thousands of obese individuals with those of thousands of lean people. Rather than looking at the entire genome, the researchers examine a set number of sites, called single-nucleotide polymorphisms (SNPs), where variations typically occur. "You screen the whole genome without any hypothesis," Loos says. Variants that consistently show up among obese individuals but not among lean individuals are predicted to be associated with obesity.

In 2007, for example, a GWAS found that individuals who carry two copies of a common variant of the *FTO* gene weigh on average 3 kg more than those who do not carry any copies[3]. The genetic variant seems to predispose people to consume greater quantities of food. And in 2013, a study showed that men who carry two copies of the *FTO* risk allele felt hungrier and had higher levels of the appetite-stimulating hormone ghrelin after they ate than men who do not carry the risk variant[4].

About 75 variants have been linked to obesity in this way, leading Loos to describe the strategy as "really successful". And new, unpublished research from an international consortium known as Genetic Investigation of Anthropometric Traits (GIANT) adds dozens more to the list. Those results "will double the number of known obesity loci", says Paul Franks, a genetic epidemiologist who studies type 2 diabetes at Lund University in Malmö, Sweden.

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But GWAS studies aren't perfect. They can lead researchers to important parts of the genome, but it can be difficult to sort out which gene within that region might be the culprit. For example, in March, researchers called into question the well-established link between *FTO* and obesity[5]. They think that the real link might involve *IRX3*, a gene whose on/off switch, called a promoter, lies next to *FTO*.

DARK MATTER

Many scientists had first assumed that the heritability of obesity would be explained by common genetic variants. But that hasn't held true. "People found the common variants with the GWAS, and they found many of them," says Farooqi. "But each variant on its own only had a very subtle effect on weight." Taken together, the variants identified through GWAS explain about 2–4% of variability that is attributable to genetics. So if these common variants don't explain the variation, then what does?

"Some people refer to this as the dark matter of quantitative genetics," says Leibel: "We know it's there, but we haven't been able to see it," says Rudolph Leibel, a geneticist at Columbia University in New York. Part of this 'missing heritability' could be explained by genetic variants that have yet to be discovered. "It may be we need to add hundreds and hundreds of SNPs with very small effect sizes to capture more of the genetic variance," Leibel says. Larger GWAS studies might be able to pick some of these up.

Franks offers another possibility. Obesity depends not just on genetics, but also on environment and the interaction between the two. Current GWAS studies don't take this complexity into account, so they may be missing genetic variants that increase the risk of obesity but only under certain conditions. The roughly 75 variants identified by GWAS, "are not intrinsically good candidates for gene–environment interactions because of the way they've been identified," Franks says.

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Some of the strongest evidence for gene–environment interactions comes from research on the risk variants of *FTO*. Soon after these variants were discovered in 2007, several groups began reporting that exercise attenuates this risk. Other studies, however, failed to find a similar relationship. To resolve the issue, more than a hundred researchers launched a meta-analysis that included 45 studies involving more than 218,000 adults and 19,000 children[6]. Not surprisingly, they found that people who carry the susceptibility gene had a higher risk of obesity. However, the researchers also observed that the risk appears to be reduced in people who are physically active. "This is a great example of a very prevalent risk allele for obesity which is very powerfully influenced by the environment," Leibel says.

But there could be another explanation: Farooqi thinks that some of this missing heritability may be accounted for by rarer variants that haven't yet been identified. GWAS do a good job of pinpointing common alleles that occur in more than 5% of the population, but these studies can't pick out variants that occur less frequently. Some of these rare variants might have a larger impact on an individual's body size than the more common variants. Farooqi and her colleagues have already shown that rare variants can drive some cases of extreme obesity, and she thinks that such variants might also explain more common forms of obesity. But as she points out, "no one has really shown that yet."

Common SNPs most often occur between genes in stretches of DNA that don't encode proteins, but Farooqi and O'Rahilly speculate that mutations in protein-encoding genes may have a greater effect. By sequencing only the regions of the genome that encode proteins — a process called whole-exome sequencing — they hope to find new rare variants that can explain more of obesity's heritability and provide new understanding of the molecular pathways that drive the condition. Farooqi and O'Rahilly have put together a cohort of 5,000 people who have been obese since childhood, and through whole-exome sequencing of nearly 1,800 of those individuals, they have already found rare, obesity-related variants in the gene *KSR2* (ref. 7).

Precisely identifying the genes and pathways involved in obesity could lead researchers to new therapies. In the case of the Pakistani cousins, the solution was simple: the children needed leptin. After the researchers began administering the hormone, the kilograms started to melt away[8]. But even when the problem is more complex, there may be ways medications that can help. For example, as many as 6% of severely obese individuals have mutations in a gene called *MC4R*[9], which encodes melanocortin 4 receptor, a protein that helps to regulate appetite. In 2003, Farooqi and her colleagues found that the severity of *MC4R* mutation affects the degree of obesity[10]. "If you've got a bad mutation that stops the receptor from working, you're worse off than if you have a mild mutation," she says. A Boston-based pharmaceutical company called Rhythm has developed a compound that stimulates melanocortin 4 receptor, and the hope is that it will help individuals who have one 'good' copy of the gene to lose weight. Rhythm launched a clinical trial to test the therapy in September 2013.

FAMILY HEIRLOOMS

Humans are especially susceptible to environmental stimuli during embryonic development. And studies suggest that what happens in the womb can cause lasting

changes in gene expression and influence disease risk even in adulthood, a concept known as fetal programming. This raises the possibility that a mother's experiences during pregnancy — such as malnutrition — can influence the next generation.

In the winter of 1944–45, a German blockade starved the western part of the Netherlands. The resulting famine, known as the *Hongerwinter* ('Hunger Winter'), killed more than 20,000 people. A landmark study published in the 1970s looked at 300,000 recruits in the Dutch army to determine whether their risk of obesity was influenced by their experience in the womb[11]. "They found hugely significant effects," says Robert Waterland, who studies the influence of nutrition on development at Baylor College of Medicine in Houston, Texas. Women who became pregnant towards the end of the famine, and so were malnourished during only the first trimester, had sons with higher rates of obesity at age 19 than sons who were born before or after the famine (all of the army recruits studied were male). However, pregnant women who were already in their second trimester when the famine began had sons with a lower risk of obesity. "That was really one of the first demonstrations of programming," says Margaret Morris, an obesity researcher at the University of New South Wales in Sydney, Australia.

Evidence now suggests that these changes were the result of epigenetics, the chemical tags that can change gene expression without altering the genetic code. When researchers looked at the genes of children conceived toward the end of the *Hongerwinter*, they found differences in the prevalence of methyl groups (the most common epigenetic mark) on a gene called *IGF2*, which encodes a hormone that promotes growth during gestation[12]. Children whose mothers had gone hungry during the early part of their pregnancy had fewer methyl tags on *IGF2* than their same-sex siblings who hadn't weathered the famine. These DNA tags tend to turn genes off. But exactly how diminished methylation on *IGF2* might lead to outcomes such as obesity is not yet fully understood.

The epigenetics of obesity isn't only about the mother — the father's experiences can have an impact too. When researchers in Australia fed male rats a fatty diet, the rats — as expected — put on weight and developed signs of diabetes[13]. But, surprisingly, the weight gain also seemed to affect the rats' daughters: the female offspring had trouble controlling their insulin levels despite being on a normal diet. And a study published in 2013 showed that children with obese fathers had less methylation on a particular region of the *IGF2* gene than children who were born to lean fathers[14].

These studies suggest that parents' experiences can have profound effects on the health of their children. What remains unclear is whether these changes are truly heritable.

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The *ob* gene, which is responsible for leptin production, was first identified in obese mice.

CLEAN SLATE

Scientists once thought that epigenetic tags could not be passed from parent to child via sperm or egg cells because any epigenetic marks these cells carry are erased soon after fertilization. But in 2013, a study found that some methyl marks can escape the reprogramming process[15]; this indicates that an epigenetic mark in the egg or sperm could be passed on from generation to generation. "What is special about epigenetics is its ability to maintain a phenotype," says Neil Youngson, an epigenetics expert at the University of New South Wales. "But also we're seeing that maybe it's being maintained beyond that into the next generation."

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To show that an epigenetic change is due to inheritance, however, researchers have to look at multiple generations. When a pregnant woman experiences malnutrition or some other environmental stress, three are directly exposed — the mother, the child in her womb, and also her grandchildren because the fetus already contains cells that will eventually become gametes. "We call those programming effects," Youngson says. "But true transgenerational epigenetic inheritance occurs when none of those generations directly experienced the environmental change." So, if a woman's great grandchildren show a particular epigenetic change that is linked to environmental stress during their great grandmother's pregnancy, that change can be said to be inherited rather than being a programming effect. On the father's side, the exposure isn't as far reaching: a fatty diet might change the epigenetics of a man's sperm, but the programming effect will only be experienced by the child and not the grandchild, unless the change is inherited. "While the son of a starved or obese man could be said to have directly experienced the effect," Youngson says, "the grandson did not directly."

There is some limited evidence to support transgenerational epigenetic inheritance of obesity risk, at least in rats. Michael Skinner, who studies epigenetics at Washington State University in Pullman, has exposed pregnant rats to various environmental contaminants: most recently, the pesticide dichlorodiphenyltrichloroethane (DDT)[16]. Although the chemical had no effect on the weight of the rats' offspring, more than half of the rats' great grandchildren grew fat. And Skinner observed epigenetic changes in the rats' sperm. The findings don't necessarily translate into humans, but Skinner argues that "we have to understand that the environment we live in is driving our health and future generations' health."

Although this study and others suggest that epigenetic marks can be passed down through the generations, it remains unclear what role this type of inheritance might have in human obesity — or whether it can explain any of the missing heritability that troubles geneticists.

Researchers working to untangle how genetics, epigenetics and the environment work together to drive obesity have set for themselves a giant task. But it's one they must accomplish if they hope to have an impact on the obesity epidemic. "A proper understanding of the biology is going to help us determine what can be done," Bouchard says. "If we don't have that, we're shooting in the dark." ■

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