With obesity remaining a critical global challenge, researchers from the University of Zürich detail their efforts to better understand the dynamics around the issue

The path to understanding

Working on the biochemical pathways leading to obesity, senior researcher PD Dr Brigitta Wichert, Institute of Animal nutrition (Director: Professor Dr Annette Liesegang), Vetsuisse Faculty Zürich, discusses problems observed due to genetic differences which were observed by chance.

Who is prone to obesity?

Overweight has become one of the major health risks worldwide. According to the World Health Organization (WHO) obesity was once considered as a problem only in high income countries, but is now dramatically on the rise in low and middle income countries as well, particularly in urban settings. Overweight and obesity in humans are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. They are known to have a complex aetiology, influenced by a wide range of different factors including excessive food intake, inappropriate nutrient composition of food, lack of physical activity and genetic factors. Companion animals like cats live under similar living conditions as humans and therefore have the same risk factors. Comparable to humans, obese cats are in danger of developing Type 2 diabetes. Increasing body weight and the associated increasing body fat lead to decreasing insulin sensitivity and hyperglycaemia. Both are known as early warning signals for Type 2 diabetes. The induced insulin resistance can be reversible with weight loss in humans and cats. It is therefore important to prevent humans and cats from becoming overweight and to reduce existing excessive body weight.

How is obesity inherited?

We observed a segregating overweight phenotype in the cat breeding family located at the Institute of Animal Nutrition at the Vetsuisse Faculty, University of Zürich (Figs. 1 and 2).

The research of PD Dr Brigitta Wichert started to uncover a genetic background of the obesity phenomenon in the cat family of the institute. It all started with an observation that under identical feeding and housing regmies, we observed differences in phenotype. There were animals that gained weight very early during growth in contrast to those that retained their weight over years. A complex segregation analysis showed a genetic involvement and indicated the presence of an autosomal recessive major gene and a possible polygenic component.

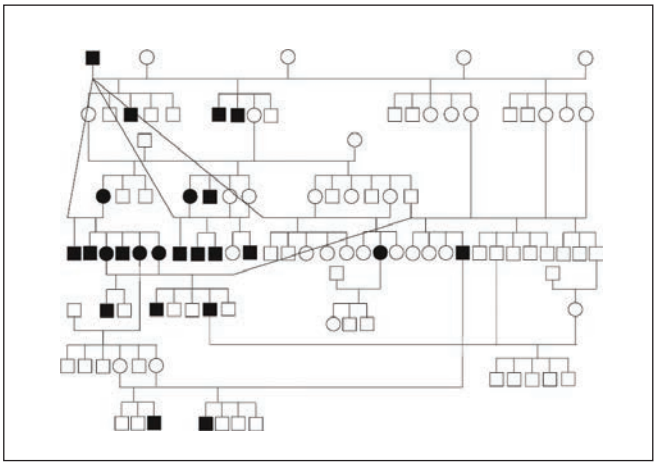

Fig. 2 Seventh-generation pedigree of the named cat breeding family with a segregating overweight phenotype. The cats were phenotyped with the help of the body condition scoring system, symbols: squares = males, circles = females; white = lean phenotype; black = obese phenotype

Fig. 1 Phenotype of two male cats aged one year (fourth generation) of the named cat breeding family. Both cats were kept under the same conditions and on the same diet and feeding regimen. On the left the lean phenotype and on the right the obese one

The animals were genotyped and a genome-wide association analysis was performed. The analysis identified genomic regions on chromosome 12 and nine associated with body condition score. The regions contain Proopiomelanocortin (POMC) and Melanocortin 4 receptor (MC4R) as positional candidate genes, and we are currently investigating the coding sequence of both genes to determine if variants or the combination of variants in those genes are associated with different body weight phenotypes. Mutations in the coding region of MC4R and POMC have been shown to be involved in development of obesity and obesity-associated phenotypes in rodents, as well as in humans.

Physiology of obesity

These findings can give new possibilities in providing an insight over the mechanisms lying behind the phenomenon of obesity.

The overweight phenotype in the cat family of the Institute of Animal Nutrition demonstrated that in addition to the genetic abnormalities, differences in physiological reactions exist; like a tendency to lower energy expenditure, a significant higher food intake (Fig. 3) and significant larger meal size. However, meal frequency and duration of a meal were not significantly different.

Although coding mutations have been shown to effect bodyweight, non-coding and epigenetic factors also play an important role in the development of obesity. This could, for instance, be the lack of an important signal for the termination of a meal. Due to our research programmes, which were already carried out at our institute, there is a large database which can be used as reference for other studies, such as the body weight development of kittens as well as growth of young animals before puberty, and body condition scoring of young animals' glucose and insulin concentrations at different timepoints of age and under different feeding regimes.

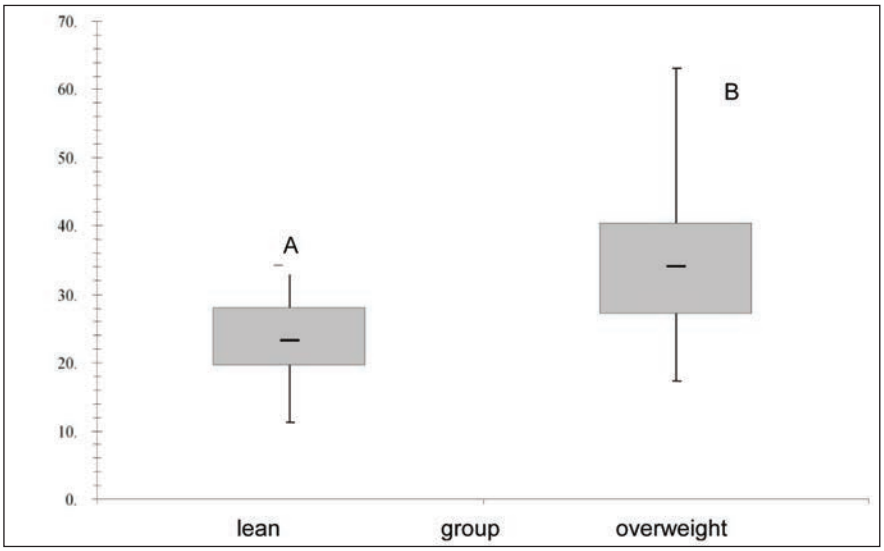

Fig. 3 Food intake (g DM/kg BW0.67) of two groups of male cats (one group belonging to the lean and one to the overweight phenotype)

Future opportunities

To further enhance the understanding of mechanisms involved in the development of obesity and obesity-associated diseases, the cat family of the Institute of Animal Nutrition is very promising due to the hereditary overweight phenotype. Besides the genotype, many other factors discussed to influence the development of obesity can be investigated in future. Among these especially is the influence of diet. The different nutrients like proteins, fat and carbohydrates may play an important role in the prevention or promotion of disease. This means higher contents of proteins might prevent diabetes in contrast to e.g. high carbohydrate diets, which might lead to a predisposition towards diabetes. Another interesting aspect would be the feeding of the mothers during gestation and lactation, the microbiome at different time points, under different feeding conditions and with different body condition scores, gene expression under differing conditions as well as other epigenetic factors. Last but not least, sterilised female cats may serve as a model for the increase of body weight during the postmenopausal period. In this context the mechanisms behind that phenomenon would also be of great interest.

Professor Dr med vet Brigitte von Rechenberg

Brigitta Wichert (second from right) and Annette Liesegang (third from right)

CABMM role

Within the Competence Center of Applied Biotechnology and Molecular Medicine (CABMM) at the University of Zürich, many possibilities are given, since the Institute of Animal Nutrition is able to use the whole infrastructure as well as playing a part within this infrastructure. The Institute of Animal Nutrition also delivers their expertise and laboratory skills to the other partners. This technically sophisticated surrounding of the CABMM is available to all institutions which need the specific expertise of the partners; and with this network a much higher impact is achieved.

PD Dr Brigitta Wichert
Senior researcher

Professor Dr Annette Liesegang
Director
Institute of Animal Nutrition
The Vetsuisse Faculty
The University of Zürich

Contact: Professor Dr med vet Brigitte von Rechenberg
Head of Steering Committee
The Competence Center of Applied Biotechnology and Molecular Medicine (CABMM)
The University of Zürich