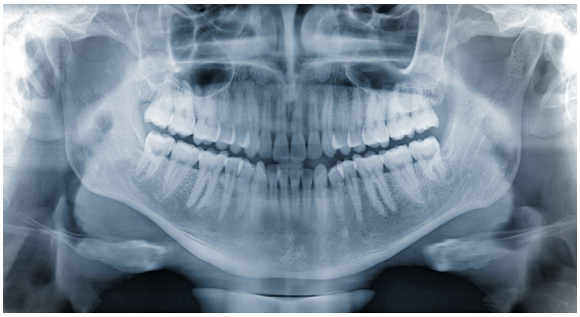

Credit: adventtr/Getty

was differentially expressed in poor outcome groups.

"We have preliminary evidence that *ATRAID* and its binding partner, *SLC37A3*, are involved in glucose metabolism," concludes author Timothy Peterson. "Thus, there is potential that these genes might sit at an important intersection of sugar and lipid homeostasis, which would be important for the metabolic syndrome, amongst other endocrine disorders."

Shimona Starling

> we identified a gene, *ATRAID*, that likely affects how well patients respond to bisphos-phonates

ORIGINAL ARTICLE Surface, L. E. et al. *ATRAID* regulates the action of nitrogen-containing bisphosphonates on bone. *Sci. Transl Med.* **12**, eaav9166 (2020)

Credit: Inok/Getty

which the variants affect regulation of body weight. However, they feel that the findings could have immediate clinical implications. "Our findings suggest that *PHIP* should be included in genetic testing recommended in clinical guidelines as part of the assessment of severe childhood obesity, particularly in children with developmental delay," say Barroso and Farooqi. "These findings might also inform treatment of people with rare variants in the *PHIP* gene, as there are treatments in clinical trials (such as melanocortin 4 receptor agonists) that work on this pathway in the brain that controls appetite."

Claire Greenhill

> Our findings suggest that *PHIP* should be included in genetic testing recommended in clinical guidelines as part of the assessment of severe childhood obesity

ORIGINAL ARTICLE Marenne, G. et al. Exome sequencing identifies genes and gene sets contributing to severe childhood obesity, linking *PHIP* variants to repressed *POMC* transcription. *Cell Metab.* **31**, 1107–1119 (2020)

GENETICS

Deciphering the genetics of resistance to weight gain

Many of the studies investigating the genetic determinants of body weight regulation have focused on obesity, with very few studies looking at the genetic underpinnings of thinness. A new study published in *Cell* has now identified *ALK* as a key gene involved in resistance to weight gain, and hence thinness.

The researchers began by analysing data from a large, well-phenotyped Estonian biobank (Estonian Genome Center of the University of Tartu; EGCUT). People with a low BMI were defined as being in the 6th percentile, and the researchers were able to exclude people with disorders such as lipodystrophy and anorexia nervosa. The genome-wide association analysis identified multiple genetic loci that were associated with thinness.

"As within our top five candidate loci there were multiple genes, we chose a strategy to quickly evaluate metabolic phenotypes for any of these in a fly model," explains author Jörg Hager. The experiments in *Drosophila* showed that knockout of *Alk* reduced levels of triglycerides.

Further experiments in mice revealed that genetic deletion of *Alk* resulted in thin mice that were resistant to diet-induced obesity compared with control animals. In addition, $Alk^{+/-}$ mice also showed reduced body weight compared with $Alk^{+/+}$ mice, which suggests there is a gene-dosage effect. The researchers also used MRI to assess the body composition of the mice. $Alk^{-/-}$ mice fed a high-fat diet had normal lean mass, but reduced adiposity and smaller white adipocytes than control mice fed a high-fat diet. In addition, the $Alk^{-/-}$ mice had increased energy expenditure compared with control mice.

"In mice we could then also map the site of action (the brain) and experimentally explore the mechanism," explains author Josef Penninger. These expression analyses showed that ALK was expressed in hypothalamic neurons that have a role in controlling energy expenditure via the sympathetic control of adipose tissue lipolysis. Supporting these findings, functional knockout experiments in mice also showed that ALK in the paraventricular nucleus was key for resisting weight gain when mice were fed a high-fat diet.

"This current work provides a nice upstream mechanism of how ALK is functioning through a brain–adipose crosstalk, regulating the release and/or local accumulation of noradrenaline in the adipose tissue, which in turn can contribute to the altered lipid metabolism that we observed in our earlier human study, and thus ultimately to one's body weight," says author Nele Gheldof. "These findings might open entirely new research avenues in the field of neural–adipose crosstalk, as well as clues for new approaches for weight management strategies."

More work is needed to fully elucidate the mechanisms underlying resistance to weight gain. "However, this work really puts the white adipose tissue in the centre of the focus of finding solutions for obesity in humans," concludes Hager.

Claire Greenhill

ORIGINAL ARTICLE Orthofer, M. et al. Identification of ALK in thinness. *Cell* https://doi.org/10.1016/j.cell.2020.04.034 (2020)

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