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## Cilia Signaling and Obesity

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### Abstract

An emerging number of rare genetic disorders termed ciliopathies are associated with pediatric obesity. It is becoming clear that the mechanisms associated with cilia dysfunction and obesity in these syndromes are complex. In addition to ciliopathic syndromic forms of obesity, several cilia-associated signaling gene mutations also lead to morbid obesity. While cilia have critical and diverse functions in energy homeostasis including their roles in centrally mediated food intake as well as in peripheral tissues many questions remain. Here, we briefly discuss the syndromic ciliopathies and monoallelic cilia signaling gene mutations associated with obesity. We also describe potential ways cilia may be involved in common obesity. We discuss how neuronal cilia impact food intake potentially through leptin signaling and changes in ciliary G protein-coupled receptor (GPCR) signaling. We highlight several recent studies that have implicated the potential for cilia in peripheral tissues such as adipose and the pancreas to contribute to metabolic dysfunction. Then we discuss the potential for cilia to impact energy homeostasis through their roles in both development and adult tissue homeostasis. The studies discussed in this review highlight how a comprehensive understanding of the requirement of cilia for the regulation of diverse biological functions will contribute to our understanding of common forms of obesity.

### Keywords

cilia; Bardet-Biedl syndrome; Alström syndrome; ciliopathy; obesity; adipose; pancreas; hypothalamus; neurons; Intraflagellar transport; Hedgehog; G protein-coupled receptors; GPCR; leptin; transition zone; Rpgrip11; FTO

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## Introduction

Obesity is a major growing public health concern [1]. The secondary health consequences including heart disease, high blood pressure, diabetes mellitus and osteoarthritis can reduce quality of life and lead to early mortality [2]. Historically, obesity has been viewed as increased body fat due to overconsumption of food combined with a sedentary lifestyle. This viewpoint largely focuses on environmental and social factors; it fails to take into account evidence that indicates a profound role for genetic contributions (for a review on obesity-associated genetic syndromes see [3]). While most monogenetic human conditions involving morbid obesity are rare, it is clear that the study of their molecular and cellular etiology will offer insights into the mechanisms that regulate appetite and satiety. The objectives of this review are to discuss syndromic forms of obesity that impact genes required for the formation or function of small hair-like cellular appendages called cilia. We also discuss the potential that cilia genes may play a role in common forms of obesity. How cilia dysfunction in both the brain and peripheral tissues may contribute to obesity is discussed by reviewing mouse and cell model data. Interesting data from genetic mouse models of ciliopathies has revealed the importance of cilia in both development and homeostasis. Ultimately, an understanding of how these organelles function to regulate energy homeostasis may reveal opportunities to address a major public health concern.

### 1. Ciliopathy Genes Associated with Human Obesity

**1.1 Ciliopathy Syndromes and Obesity**—Ciliopathies are genetic disorders associated with deficits in cilia formation, maintenance and function. As cilia are nearly ubiquitous throughout the body, these disorders present with a wide range of features impacting all organ systems [4]. Certain ciliopathies present with pediatric obesity including Bardet-Biedl syndrome (BBS, OMIM #209900), Alström syndrome (ALMS, OMIM #203800), Mental retardation, truncal obesity, retinal dystrophy and micropenis syndrome (MORM, OMIM #610156) and Carpenter syndrome (CRPT1, OMIM #201000).

BBS affects 1 in 100,000 newborns, with higher prevalence in consanguineous and geographically isolated populations, where the disease can affect as many as 1 in 17,000 individuals [5]. In addition to obesity, these children present with developmental delay, renal failure, retinitis pigmentosa, hypogonadism and polydactyly [6, 7]. They also show a higher rate of metabolic syndrome including an increased risk for type 2 diabetes [7]. To date, mutations in 22 genes have been identified to cause the disease [7–12]. Several BBS genes encode for proteins that are associated with two larger complexes, one called the BBSome which is important for transport of signaling proteins and receptors to and from cilia [13–17] and the other is a chaperone complex associated with BBSome assembly [18].

Unlike the heterogenetic nature of BBS, Alström syndrome (ALMS) is monogenic, with loss-of-function mutations found in the ALMS1 gene [19, 20]. ALMS is rare with an apparent worldwide prevalence of less than 1 in a million individuals [21]. While ALMS patients present with childhood truncal obesity and hypogonadism, they also have an earlier onset of type 2 diabetes, visual loss, progressive hearing loss, short stature and cardiomyopathy [20, 22]. ALMS1 protein localizes to centrioles and the base of cilia where

it is thought to be important for proper cilia function, maintenance and allowing signaling proteins in and out of the organelle [23–27].

Clinical efforts are being made to treat the obesity in BBS and ALMS patients. Currently, phase 3 clinical trials of Setmelanotide, a Melanocortin-4 receptor (MC4R) agonist, are underway with the aim to reduce appetite and increase energy expenditure ([ClinicalTrials.gov Identifier: NCT03746522](https://clinicaltrials.gov/ct2/show/study/NCT03746522)) [28, 29]. Interestingly, it has also recently been reported that Methionine aminopeptidase 2 inhibitors (MetAP2i) are able to reduce hyperphagia in obese ciliopathy mouse models [30]. Previous clinical studies of MetAP2i in Prader-Willi syndrome (PWS, OMIM #176270) patients showed weight loss through reduced food intake [31, 32]. Though clinical trials of MetAP2i have been suspended, development of next generation MetAP2i compounds could be beneficial for ciliopathy patients.

In addition to BBS and ALMS, other rare syndromes such as MORM and Carpenter syndromes, as well as monogenic alleles of adenylate cyclase 3 (*ACIII*), *MC4R*, and the inorganic pyrophosphate transporter *ANKH*, have been associated with cilia dysfunction and obesity. Both MORM and Carpenter syndromes are extremely rare autosomal recessive ciliopathies [6, 33]. MORM syndrome is clinically defined by its acronym, mental retardation, early onset truncal obesity, non-progressive retinal dystrophy and micropenis in males. Carpenter syndrome includes similar features with skeletal and craniofacial malformations, polydactyly, heart and eye defects, childhood obesity as well as hydrocephaly and intellectual disability [34–36]. Both arise from mutations in genes that encode for cilia-specific enzymes. In MORM, the lipid phosphatase, inositol polyphosphate-5-phosphatase E (*INPP5E*) is mutated [6, 33, 37]. *INPP5E* is found predominantly in the cilia transition zone where it is thought to help establish cilia sub-compartmentalization important for proper signaling [38–40]. The Rab-GTPase, *RAB23* is mutated in Carpenter syndrome [34–36]. *Rab23* is important for proper trafficking of ciliary proteins and receptors as well as negative regulation of hedgehog signaling. [41–44]. The primary cilium is required for proper hedgehog signaling in mammals (For an in-depth review of hedgehog signaling and primary cilia see Kopinke, Norris and Mukhopadhyay in this edition). Interestingly, disruption in hedgehog signaling produces severe clinical features such as abnormal development of the nervous system, facial structure, and limbs. Mutations in pathway ligand sonic hedgehog as well as downstream genes result in a disorder known as Holoprosencephaly (HPE), in which patients develop an abnormal brain and facial structure, with frequent midfacial clefts [45–47]. Additionally, patients with mutations in the ligands Indian hedgehog and desert hedgehog exhibit defects in skeletal and sexual development [48–52]. Many ciliopathy phenotypes such as polydactyly, external genitalia anomalies, and craniofacial defects are reminiscent of *Shh* pathway deficiencies [53, 54]. While there are currently no functional data linking hedgehog defects to human obesity, it is possible that hedgehog deficiency contributes to ciliopathy-associated obesity given that the hedgehog pathway relies on the primary cilium in mammals and that human genetic defects in this pathway cause phenotypes observed in ciliopathies. In this review, we further discuss animal and *in vitro* studies of the hedgehog pathway and potential implications in obesity.

Other ciliary genes implicated in monogenic forms of obesity are ANKH and centrosomal protein 19 (CEP19) [55, 56]. The *ANKH* gene encodes an inorganic pyrophosphate transporter that is involved in bone calcium homeostasis and localizes to cilia and basal bodies [57, 58]. While ANKH is known for its role in mineralization, mutations of the gene identified in a subset of Russian population are associated with increased BMI, waist-to-hip ratio and levels of plasma leptin [55]. How ANKH or its ciliary localization play a role in energy homeostasis is not known. However, a recent study shows mice lacking osteoblast-specific genes are fat and glucose intolerant indicating a role of the skeleton in endocrine regulation [59]. This combined with the correlation of ANKH with leptin suggests an indirect role for the protein in peripheral tissues such as adipocytes. On the other hand, autosomal recessive mutations in *CEP19* result in obesity in a large Israeli family [56]. CEP19 exclusively localizes to basal bodies of cilia to facilitate ciliogenesis and trafficking of ciliary GPCRs. [56, 60, 61]. Furthermore, CEP19 knockout mice recapitulated the human phenotype and displayed hyperphagia along with an increase in adipogenesis [56].

**1.2 Obesity Associated Gene Mutations in Cilia Signaling Proteins**—It has been a challenge for Genome-Wide Association Studies (GWAS) to arrive at consistent results for understanding the complex genetic contributions to obesity [62, 63]. These types of approaches have begun to implicate cilia-associated genes, not just in rare ciliopathy patients as described above. Interestingly, the most commonly mutated gene found in monoallelic morbid obesity is *MC4R* [64, 65]. These patients are hyperphagic, have increased fat and lean mass with homozygous patients presenting a more severe phenotype [66]. MC4R is a neuronal G $\alpha_s$ -coupling GPCR that regulates energy homeostasis and was recently found to be localized to the cilia [67, 68]. In healthy individuals, MC4R is activated by  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH) to decrease food intake when energy requirements are met [67, 69]. Clinical trials for MC4R agonists are currently underway for syndromic and non-syndromic obesity [28, 70]. Interestingly, a recent GWAS done in the United Kingdom identified gain-of-function variants in *MC4R* that were associated with lower BMI and decreased risk of obesity and type 2 diabetes. The identification of these protective variants warrants the search for newer strategies to induce weight loss in obese individuals [65].

Another gene now recognized to have a cilia role and found in human obesity is *ACIII*. Variants in *ACIII* identified in GWAS have been associated with increased BMI and type 2 diabetes [71, 72]. It was recently shown that some of these are loss-of-function variants [73–75]. ACIII catalyzes ATP to cAMP upon activation of G $\alpha_s$ -coupled GPCRs. Furthermore, ACIII is almost ubiquitously localized on cilia in the central nervous system and mice lacking ACIII are obese suggesting that ciliary localization of ACIII plays an important role in energy homeostasis [76, 77].

A striking example of GWAS comes from single-nucleotide polymorphisms (SNPs) found in the *Fat Mass and Obesity-Associated (FTO)* gene that correlate with increased body weight [78–80]. While FTO itself is not known to have any function in cilia, the *FTO* gene is located less than 100 base pairs from a cilia transition zone gene, *retinitis pigmentosa GTPase regulator-interacting protein-1 like (RPGRIP1L)* [81, 82]. This close proximity is interesting because the SNPs in *FTO* can change the expression of *RPGRIP1L* [83]. In fact,

one of these SNPs is in a regulatory site of the transcription factor CUT-like homeobox 1 (*CUX1*), whose activity modulates expression of both *FTO* and *RPGRIP1L in vitro* [83]. In mice, complete loss of *Rpgrip1l* is embryonic lethal but body weight analysis of heterozygous animals shows they are heavier than controls [84, 85]. Further, conditional loss of *Rpgrip1l* in adult mice leads to obesity [86, 87].

These findings on *FTO/RPGRIP1L* gene regulation may serve as an example of how other frequent SNPs near cilia genes might impact obesity. Recently a candidate-gene approach to analyze European GWAS data revealed SNPs in syndromic obesity genes frequently contribute to BMI variation. Strikingly, they found many SNPs in genes that have a role in primary cilia including 11 genes related to BBS, *RAB23*, and *TUB*, a member to the Tubby family of bipartite transcription factors [88]. Future studies assessing how accumulation of seemingly innocuous SNPs in cilia genes may contribute to more commonly observed forms of obesity could reveal unrecognized themes for how cilia impact energy homeostasis.

## 2 Cilia in the Central Nervous System and Feeding Behavior

Neurons and most cell types throughout the central nervous system possess primary cilia [76, 89, 90]. Yet, understanding the function of neuronal cilia has remained a challenge. As new approaches and tools have begun to be established to allow their visualization [91] it has become clear that neuronal cilia likely play diverse signaling roles throughout the brain and impact several behaviors including feeding.

Initial conditional mouse approaches to disrupt cilia formation through intraflagellar transport (IFT) alleles, (for a review of IFT see [92]), were useful for obtaining a broad understanding of phenotypes that emerge upon cilia dysfunction, including altered energy homeostasis. Near ubiquitous cilia loss in adult mice results in hyperphagia and subsequent obesity [93]. Controlling for food intake in pair-feeding experiments of conditional IFT mutants prevented obesity, indicating that cilia restrict weight gain by inhibiting the consumption of food rather than by affecting metabolism or locomotor activity. Using this same approach to remove cilia from neurons recapitulated the obesity phenotype and demonstrated a role for neuronal cilia in feeding behavior [93].

**2.1 Leptin Signaling and Cilia**—The small protein hormone, leptin, is produced in the periphery by white adipose tissue and acts on neurons to control food intake. The classic role of leptin is to act on agouti-related protein (AGRP) and proopiomelanocortin (POMC) neurons within the arcuate nucleus of the hypothalamus resulting in diminished food intake (For reviews see [94, 95]). A potential molecular mechanism for cilia in feeding behavior was revealed when studying mouse models of BBS, which display obesity like human patients [96–98]. BBS1, a component of the BBSome, was found to directly bind to the leptin receptor and participate in proper leptin receptor trafficking [99]. Similar to other models of leptin signaling deficiency, *ad libitum* fed *Bbs* mutant mice have elevated serum leptin levels [99, 100]. These *Bbs* mutants also fail to reduce food intake in response to injection of leptin, raising the possibility that a diminished response to leptin contributes to obesity in BBS [100]. Nearly all obese mice and humans show elevated levels of circulating leptin, but this leptin is insufficient to suppress appetite, a phenomenon known as leptin

resistance (for a review on leptin see [94]). Thus, leptin resistance can be either a cause or a consequence of obesity. Interestingly, when caloric restriction was used to normalize leptin levels in *Bbs* mutant mice they still failed to respond to leptin with diminished food intake [99]. However, these studies did not take into account the food anticipatory behavior that is observed upon calorie restriction.

A growing literature reports that maintaining calorie restriction in rodents can have prolonged effects on meal structure and circadian rhythm (for a review on mouse feeding behavior, see [101]). If both body composition and anticipatory feeding behavior are controlled for, adult mice lacking *Ift88* or *Bbs4* mutant mice, before the onset of obesity, display unaltered responses to leptin [102]. Leptin receptor activity was similar between these ciliopathy models and control mice, and other phenotypes associated with leptin and leptin receptor mutations, such as changes in thermoregulation and locomotor activity, are not observed. These data suggest that cilia are not directly involved in leptin signaling [102]. Further work by Guo *et al.* report a cilium-independent function of the BBSome [103]. It appears to be required for trafficking of leptin receptors to the plasma membrane, and in *Bbs* mutants the obesity appears to be primarily a result of deficits in leptin sensitivity. This is in contrast to their findings with conditional loss of *Ift88* in which they report leptin resistance upon increases in adiposity. This work begins to show that cilia mutant mouse models may display obesity through different and independent mechanisms [103]. These data also highlight the overall complexity of the cilia-associated obesity phenotype.

**2.2 Neuronal Cilia GPCRs and Obesity**—GPCR misregulation has emerged as a focus of many studies on how cilia centrally regulate appetite and satiety. Several GPCRs appear preferentially enriched at the membrane of primary cilia, some of which have well recognized roles in feeding behavior or energy homeostasis, including melanin-concentrating hormone receptor 1 (MCHR1), MC4R, neuropeptide Y receptors 2 and 5 (NPY2R and NPY5R), somatostatin receptor 3 (SSTR3), kisspeptin 1 receptor (KISS1R), serotonin receptor 6 (5HT6), dopamine receptor 1 (DRD1) [14, 68, 89, 90, 104–106].

Interestingly in mouse models of BBS, some GPCRs that are normally found in cilia no longer appear to localize to the compartment such as MCHR1 and SSTR3 [13]. Additionally, NPY2R fails to localize to primary cilia in mice lacking the BBSome subunit BBIP10 (*Bbip10*) [105]. NPY2R ciliary localization was also found to be decreased when *Bbs1* is lost specifically from POMC or AGRP neurons [107]. Furthermore, recent studies have revealed a role for the BBSome in dynamically transporting GPCRs across the transition zone of cilia [108–110]. These data indicate that the BBSome is important for proper localization of GPCRs and suggests that impaired signaling due to their mislocalization could contribute to obesity in BBS.

In ALMS mouse models, ciliary GPCRs appear to localize properly. However, the cilia signaling protein, ACIII, shows decreased localization [24]. Without ACIII, which is activated via  $G\alpha_s$ -coupled GPCRs, the normal downstream intracellular signaling events required to maintain a normal body weight may be impaired. In fact in an ACIII knock out mouse model, obesity occurs through decreased activity and increased food intake [77].

Furthermore, inhibiting ACIII specifically in a population of neurons in the PVN also leads to weight gain [68].

The most recent GPCR found to localize to primary cilia is MC4R [68]. Using *in situ* hybridization, MC4R was found to be expressed throughout the brain of rodents including the hypothalamus [67]. In mice, loss of *Mc4r* results in hyperphagia and obesity [111]. Using a GFP tag, MC4R can be seen in cilia of neurons within the paraventricular nucleus of the hypothalamus (PVN). Intriguingly, some of the mutations in *MC4R* that result in obesity in humans described above result in decreased localization of MC4R in cilia [68]. It remains to be seen if mutations associated with ciliopathies impact MC4R function.

Several proteins are needed to properly transport GPCRs into and out of the cilium. It is likely that the mechanisms are different for different ciliary GPCRs. Proteins like the atypical small GTPase RAB-like 2 (RABL2), CEP19, and TUB all have roles in transporting GPCRs to the cilia and also play a role in maintaining normal adult mouse body weight. *Rabl2* knockout mice become obese with age and recently it was found that without RABL2, ciliary GPCRs like GPR161 and 5HT6 are absent from primary cilia [61, 112]. Similarly, *Cep19* knockout mice are obese and fail to localize GPR161 to cilia [56, 61]. Obese tubby knockout mice also fail to localize SSTR3, MCHR1, and NPY2R to cilia [105, 113, 114].

The impact of the subcellular localization of these receptors in regulating feeding is not well understood. Perhaps they localize to the ciliary compartment in order to interact with specific G-proteins to produce appropriate second messengers or even to interact with other GPCRs that are also found within the cilium. For example, it has been shown that SSTR3 and MCHR1 found in the same cilium physically interact by forming heteromers [115]. Other studies have shown that ciliary GPCR signaling interacts with the ciliary hedgehog pathway. For example, GPR161, is known to influence Hedgehog pathway activity in development but little is known about functions in adult neurons [116, 117]. In the olfactory system, when smoothed, a GPCR in the hedgehog pathway, is knocked out from olfactory sensory neurons, odorant GPCRs cilia localization is attenuated [118]. Other data supporting interactions between the hedgehog pathway and GPCR signaling comes from primary hypothalamic cultures. Pharmacological activation of smoothed inhibits response to the MCHR1 agonist melanin-concentrating hormone [119]. Further studies will reveal how these pathways interact and how their localization to cilia influences their signaling and ability to modulate feeding behavior.

### 3. Cilia in Peripheral Tissues and Metabolic Phenotypes

In addition to obesity, ciliopathies like BBS and ALMS are also associated with clinical features such as type 2 diabetes and non-alcoholic fatty liver disease [120]. How cilia in peripheral tissues impact metabolism and energy homeostasis is unclear. A growing body of literature suggests that functional cilia on preadipocytes are critical for coordinating adipogenesis. Additionally, cilia have been suggested to be important for normal pancreatic morphology and function. In this section, we outline a few examples of how cilia are involved in the proper functioning of adipose tissue and the pancreas.

**3.1 Cilia in Adipose Tissue**—White adipose tissue not only serves as a site of calorie storage after feeding and the source of circulating free fatty acids during fasting but also plays an important endocrine role [121, 122]. Metabolic diseases such as obesity, type 2 diabetes, and lipodystrophies can be characterized by dysfunction of adipose tissue [123]. While the predominant cell type in adipose is mature adipocytes, the tissue is comprised of a variety of other cell types such as endothelial cells, blood cells, fibroblasts, pericytes, and preadipocytes [124]. Preadipocytes arise from mesenchymal stem cells, which can produce mature adipocytes through the process of adipogenesis [125]. However, the regulation and cellular signaling associated with this differentiation process is not fully understood [126]. It has been demonstrated that preadipocytes possess a primary cilium during differentiation and that it plays a critical role in their ability to become adipocytes [127–129]. Specifically, knockdown of BBS proteins (BBS10 and BBS12) which localize to the primary cilia induces adipogenesis. Furthermore, BBS patient derived preadipocytes accumulate more fat than controls upon differentiation *in vitro* [128]. Commensurate with these findings knockdown of *BBS12* in human primary mesenchymal stem cells also facilitated adipogenesis [130]. Additionally, this study showed that *Bbs12* knockout mice, despite being obese, were glucose and insulin tolerant and that this phenotype recapitulates observations in patients [130]. These results suggest that BBS patients are predisposed to adiposity through increases in adipogenesis.

Two recent studies provide further evidence for the roles of cilia in adipocyte differentiation. Kopinke *et al.* demonstrate that cilia-mediated hedgehog signaling is important for restricting Fibro/adipogenic progenitors in muscle from becoming adipocytes [127], suggesting an active role for hedgehog in adipogenesis. In another recent study by Hilgendorf *et al.*, conditional knockout of cilia in mouse preadipocytes resulted in reduced body weight due to a reduction in total fat mass. Furthermore, the GPCR, omega-3 fatty acid receptor FFAR4/GPR120, was found to localize to the primary cilia in preadipocytes. Interestingly, FFAR4 agonists and omega-3 fatty acids triggered mitosis and adipogenesis [131]. These findings suggest that cilia are important for adipogenesis mediated by preadipocytes in response to external cues. Future studies assessing the roles of cilia in different adipose tissue cell types and diseases such as obesity and lipid dystrophies may reveal interesting themes regarding cilia signaling.

Data from multiple systems suggest hedgehog signaling is important in adult energy homeostasis. A genome-wide RNAi screen in adult *Drosophila* identified the Hedgehog pathway as being fat specific and obesity related [132]. It has also been demonstrated in the fat body of *Drosophila* that lipid accumulation is repressed or enhanced by Hedgehog activation and inhibition respectively [133]. Furthermore, the *Drosophila* lipoprotein-associated form of hedgehog is secreted from the gut and signals to the fat body to broadly regulate lipid mobilization in order to couple growth to development [134, 135].

As described, hedgehog signaling is critical for proper adipocyte differentiation, and this process is perturbed in ciliopathy model systems. Further evidence that hedgehog pathway deficiency underlies ciliopathy phenotypes after development is suggested by data showing that the BBSome plays roles in proper ciliary trafficking of both patched and smoothened and mislocalize in *Bbs7* knockout cells [136]. In mice, hedgehog inhibits adipogenesis

and pathway activity is reduced in the adipose of obese animals [133]. Furthermore, it was demonstrated that adipose specific conditional activation of the hedgehog pathway results in white adipose reduction, but not brown [132]. However, in a separate study it was shown that *in vivo* activation of hedgehog signaling in adipose through deletion of *Ptch1* or overexpression of *SmoM2* both inhibited the formation of brown adipose tissue [137]. Through the use of inducible promoters it was further shown that hedgehog pathway activation resulted in a lean phenotype with a reduction in white adipose and improvements in whole-body glucose tolerance and insulin sensitivity [138]. It is interesting that both hedgehog pathway activation and cilia loss inhibits adipogenesis. Similarly, as we have previously discussed, BBS deficient preadipocytes are prone to adipogenesis. It should be noted that BBS defects do not often lead to complete cilia loss [96–98, 139]. Taken as a whole these findings suggest that properly functioning cilia on preadipocytes are required to coordinate multiple signaling pathways for appropriate adipogenesis to occur.

**3.2 Cilia in the Pancreas**—The pancreas is primarily responsible for glucose homeostasis and the release of digestive enzymes. It is composed of multiple cell types including endocrine cells, acinar cells, and ductal cells [140]. Initial links between cilia and pancreatic function come from polycystic kidney disease patients and their associated pancreatic pathologies [141, 142]. Indeed, cilia are present in both islet and ductal cells and the classic cilia hypomorphic Oak Ridge Polycystic Kidney (*Orpk*) mouse model of polycystic kidney disease exhibits changes in pancreas morphology and function [143, 144]. In *Bbs4* knockout mice, defects in glucose homeostasis are observed prior to the onset of obesity and insulin secretion is impaired following knockdown of *Bbs4 ex vivo* [145]. Data also suggest that the insulin receptor is directly trafficked by BBS proteins to the cell surface [146]. More recently, a critical role of cilia in  $\beta$ -cells was highlighted when conditional loss of  $\beta$ -cell cilia in adult mice led to reductions in glucose homeostasis and insulin secretion [147]. It is clear that cilia are present on diverse pancreatic cell types and future work will reveal new roles for cilia in pancreatic physiology.

The data discussed here implicate primary cilia as being critical for the proper functioning of adipose tissue and the pancreas, two peripheral organs critical for energy homeostasis. The role of primary cilia in adipogenesis and pancreatic function underlie not just the clinical phenotypes of certain ciliopathies but points to a potential involvement in general obesity and type 2 diabetes.

#### 4. Developmental and Homeostatic Roles for Cilia in Obesity

Cilia and hedgehog signaling play critical roles in hypothalamic development. Through cell fate mapping and conditional alleles it has been shown that hedgehog responsiveness and expression are dynamically regulated in the developing diencephalon [148, 149] (for a review see [150]). Additional recent studies have implicated the ciliary transition zone protein *Rpgrip11* as specifically important in differentiation of the POMC neurons in the hypothalamus. Loss of *Rpgrip11* in POMC neurons results in decreased *smoothed* expression. Induced pluripotent stem cells from Joubert syndrome patients with *Rpgrip11* mutations failed to differentiate into hypothalamic neuronal populations as compared to controls [87]. These results are interesting in light of early work demonstrating that BBS

mouse models have a loss of POMC neurons which was attributed to loss of leptin signaling [99].

Mouse models of ciliopathies have revealed complex ways in which cilia dysfunction contributes to obesity. In one example, congenital and inducible Cre recombinase-mediated removal of cilia has given insights into genes that contribute to obesity in development versus maintaining a normal body weight in adults. While systemic congenital cilia loss is lethal, using a near ubiquitously expressed inducible CAGG-CreER approach to drive cilia loss throughout the body leads to obesity when cilia are lost in adulthood [93]. Studies using a similar approach with synapsin-Cre to remove cilia from all neurons and more specifically POMC-Cre to remove cilia from only POMC neurons have shown neuronal cilia loss is sufficient to drive increases in body weight [93]. There are caveats to using congenital Cre models that can make interpretations challenging. For example, in the case of POMC-Cre, cilia loss may occur in populations of cells that transiently express the *Pomc* gene during hypothalamic development [151, 152]. Therefore, cilia loss is not limited to terminally differentiated POMC neurons and cilia loss on other cell populations may influence the obesity phenotype.

Beyond complete cilia loss, using CAGG-CreER to remove other cilia genes, such as transition zone genes, can help to understand the role of cilia in maintaining a normal adult body composition. For example, RPGRIP1L (MKS5), a transition zone member is needed to maintain a normal body weight. When ubiquitously removed in adult mice, loss of *Rpgrip1l* results in a significant increase in body weight compared to controls [86, 87]. Thus far, RPGRIP1L appears different than other transition zone proteins, such as *Cc2d2a* (MKS6), which does not result in obesity using the same conditional approach [86]. These results are intriguing and indicate several possibilities. First, cilia are important beyond patterning of the feeding regions of the brain in development. Second, certain members of the transition zone may be actively involved in signaling associated with a behavior such as feeding (in fact RPGRIP1L has been found to change expression levels based on feeding status) [83, 86]. Third, it is possible that not all cell types possess identical transition zones and in fact may have specific cell-context and functional requirements. A complete understanding of how different cilia genes are important for energy homeostasis may reveal unrecognized processes that contribute to obesity.

## Conclusions

Initially it was surprising that several rare genetic disorders having cilia dysfunction as their molecular basis present with obesity as a clinical feature. It has now led to several exciting discoveries as to how this small cellular organelle coordinates diverse aspects of feeding behavior and peripheral tissue homeostasis. As new tools for better temporal and spatial analysis of cilia and their associated signaling continue to be developed the field will continue to reveal exciting and new signaling paradigms. Continued research on rare human ciliopathies will elucidate unrecognized mechanisms behind cilia-mediated satiety, appetite, metabolism and energy homeostasis. A comprehensive understanding of cilia may reveal therapeutic opportunities to combat common forms of obesity.

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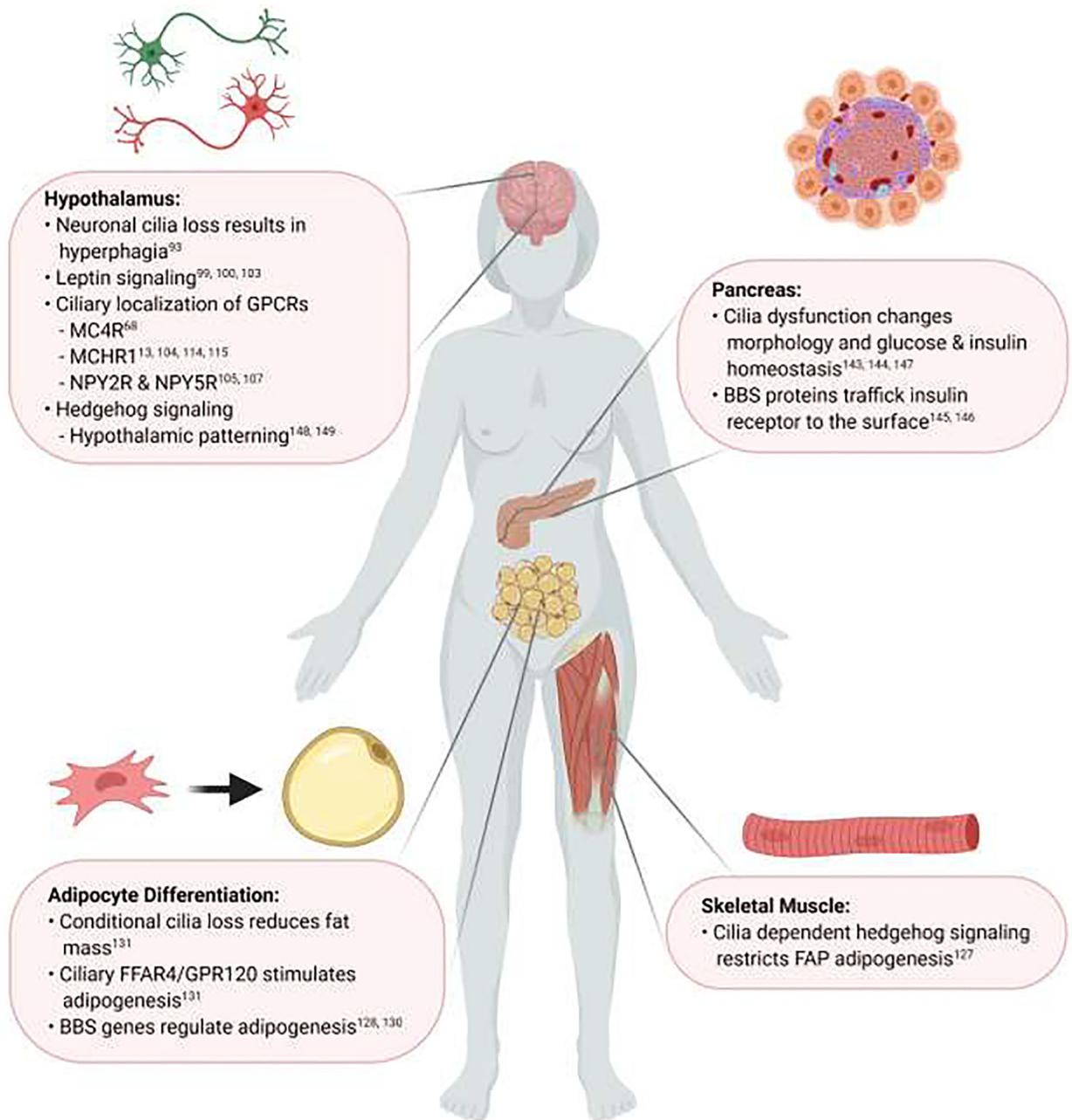
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**Figure 1: Central and Peripheral Roles of Primary Cilia in Obesity**

Cilia modulate energy homeostasis through central mediated control of feeding (Hypothalamic) and peripheral tissue signaling and homeostasis (Pancreas, Skeletal Muscle, Adipocyte Differentiation). Figure created with [BioRender.com](https://www.biorender.com).