A whole genome sequencing study in a three-generation consanguineous family with morbid obesity, learning difficulty and failure of weight loss surgery, to identify susceptibility variants for obesity

Authors: L. Al-Olabi[1], N. Chami[2], S. Radha[1], Y. Wu[2], K. Musa[1], Y. Itan[2], A. J. Buckley[1], R.J.F. Loos[2], N. Lessan[1]

[1] Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates.

[2] The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Background

Family and twin studies show that genetic factors account for 40–70% of inter-individual variation in Body Mass Index (BMI). Monogenic obesity is rare, accounting for up to 6% prevalence in morbidly obese populations, with at least 10 genes currently identified. Within a population, genetic variation mediates inter-individual differences in susceptibility to the obesogenic environment and may also contribute to the inter-individual variation reported in weight loss outcomes following bariatric surgery.

Consanguinity has been key in the elucidation of many Mendelian and complex genetic diseases. Here, we combined the power conferred by consanguinity with genome sequencing for discovery of (rare) genetic variants in obesity.

Methods

We investigated a consanguineous Emirati family of 29 individuals with a history of morbid obesity. The proband had first-cousin parents and presented with morbid obesity, type 2 diabetes, with a history of gastric bypass which was later reversed and followed by a sleeve gastrectomy surgery years later. Onset of obesity in childhood was reported for the majority of individuals in the second and third generations. The proband was diagnosed with dyslexia, learning difficulty and Attention Deficit Hyperactivity Disorder (ADHD). Same features were self-reported in eight family members; one grandchild was diagnosed with ADHD. Nine of the eleven second generation siblings gave a history of at least one bariatric surgery; eight of these regained weight. Only one female sibling in the second generation, maintained a BMI within the normal range without surgical intervention. We looked for shared variants among individuals with the most severe obesity. Thus, analyses was performed in five individuals that still had obesity after at least one weight loss surgery, or those that did not have surgery but who have morbid obesity (BMI ≥40).

Results

The proband's karyotype was reported as normal. Array-based comparative genomic hybridization was negative and whole exome sequencing did not identify any causal variants in the proband. Thus, whole genome sequencing was carried out for 10 family members.

Preliminary results from the genome analysis identified 25 rare nonsynonymous coding variants with a minor allele frequency <0.1% in 24 genes that are shared between these five individuals (in addition to the proband who carries 15 of those 25 variants).

Conclusions

We have identified candidate variants including single nucleotide variations, deletions and insertions in genes, involved in signaling pathways that play an important role in processes linked to obesity. These results are currently being validated by Sanger sequencing.