matrix metalloproteinase 9 (MMP9) were all increased by either monocular deprivation or the lack of Cx30, indicating a common signaling pathway. The authors therefore propose that astrocytes control the visual critical period by promoting the maturation of inhibitory circuits through signaling pathways that involve Cx30 and inactivation of RhoA and MMP9. This promotes the formation of perineuronal nets, the enhancement of inhibitory transmission, and the closure of ocular dominance plasticity (see the figure).

Cx30 is a member of a large family of proteins that form intercellular channels that enable the direct transfer of ions and molecules between adjacent cells, but whether a Cx30-RhoA-ROCK2 signaling pathway involves ion and molecule permeation into astrocytes remains unknown. Moreover, several human deafness diseases have been associated with Cx30 mutations (*13*). It is unknown whether any changes in critical-period plasticity are found in these patients. Notably, astrocytes in the fruit fly *Drosophila melanogaster* regulate the maturation of the motor circuit and are essential for proper critical-period closure (*14*). In this case, interaction between the cell adhesion proteins neuroligin and neurexin is the likely signaling pathway. Thus, there may be a diversity of molecular and signaling pathways in which astrocytes influence the use-dependent plasticity of neural circuits during development. ■

"...astrocytes control the visual critical period by promoting the maturation of inhibitory circuits..."

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GENOMICS

Finding genes that control body weight

DNA exome sequencing at scale reveals unknown human biology of adiposity

By **Giles S. H. Yeo** *and* **Stephen O'Rahilly**

Obesity is a common disorder with major adverse effects on morbidity and mortality. Genetic factors play an important role in determining the extent to which people acquire energy and store it as fat, which has implications for the risk of developing obesity. Studies in patients with severe early-onset obesity have identified mutations in >20 genes that have a large effect on body mass index (BMI) (*1*), whereas genome-wide association studies (GWASs) in large populations have identified hundreds of common variants with more-subtle effects (*2*). On page 73 of this issue, Akbari *et al.* (*3*) report rare genetic variants influencing BMI identified through whole-exome sequencing of >600,000 people from the United Kingdom, the United States, and Mexico. The authors identified genes in which rare nonsynonymous variants were associated with either higher or lower BMI, bringing insight to the genetics underlying human adiposity.

When the "first draft" of the human genome was announced in 2003, there was optimism that it would act as a road map that leads to improved treatment of many diseases. GWASs of common variants led to a step change in our understanding of the genetic architecture of many common diseases and traits (*4*). But making the step from variant association to precise causal mechanism has been more challenging. That most polymorphisms associated with disease reside in noncoding regions of the genome makes it difficult to identify the causative gene; and even if one can spot the right gene (recognizing that there may be several), it can be difficult to establish the direction of action and precise mechanism of its effect on phenotype (*5*). Furthermore, many of the genes implicated in disease susceptibility through association with noncoding variation have pleiotropic effects, some of which are exerted during development. These factors reduce the likelihood of beneficial pharmacological manipulation of the products of such genes.

Mutations causing or predisposing an individual to disease by disrupting the protein coding elements of genes (exons) are generally much rarer and, until now, their discovery has relied on studying rare, extreme phenotypes where the prevalence of such variants is much higher. However, such mutations are highly informative because they "self-identify" the causative gene and their impact on function can be established rapidly. Akbari *et al.* demonstrate the power of detecting such variants at scale. Although BMI is an imperfect measure of adiposity (fatness), it correlates well with measures of body fat in large populations. It is a phenotype that is easily measurable and has little day-to-day variability, reflecting a cumulative lifelong imbalance between energy intake and expenditure.

The authors found 16 genes in which rare nonsynonymous variants in exons were associated with BMI at genome-wide levels of significance. Four of these genes, *MC4R* (melanocortin 4 receptor), *PCSK1* (proprotein convertase subtilisin/kexin type 1), *GPR151* (G protein–coupled receptor 151), and *GIPR* (gastric inhibitory polypeptide receptor), have been previously reported. All of these genes are highly expressed in the central nervous system and are known to influence appetite. *GIPR* (*6*) and *GPR151* (*7*) both encode G protein–coupled receptors, and heterozygous loss-of-function (LOF) mutations in these genes are associated with lower BMI in large population studies. *PCSK1* was, together with leptin (*LEP*), one of the first two genes directly implicated in human obesity (*8*). Looking more broadly at the key elements of the signaling pathways that are directly influenced by leptin (which signals satiety), the authors found that heterozygous mutations in *LEP*, *POMC* (proopiomelanocortin), and *PCSK1* were associated with higher BMI (although not all reaching exome-wide statistical significance), whereas heterozygous mutations in *LEPR* (leptin receptor) were not.

LOF mutations in *MC4R* are well established to have a large effect on increasing

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adiposity—it is the most commonly mutated gene associated with obesity (*9*). Akbari *et al.* present information on the impact of rare variants of *MC4R* on obesity risk, suggesting that the prevalence of *MC4R* haploinsufficiency as a contributor to obesity may be seven times more common in a population in Mexico than in the UK. It is possible that the impact of rare *MC4R* variants, both in terms of the number of people affected and the size of the effect on BMI, may have been somewhat underestimated by the authors, particularly in the UK population. They used very stringent bioinformatic criteria for the categorization of a mutation as likely to be disruptive of its normal biochemical function but did not experimentally establish the functional impact of all variants. They are therefore likely to have excluded a number of variants that impair function and increase BMI. Additionally, the UK Biobank cohort examined in this study is leaner and healthier than the general UK population (*10*). A recent report in an unselected UK birth cohort (*11*) suggests that *MC4R* LOF mutations may have an impact on BMI that is substantially greater than that suggested by Akbari *et al.*, particularly at a younger age.

The other 12 genes identified by Akbari *et al.* have not been previously associated with BMI. Most are highly expressed in the hypothalamus, consistent with evidence that most genes involved in obesity predisposition are associated with parts of the central nervous system that control appetite and energy balance. One of these, *GPR75*, is a G protein–coupled receptor whose natural ligand has been reported to be either the chemokine CCL5 (C-C motif chemokine 5) (*12*) or the eicosanoid 20-hydroxyeicosatetraenoic acid (20-HETE) (*13*). The authors report heterozygous variants predicted to be LOF mutations in *GPR75* in 4 of every 10,000 individuals, with carriers having a 1.9 kg/m^2 lower BMI on average. The authors studied mice in which *Gpr75* had been deleted and found that they gained less weight on a high-fat diet than did wild-type mice. This effect was allele-dose dependent, with heterozygous *Gpr75*$^{-/+}$ mice gaining 25% less and homozygous *Gpr75*$^{-/-}$ mice gaining 44% less weight than wild-type littermates. Although it remains unclear whether the leanness of these animals is due to effects on energy intake, expenditure, or both, this study establishes that GPR75 is involved in the control of energy balance and that inhibiting its signaling might be expected to result in a loss of body weight. Mutations in *CALCR*, the receptor for both calcitonin and amylin, were associated with higher adiposity and obesity risk in humans. This is notable because amylin analogs reduce body weight in rodents and humans through actions on brain-expressed *CALCR* (*14*).

The principles of discovery exemplified in the study of Akbari *et al.* go beyond that of body weight control and obesity. The exome sequencing approach at scale increases our ability to reach deep into the rare allele frequency spectrum for functionally compromised alleles. It bypasses the twin headaches of GWAS: the identification of the causative gene and the determination of direction of causality. In continuous traits such as adiposity or blood pressure, it also allows the detection of protective alleles.

It is likely that human exome sequencing at scale will become an increasingly important entry point for the discovery of mechanistic insights into mammalian biology. Much normal physiology is shared between mammalian species, and the traditional flow of information from discovery of physiological mechanisms in animal models to confirmation in humans will probably become more bidirectional. The power to dissect physiology through tissue-specific and temporally controlled genetic manipulation in animal models will, of course, remain a hugely powerful tool. However, when it comes to disease, pathogenesis tends to be more species-specific. So, if one is interested in finding targets that might be usefully manipulated to treat a human disease, it makes particular sense to focus on the species of interest, that is, *Homo sapiens*. The challenges inherent in going from GWAS "hit" to causative gene, and the relatively slim pickings this approach has so far delivered, have engendered some skepticism regarding the power of human genetics to illuminate biology. The study of Akbari *et al.* clearly demonstrates that when sufficient rare human alleles of functional impact can be detected, and when relevant associated phenotypic information is available, then new, robust, and potentially translatable biological insights can be delivered with high efficiency. ■

There is considerable variation in human body weight, which is strongly influenced by genetic variants that often regulate appetite.

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