Genome wide study identifies genetic variants associated with childhood obesity

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Juan Carreño de Miranda's "La monstrua desnuda" (The Nude Monster) painting.

Researchers have identified four genes newly associated with severe childhood obesity. They also found an increased burden of rare structural variations in severely obese children.

The team found that structural variations can delete sections of DNA that help to maintain protein receptors known to be involved in the regulation of weight. These receptors are promising targets for the

development of new drugs against obesity.

As one of the major health issues affecting modern societies, obesity has increasingly received public attention. Genes, behavior and environment, all contribute to the development of obesity.

Children with severe obesity are more likely to have a strong genetic contribution. This study has enhanced understanding of how both common and rare variants around specific genes and genetic regions are involved in severe childhood obesity.

"We've known for a long time that changes to our genes can increase our risk of obesity. For example, the gene FTO has been unequivocally associated with BMI, obesity and other obesity-related traits," says Dr Eleanor Wheeler, first author from the Wellcome Trust Sanger Institute. "In our study of severely obese children, we found that variations in or near two of the newly associated genes seem to have a comparable or greater effect on obesity than the FTO gene: PRKCH and RMST."

The team found that different genes can be involved in severe childhood obesity compared to obesity in adults.

Rare genetic changes in one of the newly associated genes, LEPR, are known to cause a severe form of early onset obesity. The team identified a more common variant in this gene, found in 6 per cent of the population, that can increase a person's risk of obesity. This finding is an example of where rare and more common variations around the same gene or region can influence the risk of severe obesity.

Some of the children in this study had an increased number of structural variations of their DNA that delete G-protein coupled receptors, important receptors in the regulation of weight. These receptors are key targets for current drug development and may have potential therapeutic

implications for obesity.

"Some children will be obese because they have severe mutations, but our research indicates that some may have a combination of severe mutations and milder acting variants that in combination contribute to their obesity," says Professor Sadaf Farooqi, co-lead author from the University of Cambridge. "As we uncover more and more variants and genetic links, we will gain a better basic understanding of obesity, which in turn will open doors to areas of clinically relevant research."

As part of the UK10K project the team are now exploring all the genes of 1000 children with severe obesity in whom a diagnostic mutation has not been found. This work will find new severe mutations that may explain the causes of obesity in other children.

"Our study adds evidence that a range of both rare and common genetic variants are responsible for severe childhood obesity," says Dr Inês Barroso, co-lead author from the Wellcome Trust Sanger Institute. "This work brings us a step closer to understanding the biology underlying this severe form of childhood obesity and providing a potential diagnosis to the children and their parents."

More information: Eleanor Wheeler, Ni Huang, Elena G Bochukova, Julia M Keogh, Sarah Lindsay, Sumedha Garg, Elana Henning, Hannah Blackburn, Ruth J F Loos, Nick J Wareham, Stephen O'Rahilly, Matthew E Hurles, Inês Barroso & I Sadaf Farooqi (2013) 'Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity.' Advance Online Publication (AOP) on *Nature Genetics*'s website on 7 April doi:10.1038/ng.2607

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