



# IMPROVE 2022 International Meeting on Pathway-Related Obesity: Vision of Excellence

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## Summary

Nearly 90 clinicians and researchers from around the world attended the first IMPROVE 2022 International Meeting on Pathway-Related Obesity. Delegates attended in person or online from across Europe, Argentina and Israel to hear the latest scientific and clinical developments in hyperphagia and severe, early-onset obesity, and set out a vision of excellence for the future for improving the diagnosis, treatment, and care of patients with melanocortin-4 receptor (MC4R) pathway-related obesity. The meeting co-chair Peter Kühnen, Charité Universitätsmedizin

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Berlin, Germany, indicated that change was needed with the rapidly increasing prevalence of obesity and the associated complications to improve the understanding of the underlying mechanisms and acknowledge that monogenic forms of obesity can play an important role, providing insights that can be applied to a wider group of patients with obesity. World-leading experts presented the latest research and led discussions on the underlying science of obesity, diagnosis (including clinical and genetic approaches such as the role of defective MC4R signalling), and emerging clinical data and research with targeted pharmacological approaches. The aim of the meeting was to agree on the questions that needed to be addressed in future research and to ensure that optimised diagnostic work-up was used with new genetic testing tools becoming available. This should aid the planning of new evidence-based treatment strategies for the future, as explained by co-chair Martin Wabitsch, Ulm University Medical Center, Germany.

**KEYWORDS**

early-onset obesity, genetic obesity, hyperphagia, MC4R pathway, severe obesity

## 1 | WORKING COLLABORATIVELY IN RARE DISEASES

### 1.1 | Professor Annette Grüters, Charité Universitätsmedizin Berlin, Germany

Working collaboratively is essential to improve the future of patients with rare diseases. Delegates were challenged to consider the different perspectives on rare diseases: patients, science, medicine and society. Patients with rare diseases, and their families, often face a diagnostic odyssey, with high costs for fragmented and unnecessary tests (healthcare coverage can vary by country), and insecurity about prognosis. They face a lack of multidisciplinary professional expertise, systematic research, new treatments (hindered by difficulties in conducting clinical trials in general and paediatric studies specifically) and information overall. Severe childhood obesity is more than a rare disease to the patient and their family, and the impact on quality of life is similar to that of cancer,<sup>1</sup> with early mortality, severe morbidity and huge impact on families.

From a scientific perspective, research on agouti mice with obesity and yellow fur led to the identification of variants in the *POMC* gene and defective MC4R signalling.<sup>2</sup> This added a new disease to the leptin-melanocortin signalling pathway. Studies in individual patients and genome-wide association studies identified the leptin-melanocortin pathway as the major hub in human body weight regulation.<sup>3</sup> Subsequent studies explored the clinical impact of *POMC* variants. From the perspective of clinical medicine, the challenge was how best to treat patients with monogenic obesity. Studies have shown that intact MC4R signalling is required for sustainable weight loss after gastric bypass surgery<sup>4</sup> and that patients with variants in *POMC*, *LEPR* or *MC4R* genes rapidly regain weight after bariatric surgery.<sup>5</sup> The development of MC4R agonists offers a new approach with studies with setmelanotide showing weight loss and improved quality of

life in patients with obesity due to leptin receptor (*LEPR*) or pro-opiomelanocortin (*POMC*) deficiency.<sup>6</sup>

Finally, from the perspective of society, it is essential to combine disciplines from informatics to human and social sciences to make the best use of emerging understanding and treatments to benefit patients. Centres for rare diseases are essential to achieve early and precise diagnosis, provide multi-professional management, and optimise efficiency in care provision, and European Reference Networks for Rare Diseases play key roles in sharing experience and expertise, research and innovation, and promoting best practice through education, training and guidelines.

Altogether, these different components, from patient care to science, medicine and the society, must work collaboratively and in a synergistic manner to help children with rare diseases with the most urgent medical needs by providing therapeutic approaches as quickly as possible.

## 2 | THE SCIENCE AND BIOLOGY

### 2.1 | New understandings on the role of the hypothalamus in obesity: New involved genes, new mechanisms

#### 2.1.1 | Professor Sadaf Farooqi, Wellcome-MRC Institute of Metabolic Science, University of Cambridge, UK

Professor Sadaf Farooqi gave an update on the science of weight regulation and challenged participants to think about where the field is going in the future. The ongoing rise in the prevalence of obesity is driven by changes in the environment, including the amount of food and type of food we eat and being less active, but those environmental factors act on a background of genetic susceptibility in which our

genes influence how much weight we gain in a given environment. The Genetics of Obesity Study, which included 8000 children with severe obesity, identified several genes that converge on fundamental pathways located in the hypothalamus, where melanocortin circuits are key in regulating appetite and weight. Leptin, released by adipose tissue, signals via agouti-related peptide (AgRP) neurons to eat when fasted and POMC neurons to stop eating after a meal. These two groups of neurons converge on second-order neurons that express the MC4R; POMC stimulates the MC4R to reduce food intake and AgRP inhibits the MC4R to increase food intake.

Seminal studies in Berlin identified the first patients in 1998 who had a complete loss of POMC and presented with hyperphagia, obesity, isolated adrenocorticotrophic hormone (ACTH) deficiency (resulting in low cortisol) and hypopigmentation.<sup>2</sup> The Cambridge group identified patients lacking Proprotein Convertase Subtilisin/Kexin Type (PCSK) 1, the enzyme that cleaves POMC, with overlapping features because of a lack of ACTH processing.<sup>7</sup> Many of the other genetic findings from studying children with severe obesity showed the critical role of the melanocortin pathway.<sup>8</sup>

Patients with variants in the MC4R pathway present with severe hyperphagia and associated obesity in childhood. Heterozygous pathogenic variants occur in 5% of children with severe obesity (1%–2% of adults with severe obesity), with weight loss via diet and exercise regimens often not being achieved.<sup>9</sup> A study of children and adults with pathogenic MC4R variants showed that the amount of food they ate at a meal correlated with the degree of receptor dysfunction.<sup>10</sup> We now know that genetic disruption of the MC4R pathway is fundamental to the regulation of weight and that patients with MC4R variants present with severe obesity in childhood. This allows genetic diagnosis and counselling of the family. Genetic testing in patients with extreme early-onset obesity (before 5 years of age) and who have clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and/or a family history of extreme obesity is now recommended worldwide in clinical guidelines.<sup>11</sup>

The first MC4R agonist was developed in 2009; it induced weight loss but was associated with increased blood pressure. More recently, setmelanotide has been developed and Phase II/III trials have been carried out in genetic obesity syndromes affecting the MC4R pathway. These trials with setmelanotide showed dramatic reduction in body weight in patients with POMC deficiency and significant response in patients with LEPR deficiency.<sup>12–14</sup> This emphasises how critical MC4R signalling is and how regulation of signalling may change function in this pathway.

## 2.2 | The hypothalamus and obesity: Delineating central melanocortin circuitry using single cell and genetic approaches

### 2.2.1 | Professor Giles Yeo, Wellcome-MRC Institute of Metabolic Science, University of Cambridge, UK

Single-cell approaches have been used to unravel the complexity of the architecture and function of the different cell types within the

hypothalamus. We knew that there were POMC neurons that are responsive to leptin and others that are responsive to insulin; they are completely separate populations of neurons. One of the approaches taken by the community has been to use single cells to work out this heterogeneity and take apart the hypothalamus, beginning with the mouse hypothalamus. Many single-cell RNA sequencing/non-coding RNA sequencing datasets have been released over the last couple of years. Eighteen of the largest single-cell databases have been harmonised into a shared database—HypoMap version 1.0—which will be updated every year.<sup>15</sup> This is the largest single-cell mouse database available for the hypothalamus, freely available for anyone to search. It is formed of more than 400 000 cells, including 219 022 neurons and 165 903 non-neuronal cells. From this, researchers created a ‘wheel of life’, with 18 concentric layers—each representing a specific study; the outside is colour-coded to represent different areas of the hypothalamus. Putting the studies together gives a comprehensive view of the entire hypothalamus.

For those working in clinical medicine, what matters is the human hypothalamus. One reason this initial mouse work was done was to set it up to do exactly the same thing within the human hypothalamus. Researchers are now making great strides in developing a human HypoMap, working together with the MRC brain bank network to access post-mortem samples. We are now at an advanced stage, with 350 000 cells from the human hypothalamus, from eight donors. Once completed, this will be published and made available on open access. The single-cell work is being used to assign spatial context to genes of interest in obesity; POMC neurons and MC4R neurons have already been identified. Techniques being used include working on a gene-by-gene basis using *in situ* hybridisation and immunohistochemistry to map a specific gene within the human hypothalamus and spatial transcriptomics to map single-cell data into a 3D model.

## 3 | DIAGNOSIS

### 3.1 | Bardet–Biedl syndrome: Diagnosis, care and future views

#### 3.1.1 | Professor H el ene Dollfus, University of Strasbourg, France

Bardet–Biedl syndrome (BBS) is a ciliopathy, one of a large group of rare diseases in which genetic variants encode defective proteins that result in abnormal formation or function of cilia. There are 10 main target organs in BBS, including the retina, the kidney and the developing central nervous system, with complex underlying mechanisms linked to different signalling processes. In the retina, the mechanism involves photoreceptor cells, while tubular cells are involved in the kidney and peripheral and central pathways (including MC4R signalling pathways in the brain for food intake) are involved in obesity.

Obesity is a key characteristic of BBS. Although birth weight is normal, weight gain may occur rapidly in the first year of life and obesity with hyperphagia increases in severity with age.<sup>16,17</sup> Retinal

dystrophy is one of the most penetrant features in BBS, which is the commonest syndromic retinitis pigmentosa (RP), starting at the age of 4–5 years and typically being diagnosed around 5–10 years of age, although late onset is possible. Criteria for improving the diagnosis of BBS were developed in 1999, based on a population survey.<sup>18</sup> The diagnostic clinical criteria are at least four of the six primary features or three primary features plus two of the secondary features. Primary features are: retinal dystrophy (>90%); polydactyly (>75%); obesity (>80%); kidney anomaly (<50%); neurodevelopmental disorder (around 50%); hypogonadism (males) or genito-urinary anomaly (around 60%). Secondary features are: Speech disorder/delay; strabismus/cataracts/astigmatism; brachydactyly/syndactyly; developmental delay; polyuria/polydipsia (nephrogenic diabetes insipidus); ataxia/poor coordination/imbalance; mild spasticity (especially lower limbs); diabetes mellitus; dental crowding/ hypodontia/small roots/high arched palate; left ventricular hypertrophy/congenital heart disease; hepatic fibrosis. Four European Reference Networks are working together to update the criteria for clinical diagnosis of BBS, including molecular diagnostic testing.

There has been rapid progress in the genetic understanding of BBS over the last 30 years; the first BBS locus was mapped to the 18cM region of chromosome 16 (designated *BBS2*) in 1993, followed by a range of other BBS genes and identification of variants.<sup>19</sup> More than 25 genes have now been identified as being involved in BBS; the two most frequent are *BBS1* (23% of patients) and *BBS10* (15% of patients). Genes associated with BBS overlap with ciliopathy genes.<sup>20</sup>

Therapies are now being developed for BBS, including pharmacologic agents such as the *MC4R* agonist setmelanotide, which restores the balance in the *MC4R* pathway, reducing hyperphagia and increasing energy expenditure, thereby reducing weight and body mass index (BMI). Following the success of clinical trials and European Medicines Agency approval for BBS, French authorities have granted an early access programme for setmelanotide in France. BBS is a complex condition, and our patients need holistic care. This should comprise the management of the three main systems affected: weight/obesity, the kidney and the eye.

### 3.2 | Early BMI trajectories in genetic obesity: Update on a collaborative project

3.2.1 | Professor Martin Wabitsch, Ulm University Medical Center, Germany; Corjan de Groot, Leiden University Medical Center, the Netherlands; and Stefanie Zorn, Ulm University Medical Center, Germany

Good progress was reported from a collaborative project collecting data on anthropometric parameter trajectories from birth onwards in patients with monogenic obesity. The project arose from discussions at the World Obesity Meeting in 2021, where a central topic was diagnostic testing in children with obesity: who to test and how. It was agreed to start a project working together to gather more data to better define severe, early-onset obesity. The project aimed to answer

the question: what is the natural course of height, weight, and BMI from birth up to the age of 5 years in patients with monogenic obesity? Secondary questions to explore were: cut-off points in anthropometric parameters with the highest sensitivity to diagnose patients with monogenic obesity; the anthropometric parameter with the highest sensitivity to diagnose patients with monogenic obesity; and the optimal age range to identify patients with monogenic obesity. Six groups (Ulm, Rotterdam, Cambridge, Berlin, Paris, Madrid) have joined the project so far, and others are welcomed.

Inclusion criteria for this project are patients treated in the participating centres, who have been diagnosed with biallelic (likely) pathogenic variants in *LEP*, *LEPR*, *POMC*, *PCSK1* and *MC4R* genes, or monoallelic (likely) pathogenic variants in the *MC4R* gene and who have longitudinal childhood data on weight and height (e.g., >2 measurements before the age of 5 years). The core data set includes: genetic characteristics (e.g., gene, zygosity, cDNA, protein aberration, American College of Medical Genetics and Genomics classification of the variant), patient characteristics (e.g., date of birth, sex) and growth data from birth to 5 years (e.g., date of examination, weight, height).

The project is set to enrol a total of around 288 patients with monogenic obesity, with the largest group being those with heterozygous *MC4R* variants, followed by biallelic *LEPR* variants (around 66 patients). An initial analysis of data in the 50 patients recruited in Rotterdam and Ulm was presented and in the group of eight patients with biallelic *LEP* variants, the growth data showed a unique rapid increase in BMI in the first year of life, which then slowed but continued to the age of 5 years. In contrast, the group with heterozygous (likely) pathogenic *MC4R* variants ( $n = 42$ ) showed a slower course of BMI increase over time. This project provides a good basis for the establishment of a registry for rare forms of genetic obesity.

### 3.3 | Who should be tested? How to identify patients with monogenic or syndromic obesity

3.3.1 | Professor Jesús Argente, Hospital Infantil Universitario Niño Jesús, Madrid, Spain

Most childhood obesity is polygenic, but we are starting to unravel the pathophysiological basis of syndromic obesity and monogenic obesity. However, challenges remain. These include the absence of an international agreement on how to define early-onset, severe obesity and lack of clarity in current guidelines<sup>11,21</sup> on when to carry out genetic testing in these patients.

While individual variants associated with genetic obesity are uncommon, rare genetic causes of obesity are probably not uncommon among individuals with early-onset, severe obesity. Data show that around 7% of children worldwide have early-onset, severe obesity before the age of 4 years.<sup>22</sup> Monogenic obesity may range from 5% to 7% among people with early-onset obesity<sup>11,23</sup> and around 13% of children in Europe may have an underlying genetic cause of obesity.<sup>24</sup>

Key clinical features can help determine when genetic testing should be performed. In non-syndromic obesity, clinical features

include hyperphagia and endocrine abnormalities in addition to early-onset, severe obesity. For example, in POMC deficiency, endocrine abnormalities include ACTH deficiency and mild hypothyroidism, and patients may have red hair and light skin pigmentation. Syndromic obesity is associated with a range of clinical features in addition to early-onset obesity. For example, progressively poor vision and polydactyly occur in BBS. Taking a detailed patient history is important to understand hunger and eating behaviours and family history could provide additional details.

It is important to improve genetic testing in the clinical setting as this can provide information on the cause of obesity and may indicate a possible treatment; it will also suggest relevant clinical trials. We need to develop concrete protocols for genetic testing. These should include: who should be tested; how to interpret gene variants; and how to identify patients with monogenic or syndromic obesities.

### 3.4 | Workshop highlights

Three workshops were held to discuss key measures to improve the diagnosis and management of monogenic obesity.

#### 3.4.1 | How could we set up a monogenic obesity registry? Lessons from other rare diseases

*Led by Julia von Schnurbein, Ulm University Medical Center, Germany*

The workshop attendees strongly agreed that there is a need for an international monogenic obesity registry. They suggested several cogent reasons for a registry for monogenic obesity: the patient numbers are low (e.g., <20 patients worldwide with congenital POMC deficiency), research co-operation is already underway and a registry would facilitate clear agreements and structures and data that could be reusable for further research projects.

There were two different groups suggested for inclusion:

- Patients with clearly defined monogenic forms of obesity, offering the benefits of a small, defined group that would be feasible to start with and research processes are already underway in this group of patients. This approach would facilitate research into the epidemiology and natural course of disease in patients with monogenic obesity and aim to identify all patients to provide accurate information on numbers and enable them to take part in relevant clinical trials and be treated with new disease-specific drugs.
- All patients with early-onset obesity, recognising that many so-called monogenic forms of obesity are actually polygenic and that emerging genetic procedures will detect new diseases. This approach would identify new disease forms and help to investigate the interaction of different aspects, such as polygenic risk score and monogenic obesity, as well as improve treatment options for all patients with early-onset obesity.

A possible way to reconcile these approaches would be to create a combined registry for monogenic obesity (not necessarily meeting the criteria for early-onset, severe obesity) and early-onset, severe obesity (not necessarily monogenic), collecting the same core data set in addition to having disease-specific modules. The registry should include a clearly defined core data set, agree on co-operation partners (ideally global), and set out methods for data entry, aiming for interoperability with other resources. It should be governed by an international consortium and a data access committee should oversee data requests; although data ownership would remain with the entering physician. Overall, the workshop participants agreed that an international genetic obesity registry should be established in a timely manner, after further discussions and an action plan.

#### 3.4.2 | Prerequisites for a smart genetic diagnostic approach

*Led by Lotte Kleinendorst, Amsterdam UMC, The Netherlands*

There is a range of genetic tests for obesity, including single nucleotide polymorphism arrays, karyotyping, gene panels, whole-exome sequencing and whole-genome sequencing, but it is important to decide which tests to do and who to test. Genetic diagnostics essentially comprises testing chromosomes (including karyotyping and chromosomal microarray), DNA (single gene, next-generation sequencing [NGS] gene panels, whole-exome sequencing and whole-genome sequencing) and epigenetics (imprinting disorders such as Prader-Willi). The Endocrine Society Guideline on Paediatric Obesity<sup>11</sup> only contains a concise description of the possible genetic studies and does not mention, e.g., whole-exome sequencing or chromosomal microarrays.<sup>11</sup> Furthermore, the guideline recommends genetic testing only in patients with extreme early-onset obesity (<5 years of age) and clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and/or family history of extreme obesity.<sup>11</sup> However, workshop participants considered this guideline to be out of date and required updating to reflect new developments and insights. Reflecting on current practice, they reported big differences in testing between countries and between different centres in the same country.

Considering who should undergo genetic testing for obesity, participants had a wide range of different opinions. Characteristics suggested included: those with early-onset obesity, a syndromic obesity phenotype, severity of obesity, presence of hormonal abnormalities, and family history. Overall, the group agreed that it is important to work towards more evidence-based recommendations and it is essential to continue discussions on this issue. There were also big differences in which tests were carried out, ranging from no availability for testing to combinations of whole exome sequencing with chromosomal array and methylation studies. More collaboration is needed between paediatricians and geneticists on this. Lack of insurance coverage remains a problem in many countries; materials should be developed to support clinicians in talking to governments and insurance companies to improve access to testing. Workshop participants

agreed that their discussions provided a good starting point for a future consensus, and they considered it important to share and learn from best practices.

### 3.4.3 | Bardet–Biedl syndrome

*Led by Professor Hélène Dollfus, University of Strasbourg, France*

Discussion focussed on the diagnosis and natural history of BBS. Six main clinical points were covered:

- **Obesity:** Obesity and hyperphagia are very important in BBS and the main features in most patients. Patients generally rank obesity as their main problem, even more than loss of vision. Hyperphagia is very frequent in BBS, even without obesity, so it is very important that clinicians check for this; a questionnaire is currently being developed. An important point raised was that obesity is a key feature of BBS even without polydactyly. BBS should be included in panels when ordering genetic testing for patients with early-onset obesity.
- **RP:** This is one of the main features of BBS, in addition to obesity. All patients with BBS have RP by the age of 15 years. There are some patients with RP as the only feature of the disease. It is important that BBS is included in the European Reference Network Eye at the European level.
- **Diabetes:** Diabetes (mainly type 2 diabetes) can occur in young adults with BBS. It is probably maturity-onset diabetes of the young, a rare form of diabetes that is different from both types 1 and 2 diabetes. However, the workshop participants concluded that diabetes is a typical feature of BBS, whereas Alström syndrome is associated with insulin resistance.
- **Other features:** Some patients may present with early-onset kidney failure, so patients with BBS may be initially treated by nephrology specialists. Anosmia and micropenis are also major features and will be included in the new BBS guidelines as such.
- **Bariatric surgery:** The weight loss observed with bariatric surgery provides short-term benefits to patients with BBS; however, the surgery does not resolve the disease and is therefore not recommended in these patients.
- **Treatment:** With setmelanotide, a drug option is available for the treatment of obesity and control of hunger in BBS. Patients should also be offered diet recommendations, physical activity, and psychotherapy.

## 4 | CLINICAL DATA

### 4.1 | Gene–environment interaction

#### 4.1.1 | Professor Karine Clément, Inserm/Sorbonne Université Pitié–Salpêtrière, France

A lot of factors matter when it comes to obesity, with a need to disentangle the interaction between genes and environment. At an

individual level, the microbiome, transcriptome, genome and epigenome all interact with a myriad of environmental factors in the development of obesity in children who are obesity-predisposed.

There is huge variability in weight loss response to whatever method is used, including diet, medication or bariatric surgery.<sup>25</sup> Intriguingly, this has also been seen in recent trials with setmelanotide, with variability in weight loss between patients as well as between different genetic variants.<sup>23</sup> A wide range of factors may be involved in this variability, including brain setpoint, genetic background and epigenetics, gastrointestinal factors such as neurohormonal signalling, the content and composition of the microbiome, adipose tissue (particularly adipokines and inflammatory state), weight loss/regain history, and musculoskeletal parameters including muscle cell size and structure, insulin sensitivity and metabolic activity.<sup>25</sup> All of these impact an individual's basal energy requirement and thermogenic response to food.

Crosstalk between white adipose tissue (WAT) and other tissues in the body promotes physiological and cellular changes that ultimately confer protection from lipotoxicity and metabolic dysfunction.<sup>26</sup> After weight loss, there is the persistence of adipose tissue changes, with persistence of macrophages and an accumulation of T cells and maintenance of an inflammatory state, which is eventually associated with impaired systemic glucose tolerance<sup>27</sup> and weight regain,<sup>28</sup> and fibrosis.<sup>29</sup> Increased pericellular subcutaneous adipose tissue fibrosis and total fibrosis are associated with less weight loss 1 year after bariatric surgery.<sup>30</sup> There may be an adipose tissue phenotype in genetic obesity, with a study showing higher adipocyte volume and less inflammation in patients with Prader–Willi syndrome compared to body fat-matched control patients with obesity.<sup>31</sup>

Gut microbiota have also been associated with obesity, with reduced diversity, altered composition and function, increased prevalence of Bact2 and modified metabolites in subjects with obesity.<sup>32–36</sup> A study of gut microbiota in subjects with Prader–Willi syndrome has shown this is linked to metabolic health, with higher diversity than in non-genetic obesity.<sup>37</sup>

A lot of individual and environmental factors matter in the development of obesity and weight loss. Knowledge of these factors is essential to target prevention and personalised medicine.

### 4.2 | Patient, stigma and burden of the disease

#### 4.2.1 | Professor Béatrice Dubern, Sorbonne Université, Paris, France

The stigmatisation of obesity leads to a negative feedback loop. The stigma associated with obesity is a very important issue for patients with obesity and clinicians, trying to find a way to fight this stigmatisation. Weight stigmatisation leads to mockery, bullying, teasing and victimisation; one study showed that 25%–50% of adolescents had been bullied because of their weight.<sup>38</sup> People are devalued and stereotyped because of their excess weight, which can lead to prejudice and discrimination with reduced access to higher education and

employment.<sup>39</sup> In turn, this results in psychological stress and psychosocial problems, which can cause low self-esteem, depression, suicidal ideation, social isolation and impaired school performance. This can impact eating behaviours and lead to decreased physical activity, with worsening metabolic state and inflammation,<sup>40</sup> contributing further to obesity.

In a case study, a 34-year-old woman with a BMI of 65 who had obesity and hyperphagia since childhood despite nutritional interventions and bariatric surgery had experienced bullying at school and by her family and had been hospitalised at the ages of 13 and 14 years with suicidal ideation, with a suicide attempt at 17. Genetic testing showed she had POMC deficiency.

People with obesity face stigma from a wide range of sources, including healthcare professionals, the media and social media as well as peers and family. Failure to consider obesity as a disease currently results in therapeutic inertia and victim blaming. However, recognition of severe obesity as a multifaceted disorder and understanding the underlying pathophysiology can improve patient care and outcomes. Long-term MC4R agonist treatment with setmelanotide improved metabolic parameters and dramatically improved quality of life in patients with POMC deficiency and led to a clear rupture in weight trajectory.<sup>6</sup> Optimisation of genetic diagnostic testing in patients with early-onset, severe obesity is essential to combat stigma. It is important to avoid oversimplifying obesity, recognising that it is a multifactorial disease that often requires lifelong management and to explore possible causes of obesity beyond the presenting problem.<sup>41</sup>

### 4.3 | What is an optimal multimodal treatment strategy for patients with monogenic/syndromic obesity?

#### 4.3.1 | Jens-Christian Holm, Copenhagen University Hospital Holbæk, Denmark

Understanding that obesity is a disease and treating it as a disease is essential to improve the treatment of patients with obesity. All children with severe obesity should be offered individualised, proper management of their obesity. There has been a tendency for clinicians to shift responsibility to the patient rather than recognising that obesity is a chronic relapsing condition.<sup>42</sup> There is a need to a systematic education of healthcare professionals to provide a uniform and evidence-based understanding, diagnosis, treatment and follow-up of patients living with obesity and related complications.

Growing understanding of the complexity of obesity and the reduction of fat mass challenges traditional management which typically involves changes in daily life not only by increasing exercise and altering diet, but also other circumstances that affect our susceptibility to obesity and especially the fat mass regulation. For example, a study in mice showed that mice receiving 5% less food deposited 40% more fat due to adaptations to reduced energy intake.<sup>43</sup> There are several documented mechanisms which provide evidence that the fat mass is actively defended during caloric restriction, thereby affecting

body composition.<sup>44</sup> A negative energy balance induces comprehensive neuroendocrinological adaptations, ensuring sufficient energy demands in the form of fat mass. It is important to focus on body fat percentage and not body weight.

So what works in practice? The Holbaek model provides a clinic-based structured treatment programme for chronic childhood obesity with 4–5 h of healthcare professional time per patient per year.<sup>45</sup> It reduced the degree of obesity in around three quarters of children and youths,<sup>46</sup> in addition to improving metabolic abnormalities and quality of life. Obesity caused by variants in genes of the MC4R pathway can be more difficult to treat, but drug treatment can be effective for this common form of monogenic obesity.<sup>47</sup> In summary, obesity needs to be managed as a chronic disease, based on the understanding that it is driven by fat (energy) regulation, which disqualifies several commonly believed concepts such as motivation and caloric restriction. Personalised management approaches and comprehensive care for each patient are recommended.

### 4.4 | Positive effect of leptin on mood and behaviour in patients with congenital leptin deficiency

#### 4.4.1 | Julia von Schnurbein, Ulm University Medical Center, Germany

Leptin substitution can increase motor activity, social interaction, mood and emotional involvement at least in some patients with congenital leptin deficiency (CLD). Findings strengthen the hypothesis that leptin has an anti-depressive effect, so a drop in leptin levels may play an important role in mediating behavioural and emotional changes in starvation.

Leptin is an important mediator of adaptation to fasting and starvation.<sup>48</sup> Reduction of leptin levels during starvation has been proposed as a mediator of the depressive symptoms and anxiety that occur as sequelae of malnutrition in patients with anorexia nervosa.<sup>48,49</sup> A study investigated whether leptin substitution improved physical activity and mood in a group of seven patients (six children; one adult) with CLD caused by different homozygous variants, with a wide range of BMI and BMI z-scores (2.3–6.1).<sup>79</sup> The patients were filmed in play or activity situations and analysed by blinded investigators for: motor activity, social interaction, mood and emotional involvement before and during metreleptin substitution. Results showed reductions in mean body weight, BMI and BMI z-score after short-term (2–21 days) metreleptin substitution; this continued with long-term (3–4 months) leptin substitution. The youngest patient lost a lot of weight, while the older patients lost less. Apart from the oldest patient, the study participants also showed significant improvements in motor activity, social interaction, mood and emotional involvement after short-term substitution, which then continued.<sup>79</sup> Further studies with larger cohorts are needed to prove whether leptin resistance could play a role in obesity-associated depression, and overcoming leptin resistance in obesity might improve mood. Studies are needed to understand if direct stimulation of MC4R (with setmelanotide) might have similar effects.

## 4.5 | How to measure hunger in the clinical setting

### 4.5.1 | Mark Hopkins, University of Leeds, UK

Hunger and satiety are not mediated by one unique pattern of biological events. The control of appetite and its measurement involves the quantification of conscious sensations, such as hunger, and the measurement of the behavioural consequences of these sensations, such as food intake. This means we must consider appetite and its measurement in the context of a framework that integrates the underlying physiological signals with the psychological sensations of appetite in a manner that helps us explain the behavioural outcomes.

Subjective appetite is typically measured using horizontal visual analogue scales (VAS; 100 mm), anchored at each end with extremes. For example, a scale for 'how hungry do you feel now?' would range from 'not at all hungry' to 'very hungry'. Studies have confirmed the reliability of appetite VAS<sup>50</sup>; however, a reference frame before treatment is often missing. Subjective measurement of appetite can be mapped against biomarkers of appetite, such as ghrelin (the so-called 'hunger hormone') and hormones released on food consumption, such as GLP-1. However, these show large variability between individuals, therefore within-subject comparisons tend to be more useful. Long-term food intake is affected by hormones such as leptin, which provides information to the brain on the amount of energy stored in adipose tissue.

Signals from adipose tissue and the gastrointestinal tract are involved in mechanisms that suppress food intake (satiation and satiety), but the mechanisms driving food intake have been less well-defined. Over the last 10 years, we have been exploring energy expenditure and its main determinants, such as fat-free mass, as drivers of hunger and food intake. Energy requirements are primarily a consequence of metabolically active lean tissues and active energy expenditure rather than adipose tissue. Recent studies have revealed the importance of fat mass in influencing energy intake mediated by both biological and psychological factors.<sup>51</sup> In a further study, fat mass was negatively associated with energy intake in lean individuals but positively associated with those with overweight/obesity.<sup>52</sup>

## 5 | PATIENT CARE AND TRANSLATION

### 5.1 | Clinical trials with setmelanotide in patients with obesity

#### 5.1.1 | David Meeker, Rhythm Pharmaceuticals, Boston, USA

All obesity is not the same. Understanding the specific drivers may allow the utilisation of targeted therapies. Clinical trials with the MC4R agonist setmelanotide have shown clinically meaningful reductions in patients with monogenic drivers of their obesity including *POMC*, *PCSK1* and *LEPR* and the syndromic condition BBS. Exploratory trials in patients with obesity due to MC4R pathway variants

and patients with acquired hypothalamic obesity have recently been completed.

The first Phase II, open-label, basket-design study enrolled patients  $\geq 6$  years old with obesity due to rare variants in genes of the MC4R pathway, including in *MC4R*. After a screening period, patients were treated with setmelanotide for a 4-week dose titration period, followed by open-label treatment at the therapeutic dose (3 mg) for 12 weeks. Efficacy outcomes were compared by grouping patients using an in vitro MC4R functional assay for variants predicted to be either rescuable or non-rescuable with setmelanotide.

Of the patients with variants predicted to be rescuable with setmelanotide, 7 out of 23 (30.4%, 90% confidence interval [CI]: 15.3–49.6%) achieved a  $\geq 5\%$  BMI reduction at 3 months; the rate was lower (3/24 patients; 12.5%) in those with variants predicted to be non-rescuable. Weight loss, as determined by per cent change in BMI, tended to increase over time in patients achieving  $\geq 5\%$  BMI reduction at 3 months, with continued weight loss in responders at 6 and 9 months of treatment with setmelanotide. The clinical response to setmelanotide may provide important information in identifying patients with genetic variants in the MC4R pathway who may respond long term to MC4R agonist therapy.

Interim analysis for 11 patients (aged  $\geq 6$ –40 years) with acquired hypothalamic obesity treated in a Phase II open-label trial with setmelanotide demonstrated clinically meaningful reductions in BMI ( $>5\%$ ) in all patients by 16 weeks. A waterfall plot showed that setmelanotide achieved a mean BMI reduction of 19.5% in nine patients completing treatment at 16 weeks; there was a statistically significant 30.2% mean reduction in BMI z-score in patients  $< 18$  years old ( $n = 9$ ). Safety and tolerability were consistent with previous data. Setmelanotide achieved a meaningful reduction in mean 'most' hunger score at 16 weeks. The consistent response across patients to an MC4R agonist suggests that MC4R pathway impairment may be playing a critical role in the development of acquired hypothalamic obesity.

### 5.2 | A new monogenic cause of severe, early-onset childhood obesity

#### 5.2.1 | Professor Antje Körner, University Hospital Leipzig, Germany

A case study detailing a patient first seen at the age of 2 years with overgrowth, severe obesity, and hemihyperplasia, shows the need to be always open-minded. At this point, the patient was diagnosed with Beckwith–Wiedemann syndrome (BWS) and a genetic diagnosis of hypomethylation at the *LIT1*-locus. By the age of 12 years, she was very tall (181 cm) and weighed 160 kg (BMI 47.6 kg/m<sup>2</sup>); there was no hemihyperplasia, but she had impaired glucose tolerance. Investigations into adipogenesis showed this was enhanced compared to matched controls and the percentage of differentiated cells and adipogenic marker genes (including adipocyte Protein 2 and Peroxisome proliferator-activated receptor gamma-gamma) were increased.



This is not what would be expected in BWS, where there is no adipose tissue proliferation and cellular energy consumption is decreased. Genetic testing results also failed to confirm BWS, with normal methylation of the 11p15.5 region (at imprinting centres 1 and 2).

Searching for a molecular cause of the increased adipogenesis, the patient underwent transcriptomic profiling. One gene stood out: agouti signalling protein (ASIP: the human homologue to murine non-agouti), which is an antagonist to the melanocortin-1 receptor (MC1R), exclusively expressed in the skin where it determines hair pigmentation. ASIP is a homologue to AgRP and so can antagonise the MC4R. Increased expression of ASIP was detected in the patient's adipocytes, stromal vascular fraction cells, and peripheral blood leucocytes but not in controls. Searching for a genetic cause for ectopic ASIP expression, whole exome sequencing found no variant in 'classical' obesity genes; however, the 5' rapid amplification of cDNA ends method showed the patient had a tandem duplication with an *Itchy E3 Ubiquitin Protein Ligase (ITCH)-ASIP* fusion gene. The patient's phenotype included a 'constant desire to eat' and low physical activity, with decreased resting energy expenditure. The father had red hair, like the child, and was affected by obesity, despite taking part in competitive sport; he also showed expression of the ASIP fusion gene.

The team then demonstrated that the *ITCH* promoter was driving ASIP overexpression. ASIP reduced cAMP signalling at MC1R and MC4R; high ASIP expression was observed in pluripotent stem cells generated from the patient and increased ASIP expression was seen in hypothalamic-like neurons. A novel human monogenic obesity gene trait due to ubiquitous ectopic ASIP expression was identified in this patient with early-onset obesity due to a tandem duplication giving an *ITCH-ASIP* fusion gene. The team then searched for patients with ectopic ASIP expression in the Leipzig obesity cohort ( $n = 1746$ ) and found four more; they all had the *ITCH-ASIP* fusion gene. No carriers of this variant were found in a normal population.

### 5.3 | Epigenetics and obesity: Much ado about nothing

#### 5.3.1 | Professor Peter Kühnen, Charité Universitätsmedizin Berlin, Germany

How can two mice with the same genotype develop very different phenotypes, e.g., one mouse becoming very obese and having yellow fur and the other with normal body weight and brown fur? The answer lies in epigenetics—processes that establish metastable states of gene expression without altering the DNA sequence.<sup>53</sup> One of the simplest of these epigenetic processes is DNA methylation, which regulates gene expression. Understanding of in utero influences on epigenetics has shown that a wide range of factors, including maternal nutrition, can lead to alterations in DNA methylation and other epigenetic processes.

What is the potential significance of epigenetics in obesity? Analysis of a large cohort ( $n = 1383$ ) found increased DNA methylation in

a variably methylated region in the *POMC* gene, particularly in women.<sup>54</sup> *POMC* methylation is very stable over time and is present before the onset of obesity. The impact of the environment on epigenetics is very difficult to assess. However, a study in the Gambia was performed exploring why people born in the rainy season (when food is more available) were six times more likely to die by the age of 60 compared to those born in the dry season.<sup>55,56</sup> Analysis of blood samples from women around conception revealed differences in carbon-1 metabolism (which is important for DNA methylation) with seasonality and higher levels of methylation of *paired-box 8*, a metastable epiallele, in the rainy season compared to the dry season<sup>57</sup>; maternal biomarkers correlated with offspring *POMC* methylation.

Summing up, there needs to be a cautious evaluation of identified epigenetic differences, which are part of a complex network. DNA methylation variability at metastable epialleles could lead to phenotype changes. A *POMC* methylation variant has been found to be associated with increased individual risk to develop obesity, adding that methylation variability might be embedded within a complex network on different epigenetic levels.

## 6 | FUTURE RESEARCH

### 6.1 | Weight loss and adipose tissue

#### 6.1.1 | Professor Mikael Rydén, Karolinska Institute and Karolinska University Hospital, Huddinge, Sweden

WAT dysfunction plays a role in obesity and the mechanism by which disturbances in adipocyte function can promote weight gain have been explored. Adipose tissue is very plastic and can expand in two ways: in a healthy manner, with an increase in the number of fat cells and no change in insulin resistance, and unhealthy expansion associated with an increase in adipocyte size, insulin resistance, lipolysis, inflammation and fibrosis.<sup>58</sup> Subcutaneous WAT is a very important metabolic sink. Lipids are stored in subcutaneous WAT which has a very large capacity to expand. However, when the storage capacity is attenuated, e.g., by insulin resistance, this leads to ectopic lipid deposition in visceral WAT, blood vessels, muscles, pancreas and liver.

Studies on lipid turnover in cross-sectional analyses using <sup>14</sup>C-dating demonstrate a balance between lipid storage and lipolysis in lean individuals, but lipid storage greatly exceeds lipolysis in subjects with obesity, with an increase in triglyceride age.<sup>59–61</sup> Dysregulated adipocyte lipid turnover is linked to ectopic fat deposition and metabolic complications. Fat cell size and number matter, irrespective of whether a person is lean or affected by obesity. Hypertrophy, with enlarged fat cells, is associated with increased risk of type 2 diabetes<sup>62,63</sup>; hyperplasia, with many small adipocytes, is protective. WAT expansion appears to require an increase in both fat cell size and number.<sup>64,65</sup> However, emerging research suggests there may be different subtypes of adipocytes with distinct responses to clinical parameters including transcriptional response to insulin.<sup>66</sup>

Weight loss improves the WAT phenotype regardless of the method; however, in the obese/overweight state, weight loss is difficult to maintain. WAT may contribute to this, in addition to behavioural and environmental factors, by remaining 'hungry' after long-term weight loss.<sup>67</sup> Weight loss mimics starvation and initiates potent signals in WAT and/or the central nervous system to counterbalance this effect.

## 6.2 | New drugs—New mechanisms: gut hormone co-agonists from discovery to approval

### 6.2.1 | Professor Matthias Tschöp, Helmholtz Zentrum, Munich, Germany

Agonism—rather than antagonism—of the glucagon and/or the gastric inhibitor polypeptide (GIP) receptor offers unprecedented potential in the fight against obesity and diabetes. The discovery of leptin provided a molecular basis for body fat regulation, with leptin released from adipocytes acting on the brain to modulate body weight and glucose metabolism<sup>68</sup>; human genetics research has subsequently confirmed that obesity is a brain disease.<sup>69</sup> The gastrointestinal hormone ghrelin emerged as the endogenous opponent of leptin.<sup>70</sup> However, plasma ghrelin is lower in individuals with obesity than in those who are lean, so replacement therapy is not a solution.<sup>71</sup>

Clues as to how to indirectly target the brain to combat obesity have emerged from information on changes in gut-brain signals from bariatric surgery research.<sup>72</sup> Endogenous gut-brain signals offer safe and specific targeting of brain circuits controlling body weight. There was a focus on the glucagon peptide family: glucagon, GLP-1 and GIP. Although glucagon increases glucose levels, it also increases lipolysis and ketogenesis and reduces food intake.<sup>73,74</sup> This was a paradigm change: glucose receptor agonism—and not antagonism—offered additional therapeutic potential for the treatment of obesity. This led to the discovery of the first glucagon and GLP-1 co-agonist for the treatment of obesity and diabetes, which achieved significant long-term weight loss in diet-induced obese mice<sup>75</sup> and beneficial clinical effects in adults with overweight or obesity and type 2 diabetes.<sup>76</sup> Subsequent work has resulted in next-generation agents, including the GIP-GLP-1 dual agonist tirzepatide which achieved unprecedented weight loss of more than 20% in addition to improvements in glycated haemoglobin and insulin sensitivity in a recent trial.<sup>77</sup> A unimolecular triple gut hormone co-agonist has shown even greater efficacy, with a near doubling of weight loss compared to tirzepatide.<sup>78</sup>

## 6.3 | Summary: Building on excellence for the future

### 6.3.1 | Professor Peter Kühnen; Professor Martin Wabitsch; Professor Sadaf Farooqi

There were three priority questions for this meeting: Where are we now? What needs to be done in the next few years? Where should

we focus? Key priorities agreed upon during discussions were to develop an international monogenic obesity registry including clinical phenotyping and to develop recommendations for genetic testing in children with early-onset, severe obesity. There were presentations on the latest developments in pathway-related obesity, and it is clear a new era is being entered. Forces should be joined to try to move forward and reduce the number of patients with severe obesity and the burden of the disease. The high quality of the speakers and depth of discussion throughout the meeting had set out the vision of excellence hoped for when the meeting was planned and energised further collaborative working. Data can be put together to develop a common database—and ideally a registry—that allows investigation of the natural course of monogenic obesity and work on larger scientific studies together. Work together to agree on a smart genetic diagnostic approach—who to test, when to test and how to test.

The meeting effectively coalesced the current knowledge on monogenic obesity and provided clear directions for filling in the remaining gaps. The major challenge is how to take this beyond this group and beyond where we are now. How do we make sure that all children and adults with severe obesity who are likely to have genetic causes have access to testing, treatment and care, and management? Sharing information and communicating it to all healthcare professionals and more widely is key to improving the diagnosis and care of patients with severe obesity. A challenge to be dealt with collectively.

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