Korbonits M (ed): Obesity and Metabolism. Front Horm Res. Basel, Karger, 2008, vol 36, pp 37–60

Genetic Obesity Syndromes

Anthony P. Goldstone^a · Philip L. Beales^b

^aMRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London ^bMolecular Medicine Unit, UCL Institute of Child Health, London, UK

Abstract

There are numerous reports of multi-system genetic disorders with obesity. Many have a characteristic presentation and several, an overlapping phenotype indicating the likelihood of a shared common underlying mechanism or pathway. By understanding the genetic causes and functional perturbations of such syndromes we stand to gain tremendous insight into obesogenic pathways. In this review we focus particularly on Bardet-Biedl syndrome, whose molecular genetics and cell biology has been elucidated recently, and Prader-Willi syndrome, the commonest obesity syndrome due to loss of imprinted genes on 15q11–13. We also discuss highlights of other genetic obesity syndromes including Alstrom syndrome, Cohen syndrome, Albright's hereditary osteodystrophy (pseudohypoparathyroidism), Carpenter syndrome, MOMO syndrome, Rubinstein-Taybi syndrome, cases with deletions of 6q16, 1p36, 2q37 and 9q34, maternal uniparental disomy of chromosome 14, fragile X syndrome and Börjeson-Forssman-Lehman syndrome.

Copyright © 2008 S. Karger AG, Basel

Monogenic Obesity Syndromes

Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS, OMIM 209900) is a highly heterogeneous disorder inherited in a mainly recessive manner. Clinical features include retinal degeneration, cognitive impairment, obesity, renal cystic disease, polydactyly and genital hypoplasia/malformation. There are numerous secondary craniofacial, endocrine, neurological and behavioural features which can assist in early diagnosis (fig. 1) [1]. Although most infants with BBS are born with normal birth weight, by 1 year most show signs of significant weight gain. There may be few other signs of the syndrome during infancy as up to one third of cases do not have polydactyly and signs of visual impairment do not typically emerge until 6–8 years of age (night blindness). The majority of adults have a body mass index (BMI) >30 often accompanied by hypertension, dyslipidaemia and type 2 diabetes mellitus [1].



Fig. 1. BBS. **a**, **b** Post-axial polydactyly in hands and feet of the same child. **c** Brachydactyly in hands of an adult. Note the postaxial scars. **d** High arched palate is common in BBS. **e** Dental anomalies frequently include crowded dentition with hypodontia and short roots.

Twelve genes have now been identified for which there is little evidence of any phenotype-genotype correlation. The BBS genes (BBS1–12) have few sequence similarities to each other or other protein groups. Three, BBS6, BBS10 and BBS12 have strong homology with the type II group of chaperones and account for around 30% of all mutations [2–4]. Only BBS3/ARL6 (a member of the Ras superfamily of small GTP-binding proteins) and BBS11/TRIM32 (an E3 ubiquitin ligase) encode known proteins [5–7].

Recent evidence suggests that BBS is probably caused by dysfunction of primary cilia and the intraflagellar transport (IFT) process. All BBS proteins studied thus far localise to the cilium/basal body/centrosome complex (fig. 2). In mammalian cultured cells several BBS proteins localise either to the basal body and pericentriolar region or the ciliary axoneme [7–13].

Studies indicate that many BBS proteins function in microtubular processes such as IFT as demonstrated in several Bbs mouse mutants, in which each develops severe retinal degeneration similar to patients [11, 14–17]. In photoreceptors, rhodopsin relies on IFT for transport to the outer segment – in Bbs mutants rhodopsin accumulates in the cell body triggering apoptosis [11, 17]. Anosmia was recently reported in Bbs1 and Bbs4 mutants arising from depletion of olfactory proteins in the ciliary layer of olfactory neurones [15]. Subsequently, anosmia was demonstrated in BBS patients,



Fig. 2. BBS proteins. BBS proteins are found in the basal body, centrosome and occasionally the ciliary axoneme. Many are directly involved with IFT, a process dependent on the molecular motors, dynein and kinesin. BBS4 is thought to behave as an adaptor protein, facilitating loading of cargo prior to dynein (retrograde) transport.

a novel feature of the syndrome. Finally, repression of Bbs proteins in zebrafish delays IFT-dependent movement of melanosomes [18].

Obesity and BBS

Obesity is a cardinal aspect of the BBS phenotype, beginning in early childhood and progressing with age; it is usually associated with the trunk and proximal limbs. A survey of UK BBS patients identified 72% of adults as overweight (BMI >25) and 52% defined as obese (BMI >30) [1]. At present, the physiological and biochemical abnormalities underlying obesity in BBS are poorly understood. A case-control study showed no significant differences between resting metabolic rate between obese BBS and controls suggesting no underlying defect in metabolism [19]. Bbs-deficient mouse models (Bbs4 and Bbs6) are initially runty at birth but display progressive weight gain associated with increased food intake, culminating in obesity at \sim 12 weeks [11, 20].

BBS Association Studies

A study by Croft et al. [21, 22] first suggested that heterozygous carriers were at risk of obesity. Attempts to show that BBS gene sequence variants may be associated with general non-syndromic obesity have met with mixed success. Reed et al. [23] investigated 17 genetic markers spanning chromosomal regions implicated in five different obesity syndromes including BBS and BMI in 44 families segregating for non-syndromic morbid obesity. Sib-pair analyses failed to reveal evidence of linkage between any of the markers and obesity in these families. Amongst 60 Danish white men with juvenile-onset obesity who were screened for five variants in MKKS/BBS6, no significant association was found [24]. Another study did not find any association of the common M390R mutation in BBS1 with obesity among Newfoundlanders [25]. A recent large population study however, suggests that variations at BBS genes are associated with risk of common obesity. Benzinou et al. [26] genotyped 12 variants from the coding and conserved regions of BBS1, BBS2, BBS4, and BBS6 in 1,943 French-Caucasian obese subjects and 1,299 French-Caucasian non-obese, non-diabetic controls. A BBS2 polymorphism (SNP) was associated with common adult obesity whereas the BBS4 and BBS6 SNPs were associated with common early-onset childhood obesity and common adult morbid obesity, respectively.

Alström Syndrome

Alström syndrome (ALS, OMIM 203800) is a rare recessive disorder typically presenting with early-onset obesity, hyperinsulinaemia (often with acanthosis nigricans) and type 2 diabetes mellitus, dilated cardiomyopathy, short stature and male hypogonadism. Infants usually display nystagmus and photophobia, eventually progressing to cone and rod photoreceptor degeneration making it a key differential diagnosis with the BBS [27, 28]. It may be associated with hepatic dysfunction, hepatic steatosis and hyperlipidaemia. In addition, ALS patients develop variable sensorineural hearing loss owing to cochlear neuronal degeneration [28, 29].

Rapid weight gain occurs during infancy but tends to plateau in adolescence with a truncal distribution. Despite the improvement in adiposity and BMI with age, the insulin resistance continues to increase and thus ALS may represent a monogenic model of the metabolic syndrome [29]. There are numerous associated endocrine disturbances including growth hormone (GH) deficiency and hyper- or hypogonadotrophic hypogonadism in males [30, 31]. Amongst females with ALS, hirsutism, precocious puberty, and amenorrhoea have been reported. Like BBS up to 50% will have renal and/or urological dysfunction.

The underlying gene, ALMS1 was discovered in 2002 on 2p13 [32, 33]. Neither the predicted gene nor protein sequence has similarity to any other genes, although there are several conserved sequence motifs of limited functional significance. Of interest are the presence of a large 8-kb exon containing a tandem-repeat domain and in exon 1, a polyglutamic acid/polyalanine tract, the length of which does not appear to impact on the AS phenotype. There do not appear to be any phenotype-genotype correlations. ALMS1 is ubiquitously expressed throughout all organ tissues [32], and is a component protein of the centrosome with basal body localisation suggesting involvement in ciliary function and perhaps explaining the phenotypic overlap with BBS [33].

Common variations in the ALMS1 gene were not associated with type 2 diabetes mellitus in two studies of a Dutch and UK population [34, 35].

Cohen Syndrome

Cohen syndrome (CS, OMIM 216550) patients characteristically have a history of developmental delay, severe cognitive impairment, and maladaptive behaviour in addition to a typical facial appearance. They usually have down-sloping palpebral fissures, mild maxillary hypoplasia, a prominent nasal root, micrognathia, high arching palate, thick hair and an open mouth expression where the upper lip barely covers the upper incisors giving the appearance of incisoral prominence [36–38]. Many have microcephaly at birth [39]. CS babies often have low birth weights and failure to thrive owing to feeding difficulties [36, 37]. Sometime during mid-childhood, patients gain weight and develop truncal adiposity, although it is rarely severe. Short stature is common. Delayed puberty is commonly encountered and cases with GH, testosterone deficiency, hypogonadotrophic hypogonadism, and insulin resistance were reported [36, 40].

CS patients typically develop a progressive retinopathy with early-onset myopia [36,41]. There is a wide range of additional ocular defects with pigmentary changes around the macular (giving rise to the typical 'bull's eye' maculopathy) occurring as young as 3 years of age [36]. A chorioretinal dystrophy with accompanying

electroretinographic changes is usually evident by 5 years [42]. Progressive visual field loss with night blindness is present by 10 years.

Neutropenia has a variable but characteristic association with CS. Despite resting low neutrophil counts, perhaps related to increased neutrophil adhesion, patients appear to be able to mount relevant responses to bacterial infection and bone marrow analysis has shown normal cellularity [43, 44].

Mutations in the responsible gene, VPS13B (originally named COH1) were first identified in Finnish families in whom CS is most commonly found [45]. VPS13B is a large gene spanning 864 kb of genome with a transcript of 14 kb and an open-reading frame of 4,022 codons. Although common founder mutations have been observed in the Finnish and Amish CS population, the positions of mutations in other cases are variable and without any phenotype correlation. Most of the 70 plus mutations described so far are non-sense.

The function of VPS13B remains unknown although homologues such as Vps13p are involved in intracellular vesicular trafficking [46]. Expression of the Vps13B in the mouse is widespread amongst neurons of the postnatal brain, but has low level embryonic expression suggesting a role in neuronal differentiation, but not in proliferation [47]. This may explain the postnatal microcephaly seen in CS patients.

Carpenter Syndrome

Carpenter syndrome (acrocephalopolysyndactyly type II, OMIM 201000), most often presents with pre-axial polydactyly of the feet, craniosynostosis and progressive generalised or truncal obesity [48, 49]. Patients often have brachydactyly and syndactyly of the hands. It is autosomal recessively inherited. Only some 40 cases have been described. Additional clinical signs include prolonged retention of primary teeth and hypodontia. It is therefore one of the differential diagnoses to consider with polydactyly, obesity and hypodontia, overlapping with BBS. It is likely that the three sibs reported as cases of BBS by McLoughlin et al. [50] have Carpenter syndrome.

Recently mutations (truncating and missense) were reported in *RAB23*, encoding a RAB/GTPase involved in vesicle transport. RAB23 is a negative regulator of sonic hedgehog signalling and is purported to act with other intermediaries in the cilium [51]. Therefore, like BBS and ALS, Carpenter syndrome supports a link between ciliary function and obesity.

Albright's Hereditary Osteodystrophy

In the original report of Albright's hereditary osteodystrophy (AHO, OMIM 103580), the authors described a child with a short stocky build, round face, short metacarpals and metatarsals, and numerous areas of soft tissue ossification [52]. She also had

hypoparathyroidism secondary to end organ resistance to parathyroid hormone, a component of which they termed 'pseudo-hypoparathyroidism' (PHP). Since then several cases of AHO without end-organ resistance have also be reported and termed 'pseudo-pseudohypoparathyroidism' (PPHP). PHP is further subdivided into types Ia, Ib, Ic and type II. The PHP type Ia and PPHP forms of AHO are caused by inactivating mutations in the tissue-specifically imprinted gene *GNAS1* resulting in reduction of the encoded Gsα protein [53].

Despite normal or even low birth weights, 50–65% of AHO patients develop generalised obesity. The aetiology of the obesity is far from clear but there are a number of possible mechanisms. The melanocortin receptor (MC4R), mutations in which are one of the most common causes of genetic obesity, is transduced by Gs α , as are many of the other G-protein-coupled seven transmembrane receptors that mediate anorexigenic signals from hormones and other neurotransmitters. Loss of such anorexigenic signals such as through MC4R should produce hyperphagia, but this has not been widely studied in obese AHO individuals [54].

The observations that $Gs\alpha$ represses differentiation of fibroblasts (3T3L1 preadipocytes) into adipocytes, and patients with PHP1a may have reduced cAMP responses to β -adrenergic stimulation in fat cell membranes, reduced basal and adrenergic-stimulated glycerol production and reduced circulating levels of noradrenaline suggest that increased adipogenesis and reduced lipolysis and sympathetic activity may also contribute to obesity in AHO [53].

Rubinstein-Taybi Syndrome

Affected patients have a characteristic appearance which includes microcephaly, down slanting and widely placed eyes, long eyelashes, mild ptosis, posteriorly rotated ears and a convex nose with the columella protruding below the alae nasi on lateral view (OMIM 180849). The thumbs and halluces are typically broad and occasionally bifid. Many patients develop central obesity for which the cause is unknown. Recently mutations have been found in the CBP gene [55] which encodes a protein that binds the phosphorylated form of the CREB transcription factor culminating in increased expression of genes containing cAMP-responsive elements.

Obesity Syndromes with Chromosomal and Imprinting Anomalies

Prader-Willi Syndrome

Prader-Willi syndrome (PWS, OMIM 176270) is the commonest human genetic obesity syndrome with a lower estimated birth incidence of 1 in 25,000, and population prevalence of 1 in 50,000 [56]. Characteristic phenotypes, including several

Fig. 3. PWS: from genes to phenotype. **a** A 17-year-old female with PWS. With permission from Goldstone [59]. **b** PWS chromosomal region on 15q11-q13 (not to scale) showing the genetic map of the 2 Mb PWS region. Imprinted genes are in blue (paternal allele expressed) and red (maternal allele expressed). Non-imprinted genes are in green. Orange arrows indicate the area of regional imprint control through the IC at the 5' end of the bicistronic *SNURF-SNRPN* locus. Vertical bars indicate snoRNA transcripts and horizontal bars, the relative positions of identified exons and other transcripts within the *SNURF-SNRPN* locus. Also indicated are the overlapping sense and anti-sense transcripts of the Angelman syndrome (AS) gene, *UBE3A*, which is located adjacent to the PWS locus. The black crosses indicate common breakpoint (BP) regions for deletions. Adapted with permission from Goldstone [59].





suggestive of hypothalamic dysfunction, are reduced foetal movement, increased prematurity, neonatal and infantile hypotonia with poor suck and subsequent improvement with age; genital hypoplasia at birth and cryptorchidism; temporary feeding problems with poor suck and poor weight gain in infancy often needing gavage or other special feeding techniques; subsequent childhood development of obesity and then profound hyperphagia (between ages of 1 and 6 years) leading to progressive morbid obesity into adulthood (fig. 3a); short stature due to GH deficiency and (predominantly hypothalamic) hypogonadism with incomplete delayed puberty and infertility; characteristic facial features of narrow bi-frontal diameter, almond-shaped palpebral fissures and down-turned mouth; small feet and hands with straight ulnar border; developmental delay with mild to moderate mental retardation; characteristic behavioural problem with temper tantrums, obsessive compulsive behaviours, skin picking, stubbornness, rigidity, stealing and lying; central and obstructive sleep apnoea; eye abnormalities such as esotropis and myopia; thick viscous saliva and speech articulation defect; high pain threshold; decreased vomiting; altered temperature sensitivity; scoliosis or kyphosis [57–60].

PWS Genetics

PWS arises from the lack of expression of genes within the paternally derived chromosome 15q11-q13 which are silenced (imprinted) on the maternally derived chromosome [see 59, 61 for references]. These include NDN, MAGEL2, MKRN3 (previously called ZFP127), the SNURF-SNRPN locus which extends over 460 kb encoding at least 148 exons and several repeating intronic C/D box small nucleolar RNAs (snoRNAs) including HBII-52 and HBII-85 (fig. 3b).

The finding of patients with smaller microdeletions and balanced translocations has permitted narrowing of the critical PWS region from 4.5 MB to less than 4.3 kb, spanning the promoter and exon 1 of the SNRPN gene and demonstrated the importance of some snoRNAs in the PWS phenotype [61]. The promotor and first exon of the SNURF-SNRPN gene locus is an integral part of the imprinting centre (IC) in the PWS chromosomal region (fig. 3b). The mouse PWS gene homologues are particularly expressed throughout the developing brain, particularly the hypothalamus, and there is also embryonic and post-natal expression of Ndn and Magel2 outside the brain [62].

The molecular biology of the genes within the PWS critical region has not been fully established. The SmN product of the SNRPN locus (exons 4–10) is involved in RNA alternative splicing, but the role of other transcripts from the SNRPN locus, including IPW, PAR-1, -4 and -7, are poorly defined [61] (fig. 3b). The locus also encodes an anti-sense transcript for the paternally-imprinted UBE3A gene involved in Angelman syndrome.

Necdin has a pivotal role in neuronal differentiation and survival, prevention of apoptosis and axonal growth, and may interact with several neurotrophic and cell cycle-regulatory transcription factors and hence proapoptotic genes such as TrkA, p75, E2F1, Cdc2, p53, hnRNP U, and NEFA [59, 63]. Necdin and Magel2 proteins can both bind to and prevent proteasomal degradation of Fez1, a fasciculation and elongation protein implicated in axonal outgrowth and kinesin-mediated transport, which also binds to the BBS protein BBS4 at or near centrosomes [64]. Ndn-deficient mice exhibit neonatal lethality with respiratory distress; an abnormal respiratory rhythm-generating centre in the medulla; increased skin-scraping activity; improved spatial learning; hypothalamic structural abnormalities with reduced oxytocin and LHRH cell number (but preserved fertility); abnormal axonal outgrowth and fasciculation in embryos, including serotoninergic, noradrenergic, sympathetic (e.g. diaphragmatic and superior cervical ganglion), retinal ganglion cell,

and thalamocortical neurons; defective cytoarchitecture of the cuneate/gracile nuclei; increased apoptosis in spinal cord sensory neurons; and high tolerance to thermal pain [64–68].

The HBII-52 snoRNA and its mouse homologue MBII-52 have recently been found to change methylation editing and alternative splicing of the serotonin 5HT2cR receptor pre-mRNA [69, 70]. The functions of the other snoRNAs are currently unknown.

In 75% of cases, there is a 15q11-q13 paternal deletion, in 22% maternal uniparental disomy (UPD), in 1–3% imprinting errors due in around 15% of cases to a sporadic or inherited microdeletion in the IC and, in <1% there is a paternal chromosomal translocation [61]. Imprinting is achieved partly through parent-of-origin allele-specific methylation of CpG residues, established during or after fertilisation and maintained throughout embryogenesis. The IC not only plays a role in erasure of the grandmaternal imprint during spermatogenesis, but also has a role in the postzygotic maintenance of the maternal imprint.

While there are a number of phenotype-genotype correlations between those PWS patients with deletions versus UPD, particularly in the severity of several neurological, cognitive and behavioural phenotypes (including an increased risk of psychosis in UPD), hyperphagia and obesity do not seem to differ significantly between genotypes [59, 71].

Due to loss of expression of the non-imprinted *P* gene, involved in oculocutaneous albinism, there is a higher frequency of hypopigmentation of skin, hair, and eyes in subjects with deletions [61] (fig. 3b). Between the two common proximal breakpoints (BP1 and 2) are four recently identified genes *NIPA1* (mutations in which cause spastic paraplegia), *NIPA2*, *CYFIP1* (whose protein product interacts with the fragile X protein *FMRI*) and *GCP5* (γ -tubulin complex compenent-5), whose loss might cause phenotypic differences in those with the larger type 1 versus shorter type 2 deletions [72, 73] (fig. 3b).

Obesity and PWS

Birth weight is slightly reduced in PWS [74]. The initial post-natal hypotonia, poor suck and feeding difficulties (often needing special feeding strategies for weeks to months to prevent failure-to-thrive) in babies with PWS have usually improved significantly by 6 months of age. Between the ages of 1 and 6 years, there is initially development of mild obesity (from around 1 year of age), and subsequent hyperphagia and more severe obesity (usually developing between the ages of 2 and 6 years of age). Without appropriate dietary restriction, environmental control and behavioural input obesity becomes progressive into adulthood, leading to obesity-related morbidity, such as cardiopulmonary disease, type 2 diabetes mellitus, thrombophlebitis, chronic leg oedema, and mortality under the age of 35 (fig. 3a). Deaths from choking and gastric necrosis after overeating have been reported [75, 76]. Obesity-related sleep apnoea is common and responds to weight loss. The reason for the later onset development of

hyperphagia and severe obesity in PWS compared to monogenic causes of obesity such as leptin deficiency or melanocortin-4 receptor mutations is unknown.

Obesity management involves early institution of a low-calorie, well-balanced diet, with regular exercise, rigorous supervision, restriction of access to food and money with appreciation of legal and ethical obligations, appropriate psychological and behavioural counselling of the patient and family [77]. Group homes specifically designed for individuals with PWS, where available, have been particularly successful in management of these problems during adulthood. Anecdotally, pharmacological treatment, including available anorexigenic agents, has not been of benefit in treating hyperphagia, though there are few published control studies. Restrictive bariatric surgery, such as gastric banding or bypass, have not been shown to reduce hyperphagia or achieve long-term weight reduction and are associated with unacceptable morbidity and mortality, but some of the reports using biliopancreatic diversion which produces intestinal malabsorption have reported successful weight loss though with frequent complications [78].

Body composition studies show both increased body fat and reduced muscle in PWS [79]. Magnetic resonance imaging has found that PWS adults of both sexes have less visceral adiposity than expected for their overall adiposity [80, 81] (fig. 4a). This may explain the relative hypoinsulinaemia and lower triglyceride levels with preservation of insulin sensitivity and protective elevation in adiponectin levels in patients with PWS despite their overall obesity [80, 82, 83] (fig. 4b, c).

Obesity, hypersomnolence and persistent poor muscle strength contribute to reduced physical activity in PWS. Resting metabolic rate is reduced relative to body size, as a result of the abnormal body composition, which further contributes to a reduction in 24-hour energy expenditure [79]. Increased physical activity and exercise programs improve body composition in PWS.

Spontaneous or pharmacologically stimulated GH secretion and IGF-I levels are reduced in PWS children and adults, and the GH deficiency is independent of obesity [60]. In PWS children, GH therapy is now licensed and significantly improves height velocity and final height [60, 84]. GH significantly decreases total body fat, increases lean body mass, lipolysis and resting energy expenditure, and improves physical strength and agility in children and infants with PWS, and may also have neurodevelopmental benefits [60, 84, 85]. There may also be a potential benefit of lower GH doses to improve body composition in PWS adults.

PWS and Peripheral Appetite Signals

The abnormal feeding behaviour in PWS includes a morbid obsession about food, food stealing, money stealing to buy food, hording and foraging, pica behaviour, reduced satiety and earlier return of hunger after the previous meal [86]. Given free access to food, PWS subjects will consume approximately three times that of control subjects. The reduced satiation in PWS occurs despite delayed gastric emptying which would be expected to produce the opposite effect [87].



Fig. 4. Reduced visceral adiposity, preserved insulin sensitivity and hyperghrelinaemia in PWS. **a** A T₁-weighted MRI scan at the level of the lower abdomen, showing less visceral adiposity in a PWS adult female (total adipose tissue, AT, volume 86.9 l, MRI total body fat 54.4%, visceral AT 4.4% of total AT, visceral AT:subcutaneous AT ratio 0.048) compared to a similarly obese control adult female (total AT volume 86.4 l, MRI total body fat 50.5%, visceral AT 9.3% of total AT, visceral AT:subcutaneous AT ratio 0.048) compared to a similarly obese control adult female (total AT volume 86.4 l, MRI total body fat 50.5%, visceral AT 9.3% of total AT, visceral AT:subcutaneous AT ratio 0.111). With permission from Goldstone et al. [80]. **b**-**d** Mean ± SEM values for percent body fat (**b**), homeostasis model insulin resistance index (HOMA-IR; **c**) and fasting plasma ghrelin levels (**d**) in non-obese (NO, n = 15) and obese (OB, n = 16) controls, craniopharyngioma subjects with hypothalamic obesity (CRHO, n = 9) and subjects with PWS (n = 26). ^a p < 0.01 vs. PWS, ^b p < 0.01 vs. NO. Despite similar degrees of obesity, subjects with PWS have increased fasting plasma ghrelin and preserved insulin sensitivity, compared to the other two obese groups. With permission from Goldstone et al. [82].

Subjects with PWS have marked elevations in the stomach-derived orexigenic hormone ghrelin for their obesity, and increased density of ghrelin immunostaining in the stomach, though plasma levels do fall appropriately after food [82, 88, 89] (fig. 4d). This may be explained at least partly by their relative hypoinsulinaemia (fig. 4). A primary importance for hyperghrelinaemia is questioned by the overlap of ghrelin levels in PWS with lean subjects despite the former's near ubiquitous hyperphagia, and the inability of acute normalisation of ghrelin levels in PWS using somatostatin to reduce appetite [90]. However somatostatin will also suppress secretion of a wide variety of anorexigenic gut hormones that might counteract any beneficial effect of lowering orexigenic ghrelin [90]. Fasting and post-prandial levels of the anorexigenic hormone pancreatic polypeptide are also reduced in PWS children and adults which may also contribute to hyperphagia [91, 92]. It seems likely that in addition to these hormonal abnormalities in PWS, there are overriding brain defects, including hypothalamic, which lead to resistance to peripheral satiety signals [59]. Infusion of PP to subjects with PWS has only a small anorexigenic effect [93]. The possibility of therapeutic avenues for reducing hyperphagia in PWS may depend on the existence of relative rather than absolute resistance to peripheral satiety signals.

PWS and Hypothalamic Abnormalities

Quantitative neuroanatomical studies of available post-mortem human hypothalamic tissue from subjects with PWS in the Netherlands Brain Bank have yet to find any pathological abnormalities of orexigenic neuropeptide Y or agouti-related protein, anorexigenic POMC neurons or GH-releasing hormone neurons in the infundibular nucleus, or orexin/hypocretin neurons in the lateral hypothalamus, though interpretation may be complicated by small numbers and effects of pre-mortem illness [59, 94–96]. However, appropriate neuropeptide Y, agouti-related protein and GH-releasing hormone changes in illness, obesity and exogenous GH therapy were found in PWS subjects, suggesting normal neuronal function in their response to alterations in peripheral signals. Nevertheless, cerebrospinal fluid orexin concentrations have been reported to be low in cases of PWS with hypersomnia [97].

There is a reduction in total and oxytocin cell number in the hypothalamic paraventricular nucleus (PVN) of PWS adults, which may play a primary causative role in hyperphagia [98]. Reduced immunostaining of processed vasopressin, its processing enzyme, prohormone convertase 2, and its molecular chaperone polypeptide 7B2, have also been found in the PVN and supraoptic nucleus of hypothalami from subjects with PWS, though diabetes insipidus is not a recognised clinical problem [99, 100]. Oxytocin and the PVN have anorexigenic roles in rodents. A 29% reduction in PVN oxytocin neurons is also seen in ndn knockout mice, though these mice are not obese [65].

PWS and Brain Abnormalities

Detailed MR scanning including techniques such as diffusion tensor imaging are revealing neuroanatomical abnormalities within extra-hypothalamic brain structures in PWS, such as ventriculomegaly, hypoplastic or displaced pituitary gland, incomplete Sylvian fissure/insula closure, Sylvian fissure polymicrogyria, decreased parietal-occipital grey matter and white matter lesions [101–105]. These may play a role not only in cognitive, behavioural and neuroendocrine defects in PWS, but also hyperphagia.

Recent functional neuroimaging techniques such as positron emission tomography and functional magnetic resonance imaging in PWS have revealed abnormal brain activation patterns in corticolimbic structures, such as the amygdala, pre-frontal, orbitofrontal and insula cortex in response to food stimuli, after ingestion of oral glucose or a meal [106–109]. These suggest abnormal reward and motivational responses to food that may also contribute to the hyperphagia in PWS.

PWS Association Studies

Individual gene mutations or segmental deletions or duplications across the PWS chr15q region have not yet been reported in patients with PWS-like or specific PWS phenotypes, including severe early-onset morbid obesity, but negative PWS methylation testing [61, 101, 110]. No linkage of the PWS chromosomal region with obesity in sibling studies, nor any association of polymorphisms in NDN or MAGEL2 with obesity in children or adolescents has been found [23, 111, 112]. A genome-wide scan found linkage of childhood-onset severe obesity in French Caucasian families to ch15q12–15q15.1, although finer mapping has yet to be reported [113], while weak linkage of BMI to ch15q13.3 was found in a genome-wide scan from the National Heart, Lung, and Blood Institute Family Heart Study [114].

Deletion 6q16

Childhood-onset obesity and hyperphagia has been reported in 5 individuals with deletions involving chromosome 6q16 [see 115 for references]. These patients have also been reported as having almond-shaped eyes, strabismus, thin upper lip, microretrognathia, small hands and feet, hypogonadism, learning disabilities, developmental delay, behavioural problems, cerebellar signs, hypotonia, neonatal feeding difficulties, providing overlap with features seen in PWS.

Interestingly, the obesity may result from haploinsufficiency for a transcription factor involved in neurogenesis, SIM1, since obesity (but not the other syndromal features) has been seen in a subject with a balanced translocation at chr6q16.2 [116]. The sim1 heterozygote knockout mouse is hyperphagic and obese and has a non-selective loss of hypothalamic PVN neurons [117, 118]. Sim1 is also expressed in some non-hypothalamic brain regions involved in appetite, sim1 overexpression protects against diet-induced obesity and sim1 may mediate some of the anorexigenic action of the melanocortin pathways [119, 120].

Deletion 1p36

Obesity and/or hyperphagia has also been reported in 23% of 14 evaluated patients with monosomy 1p36, in whom developmental delay, hypotonia, growth delay, feeding difficulties in infancy, epilepsy, hearing loss, hypermetropia, orofacial clefting abnormalities, structural heart defects and dilated cardiomyopathy, micro- and brachycephaly, deep set eyes, flat nasal bridge and nose, pointed chin, thickened ear helices, asymmetric ears and short fifth finger are also reported [121].

Deletion 2q37

In mid-1990s, several patients with an AHO-like phenotype and a deletion of 2q37 were reported [122, 123]. Characteristically they have a round face with deep set eyes, a bulbous nasal tip, thin border of the lips, and sparse hair. Many have seizures with mild cognitive impairment and obesity is occasionally present. Cytogenetic analysis of further patients has narrowed the deleted interval down to a region including the G-protein-coupled receptor 35, glypican 1, and serine/threonine protein kinase 25 genes; the importance of each remains to be investigated [124, 125].

Deletion 9q34.3

A de novo terminal deletion of chromosome 9q34.3 has been reported in 2 unrelated children with early-onset obesity with hyperphagia (between 2 and 3 years old) and mental retardation, severe developmental delay, neonatal hypotonia, distinctive facial features (brachycephaly, synophrys, anteverted nostrils, prognathism, thin upper lip), short neck and extremities, syndactyly of toes, abnormal genitalia with cryptorchidism, micropenis, and hypospadias, sleep disturbances with repeated night awakenings, stereotypic hand movements, short attention span and intolerance to frustration [126]. However obesity was only seen in 2 of 13 other patients with 9q34.3 deletions, though 3 did die as infants with congenital heart abnormalities [127, 128]. The deleted region encompasses at least 20 genes.

Maternal UPD of Chromosome 14

Maternal UPD 14 (when both of a chromosome 14 pair are inherited exclusively from mother) is associated with muscular hypotonia, feeding problems, hypercholesterolaemia, characteristic rib anomalies (referred to as the 'coat-hanger' sign), motor delay, small hands and feet, precocious puberty and truncal obesity [129, 130]. Patients with UPD(14)mat show features overlapping with PWS and are probably underdiagnosed. In a recent study of 33 patients with low birth weight, feeding difficulties and subsequent obesity in whom PWS had been excluded by methylation analysis of SNRPN, 12% were found to have UPD(14)mat [131]. Facially, patients display a prominent forehead, prominent supra-orbital ridges, short philtrum and down-turned corners of the mouth. The cause of the obesity is unknown.

X-Linked Obesity Syndromes

Fragile X Syndrome

Fragile X syndrome (OMIM 300624), a common cause of mental retardation, is caused by an unstable expansion of a triplet repeat in the FMR1 gene. A sub-pheno-type, resembling PWS has been reported with extreme obesity, a round face, small, broad hands/feet, and regional skin hyperpigmentation [132, 133].

Börjeson-Forssman-Lehmann Syndrome

Börjeson-Forssman-Lehmann syndrome (BFLS, OMIM 301900) is a rare X-linked disorder characterised by severe cognitive impairment, obesity with gynaecomastia, hypogonadism, a course facial appearance and large fleshy ears [134]. BFLS individuals are usually born with a normal birth weight but by late childhood have developed significant truncal obesity. Although there is considerable variability in the degree of obesity, those with less generalised adiposity have a tendency to a female-type fat distribution around the lower abdomen and hips. Almost all BFLS patients develop gynaecomastia often in childhood but significant enlargement occurs at or after puberty, both from obesity and breast tissue. Multiple pituitary hormone deficiencies have been reported including GH, TSH, ACTH and gonadotrophin deficiency, and optic nerve hypoplasia [135]. These features suggest that the BFL gene product may play an important role in midline neuro-development including the hypothalamo-pituitary axis. The facial appearance in post-pubertal patients is striking with deep-set eyes, prominent supraorbital ridges, narrow palpebral fissures features which coarsen with age. The majority also have hyperextensible tapering fingers which like their toes are shortened.

Positional cloning led to the identification of PHF6 as the genetic cause of BFLS [136]. Its expression is ubiquitous, suggesting an important cellular role. Studies show that the PHF6 protein is localised in the cell nucleus and in the nucleolus, and it has been speculated that PHF6 might have a role in cell growth and proliferation, via its participation in ribosome biogenesis [137].

To date, 19 unrelated cases of BFLS with confirmed PHF6 gene mutations have been reported [137]. Amongst these, twelve different mutations have been found of which five are recurrent thus aiding molecular diagnosis for this syndrome. Several manifesting female carriers have been reported with mild to moderate intellectual impairment, the characteristic facial phenotype, large ears, obesity and short stature. Nonetheless, many female carriers have a normal phenotype. Although it is more likely for a PHF6 mutation carrier female to have skewed X inactivation, there are also families where the X inactivation is random [138]. There is no obvious correlation between X inactivation skewing and the variability of clinical presentation of the BFLS phenotype in carrier females.

Obesity Syndromes without Identified Genetic Cause

Macrosomia, Obesity, Macrocephaly, and Ocular Abnormalities

Moretti-Ferreira et al. [139] reported 2 unrelated children with similar clinical features comprising truncal obesity, mental retardation and retinal coloboma and nystagmus (MOMO, OMIM 157980). Facially, features were unremarkable with hypertelorism, downslanting palpebral fissures, a prominent forehead, and a broad nasal root. A potential third case was reported by Zannolli et al. [140] describing a 5year-old girl with mild learning impairment, morbid obesity, macrocephaly, right optic disc coloboma and left choroidal coloboma, and recurvation of the femur. The cause is unknown.

Conclusions

Although in many of the aforementioned obesity syndromes the underlying genetic cause has not yet been identified, in others these are providing potential insights into biochemical or developmental pathways involved. For example, in BBS, AS and CS there is considerable phenotypic overlap. In BBS, AS and possibly Carpenter syndrome, ciliary dysfunction has been implicated and recently the function of primary cilia has been directly linked with obesity [141]. Study of PWS has identified mechanisms of genetic imprinting, genes involved in neuronal development and growth, and hormonal, hypothalamic and cortical circuits that may be important in appetite and body weight control. By defining the genetic cause of all obesity syndromes we should enrich our understanding of obesogenic pathways in common obesity.

It is anticipated that the use of array-based comparative genomic hybridisation in patients with morbid obesity syndromes, often associated with mental retardation, developmental delay and dysmorphic features, will identify novel chromosomal regions and genes involved in body weight regulation, for example ch7q22.1–22.3 deletion and ch19q12q13.2 trisomy [142, 143]. However, care will need to be taken with assigning causality given the frequent presence of gene copy number polymorphisms between individuals.

References

- 1 Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA: New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet 1999;36:437–446.
- 2 Katsanis N, Beales PL, Woods MO, Lewis RA, Green JS, Parfrey PS, Ansley SJ, Davidson WS, Lupski JR: Mutations in MKKS cause obesity, retinal dystrophy and renal malformations associated with Bardet-Biedl syndrome. Nat Genet 2000;26: 67–70.

- 3 Slavotinek AM, Stone EM, Mykytyn K, Heckenlively JR, Green JS, Heon E, Musarella MA, Parfrey PS, Sheffield VC, Biesecker LG: Mutations in MKKS cause Bardet-Biedl syndrome. Nat Genet 2000;26: 15–16.
- 4 Stoetzel C, Laurier V, Davis EE, Muller J, Rix S, Badano JL, Leitch CC, Salem N, Chouery E, Corbani S, Jalk N, Vicaire S, Sarda P, Hamel C, Lacombe D, Holder M, Odent S, Holder S, Brooks AS, Elcioglu NH, Da Silva E, Rossillion B, Sigaudy S, de Ravel TJ, Alan Lewis R, Leheup B, Verloes A, Amati-Bonneau P, Megarbane A, Poch O, Bonneau D, Beales PL, Mandel JL, Katsanis N, Dollfus H: BBS10 encodes a vertebrate-specific chaperonin-like protein and is a major BBS locus. Nat Genet 2006;38:521–524.
- 5 Chiang AP, Beck JS, Yen HJ, Tayeh MK, Scheetz TE, Swiderski RE, Nishimura DY, Braun TA, Kim KY, Huang J, Elbedour K, Carmi R, Slusarski DC, Casavant TL, Stone EM, Sheffield VC: Homozygosity mapping with SNP arrays identifies TRIM32, an E3 ubiquitin ligase, as a Bardet-Biedl syndrome gene (BBS11). Proc Natl Acad Sci USA 2006;103: 6287–6292.
- 6 Chiang AP, Nishimura D, Searby C, Elbedour K, Carmi R, Ferguson AL, Secrist J, Braun T, Casavant T, Stone EM, Sheffield VC: Comparative genomic analysis identifies an ADP-ribosylation factor-like gene as the cause of Bardet-Biedl syndrome (BBS3). Am J Hum Genet 2004;75:475–484.
- 7 Fan Y, Esmail MA, Ansley SJ, Blacque OE, Boroevich K, Ross AJ, Moore SJ, Badano JL, May-Simera H, Compton DS, Green JS, Lewis RA, van Haelst MM, Parfrey PS, Baillie DL, Beales PL, Katsanis N, Davidson WS, Leroux MR: Mutations in a member of the Ras superfamily of small GTP-binding proteins causes Bardet-Biedl syndrome. Nat Genet 2004;36:989–993.
- 8 Li JB, Gerdes JM, Haycraft CJ, Fan Y, Teslovich TM, May-Simera H, Li H, Blacque OE, Li L, Leitch CC, Lewis RA, Green JS, Parfrey PS, Leroux MR, Davidson WS, Beales PL, Guay-Woodford LM, Yoder BK, Stormo GD, Katsanis N, Dutcher SK: Comparative genomics identifies a flagellar and basal body proteome that includes the BBS5 human disease gene. Cell 2004;117:541–552.
- 9 Kim JC, Badano JL, Sibold S, Esmail MA, Hill J, Hoskins BE, Leitch CC, Venner K, Ansley SJ, Ross AJ, Leroux MR, Katsanis N, Beales PL: The Bardet-Biedl protein BBS4 targets cargo to the pericentriolar region and is required for microtubule anchoring and cell cycle progression. Nat Genet 2004;36:462–470.
- 10 Kim JC, Ou YY, Badano JL, Esmail MA, Leitch CC, Fiedrich E, Beales PL, Archibald JM, Katsanis N, Rattner JB, Leroux MR: MKKS/BBS6, a divergent chaperonin-like protein linked to the obesity disorder Bardet-Biedl syndrome, is a novel centrosomal component required for cytokinesis. J Cell Sci 2005; 118:1007–1020.

- 11 Ross AJ, May-Simera H, Eichers ER, Kai M, Hill J, Jagger DJ, Leitch CC, Chapple JP, Munro PM, Fisher S, Tan PL, Phillips HM, Leroux MR, Henderson DJ, Murdoch JN, Copp AJ, Eliot MM, Lupski JR, Kemp DT, Dollfus H, Tada M, Katsanis N, Forge A, Beales PL: Disruption of Bardet-Biedl syndrome ciliary proteins perturbs planar cell polarity in vertebrates. Nat Genet 2005;37:1135–1140.
- 12 Ansley SJ, Badano JL, Blacque OE, Hill J, Hoskins BE, Leitch CC, Kim JC, Ross AJ, Eichers ER, Teslovich TM, Mah AK, Johnsen RC, Cavender JC, Lewis RA, Leroux MR, Beales PL, Katsanis N: Basal body dysfunction is a likely cause of pleiotropic Bardet-Biedl syndrome. Nature 2003;425:628–633.
- 13 Blacque OE, Reardon MJ, Li C, McCarthy J, Mahjoub MR, Ansley SJ, Badano JL, Mah AK, Beales PL, Davidson WS, Johnsen RC, Audeh M, Plasterk RH, Baillie DL, Katsanis N, Quarmby LM, Wicks SR, Leroux MR: Loss of C. elegans BBS-7 and BBS-8 protein function results in cilia defects and compromised intraflagellar transport. Genes Dev 2004;18:1630–1642.
- 14 Mykytyn K, Mullins RF, Andrews M, Chiang AP, Swiderski RE, Yang B, Braun T, Casavant T, Stone EM, Sheffield VC: Bardet-Biedl syndrome type 4 (BBS4)-null mice implicate Bbs4 in flagella formation but not global cilia assembly. Proc Natl Acad Sci USA 2004;101:8664–8669.
- 15 Kulaga HM, Leitch CC, Eichers ER, Badano JL, Lesemann A, Hoskins BE, Lupski JR, Beales PL, Reed RR, Katsanis N: Loss of BBS proteins causes anosmia in humans and defects in olfactory cilia structure and function in the mouse. Nat Genet 2004;36:994–998.
- 16 Fath MA, Mullins RF, Searby C, Nishimura DY, Wei J, Rahmouni K, Davis RE, Tayeh MK, Andrews M, Yang B, Sigmund CD, Stone EM, Sheffield VC: Mkks-null mice have a phenotype resembling Bardet-Biedl syndrome. Hum Mol Genet 2005;14:1109–1118.
- 17 Nishimura DY, Fath M, Mullins RF, Searby C, Andrews M, Davis R, Andorf JL, Mykytyn K, Swiderski RE, Yang B, Carmi R, Stone EM, Sheffield VC: Bbs2-null mice have neurosensory deficits, a defect in social dominance, and retinopathy associated with mislocalization of rhodopsin. Proc Natl Acad Sci USA 2004;101:16588–16593.
- 18 Yen HJ, Tayeh MK, Mullins RF, Stone EM, Sheffield VC, Slusarski DC: Bardet-Biedl syndrome genes are important in retrograde intracellular trafficking and Kupffer's vesicle cilia function. Hum Mol Genet 2006;15:667–677.
- 19 Grace C, Beales P, Summerbell C, Jebb SA, Wright A, Parker D, Kopelman P: Energy metabolism in Bardet-Biedl syndrome. Int J Obes Relat Metab Disord 2003;27:1319–1324.

- 20 Eichers ER, Abd-El-Barr MM, Paylor R, Lewis RA, Bi W, Lin X, Meehan TP, Stockton DW, WU SM, Lindsay E, Justice MJ, Beales PL, Katsanis N, Lupski JR: Phenotypic characterization of Bbs4 null mice reveals age-dependent penetrance and variable expressivity. Hum Genet 2006.
- 21 Croft JB, Morrell D, Chase CL, Swift M: Obesity in heterozygous carriers of the gene for the Bardet-Biedl syndrome. Am J Med Genet 1995;55:12–15.
- 22 Croft JB, Swift M: Obesity, hypertension, and renal disease in relatives of Bardet-Biedl syndrome sibs. Am J Med Genet 1990;36:37–42.
- 23 Reed DR, Ding Y, Xu W, Cather C, Price RA: Human obesity does not segregate with the chromosomal regions of Prader-Willi, Bardet-Biedl, Cohen, Borjeson or Wilson-Turner syndromes. Int J Obes Relat Metab Disord 1995;19:599–603.
- 24 Andersen KL, Echwald SM, Larsen LH, Hamid YH, Glumer C, Jorgensen T, Borch-Johnsen K, Andersen T, Sorensen TI, Hansen T, Pedersen O: Variation of the McKusick-Kaufman gene and studies of relationships with common forms of obesity. J Clin Endocrinol Metab 2005;90:225–230.
- 25 Fan Y, Rahman P, Peddle L, Hefferton D, Gladney N, Moore SJ, Green JS, Parfrey PS, Davidson WS: Bardet-Biedl syndrome 1 genotype and obesity in the Newfoundland population. Int J Obes Relat Metab Disord 2004;28:680–684.
- 26 Benzinou M, Walley A, Lobbens S, Charles MA, Jouret B, Fumeron F, Balkau B, Meyre D, Froguel P: Bardet-Biedl syndrome gene variants are associated with both childhood and adult common obesity in French Caucasians. Diabetes 2006;55:2876–2882.
- 27 Russell-Eggitt IM, Clayton PT, Coffey R, Kriss A, Taylor DS, Taylor JF: Alstrom syndrome. Report of 22 cases and literature review. Ophthalmology 1998; 105:1274–1280.
- 28 Marshall JD, Bronson RT, Collin GB, Nordstrom AD, Maffei P, Paisey RB, Carey C, Macdermott S, Russell-Eggitt I, Shea SE, Davis J, Beck S, Shatirishvili G, Mihai CM, Hoeltzenbein M, Pozzan GB, Hopkinson I, Sicolo N, Naggert JK, Nishina PM: New Alstrom syndrome phenotypes based on the evaluation of 182 cases. Arch Intern Med 2005; 165:675–683.
- 29 Minton JA, Owen KR, Ricketts CJ, Crabtree N, Shaikh G, Ehtisham S, Porter JR, Carey C, Hodge D, Paisey R, Walker M, Barrett TG: Syndromic obesity and diabetes: changes in body composition with age and mutation analysis of ALMS1 in 12 United Kingdom kindreds with Alstrom syndrome. J Clin Endocrinol Metab 2006;91:3110–3116.
- 30 Maffei P, Munno V, Marshall JD, Scandellari C, Sicolo N: The Alstrom syndrome: is it a rare or unknown disease? Ann Ital Med Int 2002;17: 221–228.

- 31 Alter CA, Moshang T Jr: Growth hormone deficiency in two siblings with Alstrom syndrome. Am J Dis Child 1993;147:97–99.
- 32 Collin GB, Marshall JD, Ikeda A, So WV, Russell-Eggitt I, Maffei P, Beck S, Boerkoel CF, Sicolo N, Martin M, Nishina PM, Naggert JK: Mutations in ALMS1 cause obesity, type 2 diabetes and neurosensory degeneration in Alstrom syndrome. Nat Genet 2002;31:74–78.
- 33 Hearn T, Renforth GL, Spalluto C, Hanley NA, Piper K, Brickwood S, White C, Connolly V, Taylor JF, Russell-Eggitt I, Bonneau D, Walker M, Wilson DI: Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alstrom syndrome. Nat Genet 2002;31:79–83.
- 34 Patel S, Minton JA, Weedon MN, Frayling TM, Ricketts C, Hitman GA, McCarthy MI, Hattersley AT, Walker M, Barrett TG: Common variations in the ALMS1 gene do not contribute to susceptibility to type 2 diabetes in a large white UK population. Diabetologia 2006;49:1209–1213.
- 35 Hart LM, Maassen JA, Dekker JM, Heine RJ: Lack of association between gene variants in the ALMS1 gene and Type 2 diabetes mellitus. Diabetologia 2003; 46:1023–1024.
- 36 Chandler KE, Kidd A, Al Gazali L, Kolehmainen J, Lehesjoki AE, Black GC, Clayton-Smith J: Diagnostic criteria, clinical characteristics, and natural history of Cohen syndrome. J Med Genet 2003; 40:233–241.
- 37 Kivitie-Kallio S, Norio R: Cohen syndrome: essential features, natural history, and heterogeneity. Am J Med Genet 2001;102:125–135.
- 38 Cohen MM Jr, Hall BD, Smith DW, Graham CB, Lampert KJ: A new syndrome with hypotonia, obesity, mental deficiency, and facial, oral, ocular, and limb anomalies. J Pediatr 1973;83:280–284.
- 39 Fryns JP, Legius E, Devriendt K, Meire F, Standaert L, Baten E, van den Berghe H: Cohen syndrome: the clinical symptoms and stigmata at a young age. Clin Genet 1996;49:237–241.
- 40 Seifert W, Holder-Espinasse M, Spranger S, Hoeltzenbein M, Rossier E, Dollfus H, Lacombe D, Verloes A, Chrzanowska KH, Maegawa GH, Chitayat D, Kotzot D, Huhle D, Meinecke P, Albrecht B, Mathijssen I, Leheup B, Raile K, Hennies HC, Horn D: Mutational spectrum of COH1 and clinical heterogeneity in Cohen syndrome. J Med Genet 2006; 43:e22.
- 41 Norio R, Raitta C, Lindahl E: Further delineation of the Cohen syndrome; report on chorioretinal dystrophy, leukopenia and consanguinity. Clin Genet 1984;25:1–14.
- 42 Kivitie-Kallio S, Summanen P, Raitta C, Norio R: Ophthalmologic findings in Cohen syndrome. A longterm follow-up. Ophthalmology 2000;107:1737–1745.

- 43 Olivieri O, Lombardi S, Russo C, Corrocher R: Increased neutrophil adhesive capability in Cohen syndrome, an autosomal recessive disorder associated with granulocytopenia. Haematologica 1998;83: 778–782.
- 44 Kivitie-Kallio S, Rajantie J, Juvonen E, Norio R: Granulocytopenia in Cohen syndrome. Br J Haematol 1997;98:308–311.
- 45 Kolehmainen J, Black GC, Saarinen A, Chandler K, Clayton-Smith J, Traskelin AL, Perveen R, Kivitie-Kallio S, Norio R, Warburg M, Fryns JP, de la Chapelle A, Lehesjoki AE: Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. Am J Hum Genet 2003;72:1359–1369.
- 46 Velayos-Baeza A, Vettori A, Copley RR, Dobson-Stone C, Monaco AP: Analysis of the human VPS13 gene family. Genomics 2004;84:536–549.
- 47 Mochida GH, Rajab A, Eyaid W, Lu A, Al Nouri D, Kosaki K, Noruzinia M, Sarda P, Ishihara J, Bodell A, Apse K, Walsh CA: Broader geographical spectrum of Cohen syndrome due to COH1 mutations. J Med Genet 2004;41:e87.
- 48 Temtamy SA: Carpenter's syndrome: acrocephalopolysyndactyly. An autosomal recessive syndrome. J Pediatr 1966;69:111–120.
- 49 Carpenter G: Case of acrocephaly with other congenital malformations. Proc Roy Soc Med 1909;2: 199–201.
- 50 McLoughlin TG, Krovetz LJ, Schiebler GL: Heart disease in the Laurence-Moon-Biedl-Bardet syndrome: a review and a report of 3 brothers. J Pediatr 1964;65:388–399.
- 51 Jenkins D, Seelow D, Jehee FS, Perlyn CA, Alonso LG, Bueno DF, Donnai D, Josifiova D, Mathijssen IM, Morton JE, Orstavik KH, Sweeney E, Wall SA, Marsh JL, Nurnberg P, Passos-Bueno MR, Wilkie AO: RAB23 mutations in Carpenter syndrome imply an unexpected role for hedgehog signaling in cranialsuture development and obesity. Am J Hum Genet 2007;80:1162–1170.
- 52 Albright F, Burnett C, Smith P, Parson W: Pseudohypoparathyroidism: an example of 'Seabright-Bantam syndrome'. Endocrinol 1942;30: 922–932.
- 53 Weinstein LS, Yu S, Warner DR, Liu J: Endocrine manifestations of stimulatory G protein alpha-subunit mutations and the role of genomic imprinting. Endocr Rev 2001;22:675–705.
- 54 Ong KK, Amin R, Dunger DB: Pseudohypoparathyroidism – another monogenic obesity syndrome. Clin Endocrinol (Oxf) 2000;52:389–391.
- 55 Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, Tommerup N, van Ommen GJ, Goodman RH, Peters DJ: Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 1995;376:348–351.

- 56 Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H: Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. J Med Genet 2001;38:792–798.
- 57 Prader A, Labhart A, Willi H: Ein syndrome von adipositas, kleinwuchs, kryptorchismus und oligophrenie nach myotonieartigem zustand im neugeborenenalter. Schweiz Med Wochenschr 1956;86: 1260–1261.
- 58 Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F: Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics 1993;91:398–402.
- 59 Goldstone AP: Prader-Willi syndrome: advances in its genetics, pathophysiology and treatment. Trends Endocrinol Metab 2004;15:12–20.
- 60 Burman P, Ritzen EM, Lindgren AC: Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. Endocr Rev 2001;22: 787–799.
- 61 Nicholls RD, Knepper JL: Genome organization, function, and imprinting in Prader-Willi and Angelman syndromes. Annu Rev Genomics Hum Genet 2002;2:153–175.
- 62 Lee S, Walker CL, Wevrick R: Prader-Willi syndrome transcripts are expressed in phenotypically significant regions of the developing mouse brain. Gene Expr Patterns 2003;3:599–609.
- 63 Kuwako K, Hosokawa A, Nishimura I, Uetsuki T, Yamada M, Nada S, Okada M, Yoshikawa K: Disruption of the paternal necdin gene diminishes TrkA signaling for sensory neuron survival. J Neurosci 2005; 25:7090–7099.
- 64 Lee S, Walker CL, Karten B, Kuny SL, Tennese AA, O'Neill MA, Wevrick R: Essential role for the Prader-Willi syndrome protein necdin in axonal outgrowth. Hum Mol Genet 2005;14:627–637.
- 65 Muscatelli F, Abrous DN, Massacrier A, Boccaccio I, Le Moal M, Cau P, Cremer H: Disruption of the mouse Necdin gene results in hypothalamic and behavioral alterations reminiscent of the human Prader-Willi syndrome. Hum Mol Genet 2000;9: 3101–3110.
- 66 Ren J, Lee S, Pagliardini S, Gerard M, Stewart CL, Greer JJ, Wevrick R: Absence of Ndn, encoding the Prader-Willi syndrome-deleted gene necdin, results in congenital deficiency of central respiratory drive in neonatal mice. J Neurosci 2003;23:1569–1573.
- 67 Pagliardini S, Ren J, Wevrick R, Greer JJ: Developmental abnormalities of neuronal structure and function in prenatal mice lacking the prader-willi syndrome gene necdin. Am J Pathol 2005;167: 175–191.

- 68 Andrieu D, Meziane H, Marly F, Angelats C, Fernandez PA, Muscatelli F: Sensory defects in Necdin deficient mice result from a loss of sensory neurons correlated within an increase of developmental programmed cell death. BMC Dev Biol 2006; 6:56.
- 69 Kishore S, Stamm S: The snoRNA HBII-52 regulates alternative splicing of the serotonin receptor 2C. Science 2006;311:230–232.
- 70 Vitali P, Basyuk E, Le Meur E, Bertrand E, Muscatelli F, Cavaille J, Huttenhofer A: ADAR2-mediated editing of RNA substrates in the nucleolus is inhibited by C/D small nucleolar RNAs. J Cell Biol 2005;169: 745–753.
- 71 Boer H, Holland A, Whittington J, Butler J, Webb T, Clarke D: Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. Lancet 2002;359:135–136.
- 72 Chai JH, Locke DP, Greally JM, Knoll JH, Ohta T, Dunai J, Yavor A, Eichler EE, Nicholls RD: Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/ Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. Am J Hum Genet 2003;73: 898–925.
- 73 Butler MG, Bittel DC, Kibiryeva N, Talebizadeh Z, Thompson T: Behavioral differences among subjects with Prader-Willi syndrome and type I or type II deletion and maternal disomy. Pediatrics 2004; 113:565–573.
- 74 Dudley O, Muscatelli F: Clinical evidence of intrauterine disturbance in Prader-Willi syndrome, a genetically imprinted neurodevelopmental disorder. Early Hum Dev 7 A.D.;83:471–478.
- 75 Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, Kendell P, Clericuzio CL, Scheimann AO: Deaths due to choking in Prader-Willi syndrome. Am J Med Genet A 2007;143: 484–487.
- 76 Wharton R, Wang T, GraemeCook F, Briggs S, Cole R: Acute idiopathic gastric dilatation with gastric necrosis in individuals with Prader-Willi syndrome. Am J Med Genet 1997;73:437–441.
- 77 Eiholzer U: A comprehensive approach to limiting weight gain and to normalising body composition in Prader-Willi syndrome; in Eiholzer U, l'Allemand D, Zipf W (eds): Prader-Willi syndrome as a Model for Obesity. Basel, Karger, 2003, pp 211–221.
- 78 Papavramidis ST, Kotidis EV, Gamvros O: Prader-Willi syndrome-associated obesity treated by biliopancreatic diversion with duodenal switch. Case report and literature review. J Pediatr Surg 2006;41: 1153–1158.

- 79 Goldstone AP, Brynes AE, Thomas EL, Bell JD, Frost G, Holland A, Ghatei MA, Bloom SR: Resting metabolic rate, plasma leptin concentrations, leptin receptor expression, and adipose tissue measured by whole-body magnetic resonance imaging in women with Prader-Willi syndrome. Am J Clin Nutr 2002; 75:468–475.
- 80 Goldstone AP, Thomas EL, Brynes AE, Bell JD, Frost G, Saeed N, Hajnal JV, Howard JK, Holland A, Bloom SR: Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: evidence for novel influences on body fat distribution. J Clin Endocrinol Metab 2001;86:4330–4338.
- 81 Goldstone AP, Unmehopa UA, Thomas EL et al: Hypothalamic neuropeptides and regulation of fat mass in Prader-Willi syndrome; in Eiholzer U, l'Allemand D, Zipf W (eds): Prader-Willi Syndrome as a Model for Obesity. Basel, Karger, 2003, pp 31–43.
- 82 Goldstone AP, Patterson M, Kalingag N, Ghatei MA, Brynes AE, Bloom SR, Grossman AB, Korbonits M: Fasting and post-prandial hyperghrelinemia in Prader-Willi syndrome is partially explained by hypoinsulinemia, and is not due to peptide YY 3–36 deficiency or seen in hypothalamic obesity due to craniopharyngioma. J Clin Endocrinol Metab 2005; 90:2681–2690.
- 83 Kennedy L, Bittel DC, Kibiryeva N, Kalra SP, Torto R, Butler MG: Circulating adiponectin levels, body composition and obesity-related variables in Prader-Willi syndrome: comparison with obese subjects. Int J Obes (Lond) 2006;30:382–387.
- 84 Allen DB, Carrel AL: Growth hormone therapy for Prader-Willi syndrome: a critical appraisal. J Pediatr Endocrinol Metab 2004;17(suppl 4):1297–1306.
- 85 Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB: Two years of growth hormone therapy in young children with Prader-Willi syndrome: Physical and neurodevelopmental benefits. Am J Med Genet 2007;143:443–448.
- 86 Holland AJ, Treasure J, Coskeran P, Dallow J, Milton N, Hillhouse E: Measurement of excessive appetite and metabolic changes in Prader-Willi syndrome. Int J Obes 1993;17:527–532.
- 87 Choe YH, Jin DK, Kim SE, Song SY, Paik KH, Park HY, Oh YJ, Kim AH, Kim JS, Kim CW, Chu SH, Kwon EK, Lee KH: Hyperghrelinemia does not accelerate gastric emptying in Prader-Willi syndrome patients. J Clin Endocrinol Metab 2005;90: 3367–3370.
- 88 Cummings DE, Clement K, Purnell JQ, Vaisse C, Foster KE, Frayo RS, Schwartz MW, Basdevant A, Weigle DS: Elevated plasma ghrelin levels in Praderh Willi syndrome. Nat Med 2002;8:643–644.

- 89 Choe YH, Song SY, Paik KH, Oh YJ, Chu SH, Yeo SH, Kwon EK, Kim EM, Rha MY, Jin DK: Increased density of ghrelin expressing cells in the gastric fundus and body in Prader-Willi syndrome. J Clin Endocrinol Metab 2005;90:5441–5445.
- 90 Tan TM, Vanderpump M, Khoo B, Patterson M, Ghatei MA, Goldstone AP: Somatostatin infusion lowers plasma ghrelin without reducing appetite in adults with Prader-Willi syndrome. J Clin Endocrinol Metab 2004;89:4162–4165.
- 91 Zipf WB, O'Dorisio TM, Cataland S, Dixon K: Pancreatic polypeptide responses to protein meal challenges in obese but otherwise normal children and obese children with Prader-Willi syndrome. J Clin Endocrinol Metab 1983;57:1074–1080.
- 92 Goldstone AP: The hypothalamus, hormones, and hunger: alterations in human obesity and illness. Prog Brain Res 2006;153:57–73.
- 93 Berntson GG, Zipf WB, O'Dorisio TM, Hoffman JA, Chance RE: Pancreatic polypeptide infusions reduce food intake in Prader-Willi syndrome. Peptides 1993;14:497–503.
- 94 Goldstone AP, Unmehopa UA, Bloom SR, Swaab DF: Hypothalamic NPY and agouti-related protein are increased in human illness but not in Prader-Willi syndrome and other obese subjects. J Clin Endocrinol Metab 2002;87:927–937.
- 95 Goldstone AP, Unmehopa UA, Swaab DF: Hypothalamic growth hormone-releasing hormone (GHRH) cell number is increased in human illness, but is not reduced in Prader-Willi syndrome or obesity (erratum in Clin Endocrinol 59, 266, 2003). Clin Endocrinol (Oxf) 2003;58:743–755.
- 96 Fronczek R, Lammers GJ, Balesar R, Unmehopa UA, Swaab DF: The number of hypothalamic hypocretin (orexin) neurons is not affected in Prader-Willi Syndrome. J Clin Endocrinol Metab 2005;90: 5466–5470.
- 97 Nevsimalova S, Vankova J, Stepanova I, Seemanova E, Mignot E, Nishino S: Hypocretin deficiency in Prader-Willi syndrome. Eur J Neurol 2005;12:70–72.
- 98 Swaab DF, Purba JS, Hofman MA: Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. J Clin Endocrinol Metab 1995;80:573–579.
- 99 Gabreëls BATF, Swaab DF, deKleijn DPV, Seidah NG, Van de Loo JW, Van de Ven WJM, Martens GJM, van Leeuwen FW: Attenuation of the polypeptide 7B2, prohormone convertase PC2, and vasopressin in the hypothalamus of some Prader-Willi patients: Indications for a processing defect. J Clin Endocrinol Metab 1998;83:591–599.
- 100 Swaab DF: Prader-Willi syndrome and the hypothalamus. Acta Paediatr Suppl 1997;423:50–54.

- 101 Miller J, Kranzler J, Liu Y, Schmalfuss I, Theriaque DW, Shuster JJ, Hatfield A, Mueller OT, Goldstone AP, Sahoo T, Beaudet AL, Driscoll DJ: Neurocognitive findings in Prader-Willi syndrome and early-onset morbid obesity. J Pediatr 2006;149:192–198.
- 102 Leonard CM, Williams CA, Nicholls RD, Agee OF, Voeller KK, Honeyman JC, Staab EV: Angelman and Prader-Willi syndrome: a magnetic resonance imaging study of differences in cerebral structure. Am J Med Genet 1993;46:26–33.
- 103 Yamada K, Matsuzawa H, Uchiyama M, Kwee IL, Nakada T: Brain developmental abnormalities in Prader-Willi syndrome detected by diffusion tensor imaging. Pediatrics 2006;118:E442–E448.
- 104 Miller JL, Couch JA, Schmalfuss I, He G, Liu Y, Driscoll DJ: Intracranial abnormalities detected by three-dimensional magnetic resonance imaging in Prader-Willi syndrome. Am J Med Genet A 2007; 143:476–483.
- 105 Miller JL, Goldstone AP, Couch JA, Shuster J, He G, Driscoll DJ, Liu Y, Schmalfuss IM: Pituitary abnormalities in Prader-Willi syndrome and early-onset morbid obesity. Am J Med Genet 2007, Part A, in press.
- 106 Shapira NA, Lessig MC, He GA, James GA, Driscoll DJ, Liu Y: Satiety dysfunction in Prader-Willi syndrome demonstrated by fMRI. J Neurol Neurosurg Psych 2005;76:260–262.
- 107 Hinton EC, Holland AJ, Gellatly MS, Soni S, Patterson M, Ghatei MA, Owen AM: Neural representations of hunger and satiety in Prader-Willi syndrome. Int J Obes 2005;30:313–321.
- 108 Holsen LM, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, Nollen NL, Savage CR: Neural mechanisms underlying hyperphagia in Prader-Willi Syndrome. Obesity 2006;14: 1028–1037.
- 109 Miller JL, James GA, Goldstone AP, Couch JA, He G, Driscoll DJ, Liu Y: Enhanced activation of reward-mediating prefrontal regions in response to food stimuli in Prader-Willi syndrome. J Neurol Neurosurg Psychiatry 2007;78:615–619.
- 110 Maina EN, Webb T, Soni S, Whittington J, Boer H, Clarke D, Holland A: Analysis of candidate imprinted genes in PWS subjects with atypical genetics: a possible inactivating mutation in the SNURF/SNRPN minimal promoter. J Hum Genet 2007;52:297–307.
- 111 Oeffner F, Korn T, Roth H, Ziegler A, Hinney A, Goldschmidt H, Siegfried W, Hebebrand J, Grzeschik KH: Systematic screening for mutations in the human necdin gene (NDN): identification of two naturally occurring polymorphisms and association analysis in body weight regulation. Int J Obes Relat Metab Disord 2001;25:767–769.

- 112 O'Neill MA, Farooqi IS, Wevrick R: Evaluation of Prader-Willi Syndrome gene MAGEL2 in severe childhood-onset obesity. Obes Res 2005;13: 1841–1842.
- 113 Meyre D, Lecoeur C, Delplanque J, Francke S, Vatin V, Durand E, Weill J, Dina C, Froguel P: A genome-wide scan for childhood obesity-associated traits in French families shows significant linkage on chromosome 6q22.31-q23.2. Diabetes 2004;53:803–811.
- 114 Feitosa MF, Borecki IB, Rich SS, Arnett DK, Sholinsky P, Myers RH, Leppert M, Province MA: Quantitative-trait loci influencing body-mass index reside on chromosomes 7 and 13: the National Heart, Lung, and Blood Institute Family Heart Study. Am J Hum Genet 2002;70:72–82.
- 115 Varela MC, Simoes-Sato AY, Kim CA, Bertola DR, de Castro CI, Koiffmann CP: A new case of interstitial 6q16.2 deletion in a patient with Prader-Willilike phenotype and investigation of SIM1 gene deletion in 87 patients with syndromic obesity. Eur J Med Genet 2006;49:298–305.
- 116 Holder JLJ, Butte NF, Zinn AR: Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. Hum Mol Genet 2000;9: 101–108.
- 117 Michaud JL, Boucher F, Melnyk A, Gauthier F, Goshu E, Levy E, Mitchell GA, Himms-Hagen J, Fan CM: Sim1 haploinsufficiency causes hyperphagia, obesity and reduction of the paraventricular nucleus of the hypothalamus. Hum Mol Genet 2001;10: 1465–1473.
- 118 Holder Jr JL, Zhang L, Kublaoui BM, DiLeone RJ, Oz OK, Bair CH, Lee YH, Zinn AR: Sim1 gene dosage modulates the homeostatic feeding response to increased dietary fat in mice. Am J Physiol Endocrinol Metab 2004;287:E105–E113.
- 119 Kublaoui BM, Holder JL Jr, Tolson KP, Gemelli T, Zinn AR: SIM1 overexpression partially rescues agouti yellow and diet-induced obesity by normalizing food intake. Endocrinol 2006;147:4542–4549.
- 120 Kublaoui BM, Holder JL Jr, Gemelli T, Zinn AR: Sim1 haploinsufficiency impairs melanocortin-mediated anorexia and activation of paraventricular nucleus neurons. Mol Endocrinol 2006;20: 2483–2492.
- 121 D'Angelo CS, Da Paz JA, Kim CA, Bertola DR, Castro CI, Varela MC, Koiffmann CP: Prader-Willilike phenotype: investigation of 1p36 deletion in 41 patients with delayed psychomotor development, hypotonia, obesity and/or hyperphagia, learning disabilities and behavioral problems. Eur J Med Genet 2006;49:451–460.
- 122 Phelan MC, Rogers RC, Clarkson KB, Bowyer FP, Levine MA, Estabrooks LL, Severson MC, Dobyns WB: Albright hereditary osteodystrophy and del(2) (q37.3) in four unrelated individuals. Am J Med Genet 1995;58:1–7.

- 123 Wilson LC, Leverton K, Oude Luttikhuis ME, Oley CA, Flint J, Wolstenholme J, Duckett DP, Barrow MA, Leonard JV, Read AP: Brachydactyly and mental retardation: an Albright hereditary osteodystrophy-like syndrome localized to 2q37. Am J Hum Genet 1995;56:400–407.
- 124 Shrimpton AE, Braddock BR, Thomson LL, Stein CK, Hoo JJ: Molecular delineation of deletions on 2q37.3 in three cases with an Albright hereditary osteodystrophy-like phenotype. Clin Genet 2004; 66:537–544.
- 125 Polityko A, Maltseva O, Rumyantseva N, Khurs O, Seidel J, Claussen U, Weise A, Liehr T, Starke H: Two further AHO-like syndrome patients with deletion of glypican 1 gene region in 2q37.2-q37.3. Int J Mol Med 2004;14:977–979.
- 126 Cormier-Daire V, Molinari F, Rio M, Raoul O, De Blois MC, Romana S, Vekemans M, Munnich A, Colleaux L: Cryptic terminal deletion of chromosome 9q34: a novel cause of syndromic obesity in childhood? J Med Genet 2003;40:300–303.
- 127 Neas KR, Smith JM, Chia N, Huseyin S, St Heaps L, Peters G, Sholler G, Tzioumi D, Sillence DO, Mowat D: Three patients with terminal deletions within the subtelomeric region of chromosome 9q. Am J Med Genet A 2005;132:425–430.
- 128 Harada N, Visser R, Dawson A, Fukamachi M, Iwakoshi M, Okamoto N, Kishino T, Niikawa N, Matsumoto N: A 1-Mb critical region in six patients with 9q34.3 terminal deletion syndrome. J Hum Genet 2004;49:440–444.
- 129 Cotter PD, Kaffe S, McCurdy LD, Jhaveri M, Willner JP, Hirschhorn K: Paternal uniparental disomy for chromosome 14: a case report and review. Am J Med Genet 1997;70:74–79.
- 130 Kurosawa K, Sasaki H, Sato Y, Yamanaka M, Shimizu M, Ito Y, Okuyama T, Matsuo M, Imaizumi K, Kuroki Y, Nishimura G: Paternal UPD14 is responsible for a distinctive malformation complex. Am J Med Genet 2002;110:268–272.
- 131 Mitter D, Buiting K, von Eggeling F, Kuechler A, Liehr T, Mau-Holzmann UA, Prott EC, Wieczorek D, Gillessen-Kaesbach G: Is there a higher incidence of maternal uniparental disomy 14 [upd(14) mat]? Detection of 10 new patients by methylation-specific PCR. Am J Med Genet A 2006;140: 2039–2049.
- 132 Fryns JP, Haspeslagh M, Dereymaeker AM, Volcke P, van den BH: A peculiar subphenotype in the fra(X) syndrome: extreme obesity-short stature-stubby hands and feet-diffuse hyperpigmentation. Further evidence of disturbed hypothalamic function in the fra(X) syndrome? Clin Genet 1987;32: 388–392.
- 133 de Vries BB, Fryns JP, Butler MG, Canziani F, Wesby-van Swaay E, van Hemel JO, Oostra BA, Halley DJ, Niermeijer MF: Clinical and molecular studies in fragile X patients with a Prader-Willi-like phenotype. J Med Genet 1993;30:761–766.

- 134 Borjeson M, Forssman H, Lehmann O: An X-linked, recessively inherited syndrome characterized by grave mental deficiency, epilepsy, and endocrine disorder. Acta Med Scand 1962;171: 13–21.
- 135 Birrell G, Lampe A, Richmond S, Bruce SN, Gecz J, Lower K, Wright M, Cheetham TD: Borjeson-Forssman-Lehmann syndrome and multiple pituitary hormone deficiency. J Pediatr Endocrinol Metab 2003;16:1295–1300.
- 136 Lower KM, Turner G, Kerr BA, Mathews KD, Shaw MA, Gedeon AK, Schelley S, Hoyme HE, White SM, Delatycki MB, Lampe AK, Clayton-Smith J, Stewart H, van Ravenswaay CM, de Vries BB, Cox B, Grompe M, Ross S, Thomas P, Mulley JC, Gecz J: Mutations in PHF6 are associated with Borjeson-Forssman-Lehmann syndrome. Nat Genet 2002;32: 661–665.
- 137 Gecz J, Turner G, Nelson J, Partington M: The Borjeson-Forssman-Lehman syndrome (BFLS, MIM #301900). Eur J Hum Genet 2006;14: 1233–1237.
- 138 Crawford J, Lower KM, Hennekam RC, Van Esch H, Megarbane A, Lynch SA, Turner G, Gecz J: Mutation screening in Borjeson-Forssman-Lehmann syndrome: identification of a novel de novo PHF6 mutation in a female patient. J Med Genet 2006;43: 238–243.

- 139 Moretti-Ferreira D, Koiffmann CP, Listik M, Setian N, Wajntal A: Macrosomia, obesity, macrocephaly and ocular abnormalities (MOMO syndrome) in two unrelated patients: delineation of a newly recognized overgrowth syndrome. Am J Med Genet 1993;46:555–558.
- 140 Zannolli R, Mostardini R, Hadjistilianou T, Rosi A, Berardi R, Morgese G: MOMO syndrome: a possible third case. Clin Dysmorphol 2000;9:281–284.
- 141 Davenport JR, Watts AJ, Roper VC, Croyle MJ, van Groen T, Wyss JM, Nagy TR, Kesterson RA, Yoder BK: Disruption of intraflagellar transport in adult mice leads to obesity and slow-onset cystic kidney disease. Curr Biol 2007;17:1586–1594.
- 142 Krepischi-Santos AC, Vianna-Morgante AM, Jehee FS, Passos-Bueno MR, Knijnenburg J, Szuhai K, Sloos W, Mazzeu JF, Kok F, Cheroki C, Otto PA, Mingroni-Netto RC, Varela M, Koiffmann C, Kim CA, Bertola DR, Pearson PL, Rosenberg C: Wholegenome array-CGH screening in undiagnosed syndromic patients: old syndromes revisited and new alterations. Cytogenet Genome Res 2006;115: 254–261.
- 143 Zung A, Rienstein S, Rosensaft J, Aviram-Goldring A, Zadik Z: Proximal 19q trisomy: a new syndrome of morbid obesity and mental retardation. Horm Res 2006;67:105–110.

Anthony P. Goldstone Senior Clinician Scientist and Consultant Endocrinologist MRC Clinical Sciences Centre, Imperial College London Hammersmith Hospital Campus Du Cane Road, London W12 0NN (UK) Tel. + 44 20 8383 1029, Fax +44 20 8743 5409, E-Mail tony.goldstone@imperial.ac.uk