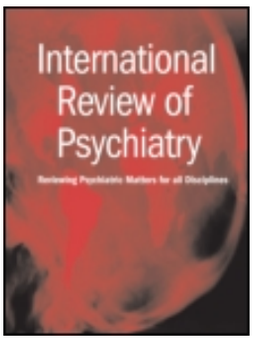

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Obesity and eating behaviour in children and adolescents: Contribution of common gene polymorphisms

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Abstract

The prevalence of childhood obesity is increasing in many countries and confers risks for early type 2 diabetes, cardiovascular disease and metabolic syndrome. In the presence of potent 'obesogenic' environments not all children become obese, indicating the presence of susceptibility and resistance. Taking an energy balance approach, susceptibility could be mediated through a failure of appetite regulation leading to increased energy intake or via diminished energy expenditure. Evidence shows that heritability estimates for BMI and body fat are paralleled by similar coefficients for energy intake and preferences for dietary fat. Twin studies implicate weak satiety and enhanced food responsiveness as factors determining an increase in BMI. Single gene mutations, for example in the leptin receptor gene, that lead to extreme obesity appear to operate through appetite regulating mechanisms and the phenotypic response involves overconsumption and a failure to inhibit eating. Investigations of robustly characterized common gene variants of fat mass and obesity associated (*FTO*), peroxisome proliferator-activated receptor (*PPARG*) and melanocortin 4 receptor (*MC4R*) which contribute to variance in BMI also influence the variance in appetite factors such as measured energy intake, satiety responsiveness and the intake of palatable energy-dense food. A review of the evidence suggests that susceptibility to childhood obesity involving specific allelic variants of certain genes is mediated primarily through food consumption (appetite regulation) rather than through a decrease in activity-related energy expenditure. This conclusion has implications for early detection of susceptibility, and for prevention and management of childhood obesity.

Introduction

Childhood obesity is a significant challenge to public health worldwide. Globally, an estimated 43 million children below the age of 5 years carry excess fat mass (de Onis et al., 2010). Many children present with symptoms of adult diseases associated with obesity. Thus impaired glucose tolerance, type 2 diabetes, cardiovascular and metabolic syndrome diseases are now commonly diagnosed in overweight children (Ferreira et al., 2007; Nadeau et al., 2011; Wiegand et al., 2005; Zimmet et al., 2007). Despite an increasingly permissive (obesogenic) environment, it is clear that not all individuals become overweight or obese; susceptibility to obesity is heterogeneous, suggesting that differences in allelic variation and genetic predisposition interact with environment to determine the expressed phenotype.

The genetic contribution to the pathogenesis of obesity is well defined. Evidence for a strong heritable link between the influence of genes and human obesity is consistently documented by twin, family and adoption studies (Maes et al., 1997). Twin studies, which typically yield the greatest heritability estimates, have indicated that heritability of BMI in children and adolescents is as much as 70–80% (Haworth et al., 2008b; Maes et al., 1997). Variation within heritability estimates for BMI across studies is probably a result of differences in study design and power, population being assessed, age, gender, and may also be related to bias in distinguishing shared environmental effects from direct genetic effects in twin studies (Salsberry & Reagan, 2010). Evidence from longitudinal studies in twins also suggests that heritability of BMI increases with age through childhood and adolescence (Dubois et al., 2012; Haworth et al., 2008b; Lajunen et al., 2009). Body fatness in children, distinct from BMI, is similarly highly heritable (Faith et al., 1999; Wardle et al., 2008a).

Consistent with genetic evidence for obesity, heritability studies have revealed that appetite and eating behaviour associated with susceptibility to weight gain are also under considerable genetic control (reviewed in Rankinen & Bouchard, 2006). Much of this work has been conducted in adults, where

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heritability estimates of the order of 65% have been observed for energy intake (de Castro, 1993); meal size, meal frequency, macronutrient intake and eating behavioural phenotypes such as restraint, hunger, emotional and uncontrolled eating are also under genetic control (de Castro, 2002; Keskitalo et al., 2008; Sung et al., 2010). In children, studies that use a family design have indicated a modest genetic contribution to energy intake and food preference (eg. Perusse et al., 1988), though when food intake is examined under controlled laboratory conditions, familial aggregation of energy intake, and preference for fat, carbohydrate and protein is significant (Faith et al., 2004). Notably, a recent family-based study using a genome-wide screening approach has revealed significant heritability estimates for dietary intake (fat, protein, carbohydrate) in children, ranging from 47–69% (Cai et al., 2006). Twin studies in children generally produce strong estimates for food intake, including frequency of eating specific foods (Breen et al., 2006; Falciglia & Norton, 1994), satiety and enjoyment of foods (Carnell et al., 2008). Hyperphagic eating behavioural traits, linked positively to weight, such as eating in the absence of hunger (EAH), used in children to measure opportunistic eating, and eating rate, are also identified as being under significant genetic control in children (Fisher et al., 2007; Llewellyn et al., 2008).

Single gene mutations have been linked to extreme obesity, identified from functional studies, and have critically advanced an understanding of key pathways regulating energy balance. The most important of these include the leptin (*LEP*), leptin receptor (*LEPR*), melanocortin 4 receptor (*MC4R*), pro-opiomelanocortin (*POMC*) and prohormone convertase 1 (*PCSK1*) genes (Farooqi & O'Rahilly, 2005) where single mutations in these genes have been linked to severe obesity in childhood and, in almost all cases, a disruption in appetite pathways that control food intake, leading to hyperphagia. These monogenic disorders are low in frequency and represent only a very small number of obese cases (5–7%) at the population level. Most known obesities are probably polygenic, involving complex gene–gene and gene–environment (nutrition, activity) interactions, providing frequent multiple but small effects. Several candidate common gene variants have been identified as contributing to variance in BMI from functional analysis, linkage scans and association studies, based on their functional role in regulating central or peripheral pathways that influence energy balance. However, the discovery of new candidate gene variants through the more recent 'genome-wide association study' (GWAS) molecular genetics approach has undoubtedly revolutionized our understanding of complex common gene variants and their contribution to polygenic obesity.

The current review focuses on some of the most robustly characterized common gene variants that contribute to human obesity and eating behaviour (food intake and eating behaviour traits) in children and adolescents from a molecular genetics evidence base, namely the fat mass and obesity associated (*FTO*) gene, peroxisome proliferator-activated receptor (*PPARG*), melanocortin 4 receptor (*MC4R*) and adrenergic receptors. Recent evidence for candidate common gene variants linked to variation in weight and patterns of eating via reward pathways are also considered. The review does not include a discussion on (pathological) eating disorders and excludes the literature on genes linked to taste.

Fat mass and obesity associated gene – a role in common obesity

A set of single nucleotide polymorphisms (SNP) in the *FTO* locus on chromosome 16, has provided the most robust evidence to date for contribution of common variants in predisposing to polygenic obesity (Dina et al., 2007; Frayling et al., 2007; Loos & Bouchard, 2008; Scuteri et al., 2007). *FTO* encodes a protein with 2-oxoglutarate-dependent nucleic acid demethylase activity (Gerken et al., 2007) concerned with metabolism of fatty acids, DNA repair, and post-translational changes (Clifton et al., 2006). *FTO* is expressed predominantly in brain, pancreatic islet tissue, adipose tissue and adrenal glands (Frayling et al., 2007). Its high expression in the hypothalamus, pituitary and adrenal glands indicates a putative role in the hypothalamic-pituitary-adrenal (HPA) axis, itself implicated in body weight and satiety regulation (Dina et al., 2007; Su et al., 2004). Experiments in rodents where expression of *FTO* in regions of the brain that control feeding is regulated by food deprivation (Fredriksson et al., 2008; Gerken et al., 2007; Stratigopoulos et al., 2008) lend further support for the functional role of this gene in the central control of energy homeostasis.

The most frequently studied *FTO* SNP is the rs9939609 variant, located in intron-1 and present at a high allelic frequency (c. 39% in European populations). In children from the UK Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, one copy of the minor (A) allele was associated with an increase in BMI of ~0.2 kg/m^2 at age 7 and this increased to ~0.4 kg/m^2 at age 11 (Frayling et al., 2007), an effect mediated through changes in adiposity. Reports confirm the role of *FTO* rs9939609, and surrogates for this variant, on BMI and fat mass in children and adolescents from Caucasian and non-Caucasian populations (Cecil et al., 2008; Fang et al., 2010; Grant et al., 2008; Hakanen et al., 2009; Okuda et al., 2011; Tanofsky-Kraff et al., 2009;

Xi et al., 2010). Additionally, several studies have confirmed an *increasing* association between rs9939609 and BMI from early childhood to adolescence (Hardy et al., 2010; Haworth et al., 2008b; Rzehak et al., 2010; Sovio et al., 2011). Sovio and colleagues, in their meta-analysis of European children (8 cohorts, infants to 13 year olds) found that the minor (A) allele of the rs9939609 was additively associated with increasing BMI as early as 5.5 years onwards, and interestingly an inverse association was found below the age of 2.5 years (Sovio et al., 2011), supporting what is known about the timing of adiposity rebound and risk of adult obesity (Whitaker et al., 1998) and the interplay between behaviour (appetite, physical activity) and environment with age (Haworth et al., 2008b; Wright et al., 2011). A temporal dip in the effect of *FTO* rs9939609 on BMI in children is proposed at the mid-pubertal age of around 13–14 years which may be linked to alterations in physiologic and endocrine factors that trigger puberty (Rutters et al., 2011). Current thinking is that there is no *FTO* association with foetal growth (Frayling et al., 2007; Hakanen et al., 2009).

Fat mass and obesity associated gene and eating behaviour

Despite the vast evidence base for *FTO*, the functional mechanism for this gene in the central control of energy homeostasis remains unclear. However, a growing number of studies link the *FTO* gene to a role in the central control of food intake (Fredriksson et al., 2008; Gerken et al., 2007; Stratigopoulos et al., 2008). Additionally, *FTO* genotype has been shown to influence central insulin resistance (Tschritter et al., 2007), where insulin is critical for control of normal body weight, and this gene is associated with increased insulin resistance in type 2 diabetics (Doney et al., 2009).

A small number of studies conducted in children have measured energy intake either directly or indirectly using parental report and show that the *FTO* locus confers risk of obesity through increasing energy intake (Cecil et al., 2008; Rendo et al., 2009; Timpson et al., 2008; Wardle et al., 2008b), through reduced satiety responsiveness (Wardle et al., 2008b) and a preference for energy dense foods (Cecil et al., 2008; Lee et al., 2010; Tanofsky-Kraff et al., 2009; Timpson et al., 2008), but not through energy expenditure (Hakanen et al., 2009), supporting the adult literature (Haupt et al., 2009; Speakman et al., 2008). In a preload paradigm study, food intake from a test meal was significantly increased in young children (4–10 years) carrying the minor (A) allele for *FTO* rs9939609, independent of body weight, through greater ingestion of energy dense foods, compared with wildtypes (Cecil et al., 2008). Consistent with this observation is evidence from the ALSPAC study using 3 day dietary records, where children (10–11years) carrying the risk allele for *FTO* ingested more energy and specifically more dietary fat than those not carrying the risk allele (Timpson et al., 2008). These findings contrast with at least three studies which report no associations with energy intake in children (Hakanen et al., 2009; Okuda et al., 2011; Stutzmann et al., 2009) and to the observation in mice that *FTO* may modulate energy homeostasis through energy expenditure (Fischer et al., 2009; Speakman, 2010). However, several studies, including a large meta-analysis have recently shown that energy expenditure through activity appears to attenuate the genetic susceptibility to overweight and obesity from *FTO* in children (Lee et al., 2010; Scott et al., 2010) and adults (Andreasen et al., 2008; Kilpelainen et al., 2011).

Generally, studies in children investigating the effects of common gene variants on eating behavioural traits or phenotypes associated with risky eating patterns or the tendency to overeat are equally limited, but have included loss of control over eating, emotional eating defined as eating in response to psychological stress, and EAH. Thus associations between the *FTO* minor (A) allele and higher intakes of palatable, energy dense foods through EAH in 4–5 year old children (Wardle et al., 2009) and through loss of control eating in children and adolescents aged 6–19 years (Tanofsky-Kraff et al., 2009) have been observed supporting the evidence that *FTO* genotype appears to predispose to obesity risk through overeating specifically foods high in energy density and palatability. At present, the evidence strongly suggests that *FTO* effects its influence on human adiposity and BMI via alterations to appetitive pathways, expressed through specific eating patterns rather than though energy expenditure. Thus *FTO* may belong to a group of genes that predispose towards a hyperphagic phenotype (Bouchard, 2007).

Peroxisome proliferator-activated receptor gene – a candidate gene for adiposity and energy balance

The peroxisome proliferator-activated receptor (*PPARG*) locus has been studied extensively for obesity associated traits (Auwerx, 1999; Evans et al., 2004; Spiegelman, 1998; Tonjes et al., 2006). *PPARG* resides on chromosome 3 and encodes peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor involved in fatty acid sensing. Expressed predominantly in adipose tissue, PPARγ regulates adipocyte differentiation, lipid metabolism, fat storage and insulin sensitivity. Loss of function studies in mice (Rosen et al., 2002) and gene expression studies in human tissue (Vidal-Puig et al., 1997) have identified

PPARγ as central in mediating a causal pathway between increased adiposity and body weight.

Common variation at the *PPARG* gene is reliably linked to BMI and obesity in Caucasian populations (Beamer et al., 1998; Cecil et al., 2005; Deeb et al., 1998; Tonjes et al., 2006; Valve et al., 1999). Three common *PPARG* SNPs at high allelic frequency (c. 20%), and in linkage disequilibrium (LD), include: codon 12-Pro12Ala; intron A2-C681G and exon 6 C1431T (C478T). The most frequently investigated of these is the proline to alanine substitution at codon 12, an amino acid change which reduces receptor activity to natural and synthetic ligands (Gearing et al., 1994). Research into variation at the *PPARG* locus and BMI has largely involved adults, but in a follow up study on weight and body composition, Pro12Ala was shown to regulate weight and body composition from birth through to adulthood (Pihlajamaki et al., 2004). Importantly, the alanine substitution has been associated with reduced BMI and increased insulin sensitivity in children (Buzzetti et al., 2005; Cecil et al., 2005; Dedoussis et al., 2009), indicating that this variant confers some sort of protection from obesity and type 2 diabetes at an early age. These data support much of the evidence in adults (Deeb et al., 1998; Doney et al., 2004), though reports are inconsistent (Hamann et al., 1999; Lagou et al., 2008; Scaglioni et al., 2006), possibly because of the action of multiple variants within the *PPARG* gene itself (Doney et al., 2004), and or other gene-gene and gene-environment interactions. In young children and peri-adolescents, this protection from an increased BMI is also associated with variation in measures of adiposity (Cecil et al., 2005; Dedoussis et al., 2009), suggesting that *PPARG* may influence fat deposition in childhood and well as adulthood. Emerging evidence in children suggests that *PPARG* Pro12Ala regulation of child adiposity (including measures of cholesterol/HDL and apoB/apoA1 ratios, skinfolds), may even be gender dependent (Dedoussis et al., 2009; Dedoussis et al., 2007; Lagou et al., 2008).

At least one study has presented evidence in children for an interaction effect between *PPARG* Pro12Ala and *PPARG* variant C-681G (Cecil et al., 2005), in tight LD with pro12ala and with a putative role in bone deposition and mineralisation and adult growth (Meirhaeghe et al., 2003). Thus Pro12Ala and C-681G variants were associated with opposing growth phenotypes in 4–10 years olds (Cecil et al., 2005), where Pro12Ala was associated with reduced growth and C-681G with accelerated growth. Few studies in children have considered the role of *PPARG* C1431T variant, a synonymous codon substitution in exon 6, linked to susceptibility to cardiovascular disease (Wang et al., 1999), and increased BMI in adults (Doney et al., 2002). This variant may have little effect on child BMI (Cecil et al., 2005) however, a recent study suggests that C1431T may be linked to increased adiposity in children aged 3–4 years (Lagou et al., 2008). Together these data indicate that common variation at the *PPARG* locus has a complex role in determining fat deposition, insulin sensitivity and growth early in life.

Some of the best evidence for a *PPARG* role in the control of appetite and energy balance comes from functional experiments. A ligand activated transcription factor, *PPARG* is activated by dietary fatty acids (Gearing et al., 1994) to modulate gene transcription in a feed-forward pathway to influence energy balance. In mice, adipose tissue expression of *PPARG* is down-regulated by fasting and increased when exposed to high fat feeding (Vidal-Puig et al., 1996) supporting data in obese humans demonstrating that a low energy diet can down-regulate adipocyte PPARγ mRNA expression (Vidal-Puig et al., 1997). Additionally, its association with alterations in insulin sensitivity (Hsiao et al., 2011) and down-regulation of leptin expression in response to agonists (Zhang et al., 1996), both critical neuroendocrine signals/hormones for orchestrating the central control of ingestive behaviour, are consistent with the notion that PPARγ may be significant in mediating the response to food and appetite.

Peroxisome proliferator-activated receptor gene and eating behaviour

Clearly the *PPARG* locus directs the efficiency of adipose tissue accumulation and this would likely have interactions with dietary macronutrients. Thus *PPARG* genotype appears to interact with dietary fat (Luan et al., 2001; Memisoglu et al., 2003; Rosado et al., 2010) and carbohydrate (Marti et al., 2002) to determine body weight in adults and more recently has been associated with variations in body weight in response to dietary fat in children (Bouchard-Mercier et al.,2011; Dedoussis et al., 2011).

PPARG also appears to affect food intake through heightened satiety (Rosado et al., 2007) and reduced fat intake, where the 12Ala variant was associated with reduced saturated fatty acid intake in adolescent girls (Dedoussis et al., 2009). In addition, *PPARG* genotype may influence child eating behaviour through variation in short-term energy compensation, a direct measure of satiety expression. Thus *PPARG* T1431 was associated with poor energy compensation, consistent with the evidence for an increased BMI in adults (Doney et al., 2002) and altered BMI/leptin ratios (Meirhaeghe et al., 1998) by this variant. This may be due in part to an interaction with the Trp64Arg variant of the beta-3 adrenoreceptor, another candidate SNP for obesity (Clement et al., 1995). Interestingly, at least two

reports in children and adolescents show that *PPARG* (Pro12Ala) and *ADRB3* (Trp64Arg) variants act synergistically to modulate the risk for obesity (Chen et al., 2007; Ochoa et al., 2004) and support what is known in adults (Hsueh et al., 2001), and is probably a consequence of close linkage with C1431T.

Melanocortin 4 receptor gene and a role in polygenic obesity

The melanocortin 4 receptor has come under scrutiny for a polygenic role in obesity. Located on chromosome 18, *MC4R* is a 7-transmembrane G-coupled receptor widely expressed in hypothalamic regions of the brain acting through melanocortin neuroendocrine pathways to control appetite and energy homeostasis (Balthasar et al., 2005). Mutations at the *MC4R* locus have previously been associated with severe monogenic obesity onset early in childhood (Farooqi et al., 2003). Common polymorphisms in the *MC4R* gene have now been identified using a GWAS approach and linked to variation in fat mass and obesity in children and adults (Loos et al., 2008). Amongst a group of SNPs located downstream of *MC4R*, the SNP variant rs17782313 has provided the most robust association signal with BMI. In children from the UK ALSPAC cohort, the rs17782313 C allele was additively associated with an increase in BMI from the age of 7–11 years, of a magnitude greater than that seen in adults, linked both to variation in weight and also increased body fatness (Loos et al., 2008). A functional role for common variants near *MC4R* in body weight regulation in children has been confirmed in other studies (Cole et al., 2010; Stutzmann et al., 2009). Thus, the example of *MC4R* illustrates the considerable and complex overlap in the genetic susceptibility for monogenic and polygenic obesity.

Melanocortin 4 receptor and eating behaviour

Common variation at the *MC4R* locus has also been identified as important in contributing to variation in food intake and eating behaviour at the population level, consistent with features of *MC4R* loss-of-function mutations that relate to ingestive behaviour (hyperphagia). In studies assessing patterns of eating through self-report and dietary recall, the rs17782313 C allele has been associated with increased snacking and food intake in obese and non-obese European children and adolescents (Cole et al., 2010; Stutzmann et al., 2009). Similarly, rs17782313 has been linked to eating behaviours related to obesity such as low satiety responsiveness and increased enjoyment of food in obese children assessed by a psychometric tool to characterize children's eating behaviour (Valladares et al., 2010). These data strongly suggest that this region downstream of *MC4R* may be important in modulating appetitive pathways to weight gain and obesity compatible with its functional role in monogenic obesity.

Adrenergic receptor gene variants – a role in polygenic obesity and eating behaviour?

The adrenergic system is an important regulator of energy balance through its actions on thermogenesis and on lipid metabolism through lipid mobilization and storage (Emorine et al., 1994; Krief et al., 1993) and common variation in beta-adrenergic (*ADRB*) receptor gene subtypes has been implicated in variation in BMI (Angeli et al., 2011; Clement et al., 1995; Dahlman & Arner, 2010; Lima et al., 2007; Widen et al., 1995). The Trp64Arg polymorphism, located in codon 64 of the beta-3 adrenergic receptor, is the most commonly studied *ADRB* SNP. In humans, the beta-3 adrenergic receptor is predominantly expressed in visceral adipose tissue (Krief et al., 1993). Notably, the Arg allele of this SNP has been linked with increased BMI, adiposity and obesity in children (Arashiro et al., 2003; Endo et al., 2000; Erhardt et al., 2005; Ochoa et al., 2004; Park et al., 2005) supporting the evidence in adults (Marti et al., 2002; Pierola et al., 2007), and the increased risk for obesity at this *ADRB3* loci may be driven partly by an interaction effect of the *PPARG* SNP Pro12Ala (Chen et al., 2007; Hsueh et al., 2001; Ochoa et al., 2004). Other studies in young children between the ages 4–10 years and in adolescents report no significant effects of Trp64Arg variants on BMI, weight or height when this variant is examined in isolation (Cecil et al., 2007; Haworth et al., 2008a; Hinney et al., 1997; Kurokawa et al., 2003). Additionally, there is some evidence to suggest that polymorphisms on the beta-2 adrenergic receptor, expressed mainly in subcutaneous adipose tissue, may also be linked to variation in BMI and obesity related phenotypes. Thus, the Arg16Glyn variant of *ADRB2* has been associated with significant weight gain in childhood through to young adults (Angeli et al., 2011; Ellsworth et al., 2002; Lagou et al., 2011) though data are mixed (Haworth et al., 2008a; Tafel et al., 2004). This variant appears to act synergistically with the LEPR Gln223Arg SNP for risk of obesity (Angeli et al., 2011) and may moderate (ameliorate) the effect on adiposity by increased vigorous activity (Lagou et al., 2011).

Though limited, there is some evidence to suggest that *ADRB* receptor polymorphisms interact with dietary nutrients (de Luis et al., 2009) and may also be involved in regulating food intake. In adults, *ADRB3* Trp64Arg appears to interact

with carbohydrate preference/consumption (Aoyama et al., 2003), and may also operate synergistically with *PPARG* variants to modulate satiety expression (Cecil et al., 2007). In children the Trp64Arg genotype may also moderate the effect of dietary interventions in obese children (Xinli et al., 2001).

Reward related genes and evidence for obesity, food intake and eating behaviour

Evidence of genes that influence weight gain through reward pathways is also emerging (Heard-Costa et al., 2009). Reward processes generated by the anticipation and consumption of highly-palatable foods rich in fat sugar and salt promote their intake and are strongly implicated in non-homeostatic overconsumption, weight gain and obesity (Finlayson et al., 2007). The reward circuitry in the brain is predominantly underpinned by neurotransmission of dopamine and endogenous opioids in the striatum (Lutter & Nestler, 2009), but there is considerable overlap and cross-talk between reward signalling and feeding centres in the hypothalamus (Berthoud, 2004). Gene polymorphisms relating to reward function could influence eating behaviour by amplifying the motivation to eat (Temple et al., 2008), altering sensory/hedonic perception of food (Davis et al., 2011), or via weak satiety responsiveness (Wardle et al., 2008).

Reward related genes and obesity/weight change

Pleasure from eating correlates with the quantity of dopamine released in the brain (Comings & Blum, 2000), and brain dopamine levels increase during food consumption in humans (Small et al., 2003). Obese individuals have fewer dopamine D2 receptors (Volkow et al., 2008; G. Wang et al., 2001), compared with lean individuals, and may overeat as a means of compensating for this deficiency consistent with a hypo-functioning reward system, or reward deficiency syndrome (RDS) (Stice et al., 2008). D2 dopamine receptor (DRD2) gene polymorphisms (Taq1A) have been associated with reduced brain dopamine function (Noble et al., 1991) and the A1 allele of the DRD2 gene has been linked to an increased BMI (Blum et al., 1996), though reports are mixed. Few studies have looked at dopaminergic genotype and obesity in children, however, the Taq1 allele has been linked to concordance in zBMI change between parents and children (8–12 years) at 6 and 12 months in a family-based weight loss program (Epstein et al., 2010) suggesting that Taq1 genotype is also involved in weight change at a young age.

Reward related genes, food intake and eating behavioural traits

Compatible with evidence for genes involved in reward behaviours predicting variation in body weight, dopamine gene polymorphisms have been associated with reward seeking food intake behaviours including food cravings, increased energy intake from fat and carbohydrate. In a recent fMRI study investigating the effects of dopamine genotypes on reward in response to food, DRD2A1 and DRD4R7 risk alleles were associated with an attenuated activation of the reward circuitry in response to anticipated food intake and this predicted risk of future weight gain in female adolescents (Stice et al., 2010). Consistent with these data, DRD2 genotype appears to moderate the relationship between psychological control and emotional eating, where adolescents with at least one DRD2 A1 allele showed an increase in emotional eating in relation to high parental psychological control (van Strien et al., 2010). Additionally, there is evidence in female adolescents to suggest that symptoms of depression and dopamine transporter SLC6A3 genotype interact producing a synergistic increase in intake of high-energy sweet foods (Agurs-Collins & Fuemmeler, 2011). Together, these findings suggest that dopamine polymorphisms may be important moderators of reward related food intake associated with a hypo-functioning reward system, and may confer an increased risk of early onset obesity. This is further supported by recent evidence in young children aged 3–4 years suggesting that genes that encode enzymes controlling the availability of dopamine including catechol-o-methyltransferase (COMT) and monoamine oxidase A (MAOA) may also play a role in moderating intake of palatable food (Galvao et al., 2012).

Summary and future perspectives

Obesity is a complex multifactorial disorder, underpinned by environmental and genetic risk factors. Substantial evidence from molecular studies has shown that several genes are robustly linked to contributing to variance in childhood and adolescent BMI, and include variants of the *FTO*, peroxisome *PPARG* and *MC4R* genes. The molecular genetics approach to investigate those pathways involved in susceptibility to obesity related to appetite and eating behaviour is a relatively new and emerging field, and work conducted in children is limited, often underpowered and frequently hindered by logistical difficulties. However, evidence is beginning to throw light on specific patterns of eating, eating behavioural traits and reward-related behaviours associated with alterations in allelic variation that predispose to obesity, and suggests that genetic susceptibility to

childhood obesity is mediated primarily through variation in appetitive pathways. This approach has the potential to yield important insights into the complex genetic architecture of human food intake and eating behaviour, with significant implications for early detection of susceptibility, and for prevention and management of childhood obesity.

To date, the evidence for nearly 50 loci regulating body weight has been amassed from GWAS of 250,000 adults (Speliotes et al., 2010), and it would appear that most of these genes play some role in childhood obesity (den Hoed et al., 2010). However the mechanisms by which these loci act on body weight are still largely unknown and may be complicated further by alterations in gene-expression via epigenetic events in specific genes (Lillycrop & Burdge, 2011), in addition to alterations to DNA sequence variation. Although a role in general neuronal development has been postulated (Willer et al., 2009), and current attempts to address this issue systematically in adults are largely underpowered, it will be important to evaluate their role in childhood eating behaviours using sophisticated and direct behavioural assessments (Blundell et al., 2009) across specific growth points. It will also be interesting to determine if large scale studies of BMI in children reveal differential loci to adults, and what possible mechanisms underlie any such differential effects.

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