

Title: Shared genetic architecture underlying sleep and weight in children

Running title: Shared genetics of sleep and weight in children

Victoria Garfield, PhD¹, Clare Llewellyn, PhD², Lars Wichstrøm, PhD³ & Silje Steinsbekk, PhD³

Author Affiliations

¹MRC Unit for Lifelong Health and Ageing at UCL, Institute of Cardiovascular Science, University College London, London, United Kingdom

²Department of Behavioural Science & Health, University College London, London, United Kingdom

³Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway

Corresponding author: Victoria Garfield, MSc PhD, MRC LHA at UCL, Institute of Cardiovascular Science, University College London, 1-19 Torrington Place, WC1E 7HB, London, United Kingdom. Email address: v.garfield@ucl.ac.uk

Conflict of interest: the authors declare that there is no conflict of interest.

Acknowledgements: this work was supported by a multidisciplinary doctoral training grant from the Economic and Social Council and Medical Research Council [grant number ES/J500185/1].

Author contributions: VG conceived the study idea, performed statistical analyses and wrote the manuscript. CL, LW and SS provided revised the manuscript for intellectual and scientific content. All authors approved the final manuscript. This work was carried out at the Norwegian University of Science and Technology.

Abstract

Meta-analyses suggest shorter sleep as a risk factor for obesity in children. The prevailing hypothesis is that shorter sleep causes obesity by impacting homeostatic processes. Sleep duration and adiposity are both heritable, and the association may reflect shared genetic aetiology. We examined the association between a body mass index (BMI) genetic risk score (GRS) and objectively-measured total sleep time (TST) in a cohort of Norwegian children (enrolled at age 4 in 2007-2008) using cross-sectional data at age 6. The analytical sample included 452 6-year old children with complete genotype and phenotype data. The outcome was actigraphic total sleep time (TST) measured at age 6, categorized into <9 hours and ≥ 9 hours. Genetic risk of obesity was inferred using a 32-single nucleotide polymorphism (SNP) weighted GRS of BMI. Covariates included age, sex, BMI and BMI-Standard deviation scores (SDS). Analyses consisted of Pearson's correlations and linear regressions. In our sample, 54% of participants were male; mean TST, age and BMI were 9.59 hours, 6.01 years and 15.35 kg/m², respectively. BMI and TST were not correlated, $r = -0.0032$, $p = 0.946$. However, the BMI GRS was associated with TST after adjusting for age, sex and BMI, standardised $\beta = -0.11$, 95% confidence interval (CI) = $-0.21; -0.01$. To our knowledge, this is the first study to establish a relationship between genetic risk of obesity and objective sleep duration in children. Findings suggest some shared genetic aetiology underlying these traits. Future research could identify the common biological pathways through which common genes predispose to both shorter sleep and increased risk of obesity.

Keywords: total sleep time, body mass index, genetic risk score, objective measurements.

Main text

Introduction

Meta-analyses have established that shorter sleep duration is robustly associated with increased obesity risk in children[1–4]. Some studies find that boys are more susceptible to sleep loss and thus, at greater risk of becoming obese [5]. The prevailing hypothesis is that shorter sleep causes homeostatic changes that may causally increase obesity risk. For example, evidence suggests that short sleep can lead to alterations in the ‘hunger hormones’, leptin and ghrelin and that these changes lie on the causal pathway between sleep duration and obesity[6–8]. In one of the first studies to show this, participants were subjected to two days of sleep restriction and two days of sleep extension, during which calorie intake and exercise were under systematic control [8]. Findings indicated that leptin levels decreased by 18%, whilst hunger, ghrelin and appetite increased by 24%, 28% and 23%, respectively [8]. Recent research has also started to examine the reverse relationship, as well as a bidirectional relationship between sleep and weight, such that baseline BMI might also predict prospective changes in sleep duration, yet this has only been found in South Asian children, to date [9]. An alternative hypothesis is that sleep and weight are associated because they share some of their common genetic aetiology. Twin and family studies report high heritability for body mass index (50%-90%) [10–12], and moderate heritability for self-reported sleep duration (30%-50%)[11,13,14] in both adults and children. One of these twin studies found no evidence of shared underlying genetic components between BMI and sleep duration[14].

Another method for examining shared genetic aetiology underlying sleep and adiposity is to establish if common genetic variants that predispose to higher BMI, predispose also to shorter sleep duration. Genetic risk scores (GRS) are now widely used to aggregate genome-wide markers to infer individuals’ genetic predisposition to a trait of interest, as well as to highlight potential shared genetic aetiology between two traits [15]. Genome-wide meta-analyses have identified 97 common genetic variants that are robustly associated with BMI in adults and children, and in the aggregate explain approximately 3% of the variation.

Two studies to date have examined the relationship between a genetic risk score for obesity (comprising 69 single nucleotide polymorphisms identified through a genome-wide meta-analysis of BMI) and self-reported sleep duration in approximately 120,000 adults from the UK Biobank [16,17]. They found no association between the genetic risk score and sleep duration, but this does not imply that BMI and sleep duration do not share underlying genetic

influences in children, via perhaps, previously understudied biological pathways. This is also important because research suggests that the relationship between sleep duration and BMI weakens with age (Gangwisch et al., 2005; Hasler et al., 2004). Further, although individuals' genomes remain unchanged throughout the life course, differing levels of gene expression have been linked to specific disease states and cellular responses and these processes can be age-related (de Magalhães et al., 2009).

No previous studies have investigated the association between genetic risk of obesity and sleep duration in children, and no studies with children or adults have used objectively measured sleep duration. This is a considerable advantage, as self-reported sleep duration may be prone to misreporting and bias (Van Den Berg et al., 2008). However, actigraphy has been validated against polysomnography (Sadeh et al., 1989; Belanger et al., 2013; Hyde et al., 2007; Spruyt et al., 2011), which is the gold standard measurement. The study reported here examined, for the first time, the association between a BMI GRS and actigraphy-measured sleep duration in a community sample of Norwegian children. We hypothesised that higher genetic risk of obesity would be associated with shorter sleep duration, suggestive of common genetic architecture underlying both sleep and weight in children.

Methods

Sample

We analysed data from the second wave (age 6) of the Trondheim Early Secure Study (TESS), comprised of Norwegian children born in Trondheim in 2003 and 2004. Detailed recruitment procedure and sample characteristics are described elsewhere (Steinsbekk et al., 2016). Ethical approval for TESS was granted by the Regional Committee for Medical and Health Research Ethics, Mid-Norway and written informed consent was obtained. Participants were included who had genotype data, as well as BMI, actigraphy-measured total sleep time (TST). Thus, we had a total of 452 children for this analysis, the majority (>95%) of whom were of White ethnicity (Table 1).

Measures

TST was measured with the ActiGraph™ GT3X accelerometer (Manufacturing Technology Incorporated, Fort Walton Beach, FL, USA). Participants wore the actigraphs on their hip for 7 consecutive days, including whilst asleep, only instructed to remove them whilst showering or bathing. TST was converted from raw data by employing Sadeh's algorithm (Sadeh et al., 1994), once time in bed and out of bed was manually set by examining each night, using ActiLife software. Sadeh's algorithm automatically differentiates prolonged sitting from

sleep. In addition to actigraphy, a questionnaire was supplied asking whether participants had been ill and more or less active than usual during the seven days of measurement. Actigraphy has been shown to be valid and reliable for measuring TST, when compared to polysomnography (PSG), which, as mentioned earlier, is the gold standard method.

Researchers measured body weight (kg) and height (m) of the children using digital scales (Heightronic digital stadiometer: QuickMedical, Model 235A and Tanita BC420MA). BMI was converted to age- and sex-adjusted standard deviation scores (SDS) derived using British reference data (Cole et al., 1990) as previous TESS papers have used these, rather than Norwegian reference data [26]. Weight status (healthy weight, overweight and obese) was determined using the BMI IOTF cut-offs for children. Sleep duration categorization of <9 and ≥9 hours was used as per the latest recommendations from the American Academy of Sleep Medicine (AASM) [29].

Genotyping and genetic risk score (GRS)

DNA was extracted and stored from a 2-millilitre saliva sample taken from TESS participants at the second data collection wave (age 6), using the Oragene DNA saliva kit (DNA Genotek). To generate a Custom Oligo Assay Pool, genetic loci of interest were sent to Illumina. Genotyping was performed at the Norwegian University of Science and Technology's Genomics Core Facility, with the GoldenGate Genotyping Universal-32 assays (Illumina). The arrays were subsequently scanned using an Illumina HiScan and processed in GenomeStudio.

A 32-SNP BMI GRS was constructed using external weights from the Genetic Investigation of Anthropometric Traits Consortium (GIANT) [30]. These SNPs were the ones that had been discovered through GWAS when TESS participants were genotyped. This GRS was also recently used in another TESS publication [26].

Statistical analyses

We obtained either means and SDs for continuous measures, or frequency and %s for categorical measures to describe our sample (Table 1). We examined the phenotypic association between BMI and TST, as well as BMI-SDS and TST, using Pearson's correlations. Assumptions for Pearson's correlations were checked, including: level of measurement (BMI and TST are both continuous), linearity and outlier influence.

Linear regression analyses were used to investigate the association between the BMI GRS and TST, whereby we first ran a crude univariate model, followed by multivariable models adjusted for **age and sex**, and then additional adjustments for BMI and BMI-SDS. We also performed exploratory analyses to understand the potential interaction between the BMI GRS and sex in relation to TST, but as this interaction was not significant ($p=0.151$) in a regression model that included the BMI GRS and the BMI GRS*sex term we did not include this in any further analyses. Analyses were performed in Stata, v.14 and we used sample weighting to ensure representativeness of the general population, as this is a common approach when analysing TESS data [26]. A 5% level of significance was adopted and our main hypothesis **was 2-sided**.

Results

Sample characteristics

Mean sleep duration in our sample was 9.59 hours (SD=0.76, minimum= 6.31, maximum= 12.45). As there was only one obese participant, we merged the overweight and obese categories (Table 1). The mean age was 6.01 years (SD=0.16) and our sample was 54% male. We also observed no phenotypic correlation between BMI and TST, $r= -0.0032$, $p=0.946$, or between BMI-SDS and TST, $r=-0.0009$, $p=0.98$.

Association between the BMI GRS and measured BMI, and variance explained by the BMI GRS

The BMI GRS was associated with BMI, B (unstandardized coefficient) = 0.17, 95% CI= 0.03; 0.31, $p=0.016$. The BMI GRS explained 1.7% of the variance in BMI, 1.5% of the variance in BMI-SDS and 2.6% of the variance in TST.

Associations between the BMI GRS and TST

In the crude linear regression, the BMI GRS was associated with a 4.87-minutes fewer of TST, 95% CI=-9.23; -0.51, $p=0.029$. In the multiple linear regression, the BMI GRS was associated with a 4.52-minutes fewer of TST, 95% CI= -8.86; -0.17, $p=0.041$. Thus, we observed a slight attenuation of the effect when including age and sex as covariates, yet it remained significant. When we then adjusted for BMI in addition to age and sex, we observed that the GRS was associated with TST independently of BMI: B=-4.85, 95%CI=- 9.29; -0.42, $p=0.032$. Our final model was adjusted only for BMI-SDS, as it takes into account age and sex, the result of which was: B=-4.88, 95%CI= -9.49; -0.27, $p=0.038$.

Discussion

To our knowledge, this was the first study to examine the association between measured genetic risk of obesity, and objectively measured sleep duration in children. We found that higher genetic risk of obesity was associated with a 5-minute decrease in objectively-measured TST independently of age, sex and BMI, in this representative sample of 6-year-old children. Our 32-SNP BMI GRS accounted for 2.6% of the variance in TST in our sample, comparable to its ability to explain variability in BMI (1.7%). These results suggest that shared genetic aetiology exists between BMI and total sleep time, as measured by waist actigraphy. Our genetic findings support the cross-sectional observational literature on BMI and sleep duration in children (Liu et al., 2012) and highlight one important potential pathway via which this association may operate.

The phenotypic correlation between BMI and TST in our data was very small and not significant, although it was in the same direction as the association between the BMI GRS and TST. One possible explanation for the discrepancy between phenotypic and genetic results could be that because Trondheim is not a particularly obesogenic environment, the children in our sample are able to maintain their BMI within a healthy range, irrespective of their genetic risk of obesity. This is reflected in our sample characteristics which clearly shows that 84.51% of the sample are within the normal weight range. In line with this, a recent study in adults found that living in an obesogenic environment, particularly in highly deprived areas, can exacerbate the genetic risk of obesity [32] and thus, increase an individual's odds of becoming overweight or obese. However, this has not yet been investigated in children. Also, interestingly, a recent analysis of TESS showed that although most children in the sample have a BMI within the healthy range, genetic risk did in fact predict increased BMI over time [26].

Although the biological mechanisms that might be shared by BMI and sleep duration remain largely unknown, we consider a specific pathway that could at least, partially underlie this shared aetiology. Our 32-SNP GRS included an intron (rs9939609) in the fat-mass and obesity-associated (FTO) gene, as well as a variant in the melanocortin receptor-4 (MC4R) gene. FTO and MC4R are both highly expressed in the hypothalamus [33], which contains the ventrolateral preoptic nucleus (VLPO), a modest cluster of neurons that are activated by sleep-promoting neurotransmitters. However, this is only one example of a relevant pathway, but future research could perform downstream analysis to explore whether any robustly-associated BMI genetic variants are on the causal pathway for sleep duration.

Briefly, we acknowledge that our study has certain limitations. Firstly, our sample size was modest, yet due to the expense of using actigraphy, it is not possible to compete with sample sizes analysed in studies using self-report sleep measures. However, of note, self-

or proxy reported sleep time generally correlate only moderately with objectively measured sleep (Lauderdale et al., 2008). Secondly, our findings may only be applicable to children of White/European descent. Thirdly, our BMI GRS was constructed using only 32 GWAS SNPs, which does not cover the whole spectrum of more recent BMI genome-wide SNPs [33]. However, this GRS was significantly related to BMI in our sample and has previously been shown to be associated with prospective BMI in TESS [26].

Our study also possesses important strengths. It is particularly novel, as no previous research has investigated the potential shared genetic aetiology between BMI and sleep duration in children. We analysed objective total sleep time, measured by actigraphy, which is less prone to error than self-reported sleep duration[34,35]. Finally, BMI was researcher-measured, rather than parent-reported.

In conclusion, this study is the first to report an association between a BMI GRS and sleep duration in children. Our findings highlight the existence of potentially important shared genetic underpinnings between these two highly complex phenotypes. Future studies should investigate this association in larger samples, with other sleep phenotypes, in distinct age groups, and with prospective data.

References

- [1] Cappuccio FP, Taggart FM, Kandala N-B, Currie A, Peile E, Stranges S, et al. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep* 2008;31:619–26.
- [2] Chen X, Beydoun MA, Wang Y. Is Sleep Duration Associated With Childhood Obesity? A Systematic Review and Meta-analysis. *Obesity* 2008;16:265–74. <https://doi.org/10.1038/oby.2007.63>.
- [3] Fatima Y, Doi SAR, Mamun AA. Longitudinal impact of sleep on overweight and obesity in children and adolescents: a systematic review and bias-adjusted meta-analysis. *Obes Rev* 2015;16:137–49. <https://doi.org/10.1111/obr.12245>.
- [4] Wang J, Adab P, Liu W, Chen Y, Li B, Lin R, et al. Prevalence of adiposity and its association with sleep duration, quality, and timing among 9-12-year-old children in Guangzhou, China. *J Epidemiol* 2017. <https://doi.org/10.1016/j.je.2016.11.003>.
- [5] Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. *Obesity (Silver Spring)* 2008;16:643–53. <https://doi.org/10.1038/oby.2007.118>.
- [6] Chaput J-P, Després J-P, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: Results from the Quebec family study. *Obesity (Silver Spring)* 2007;15:253–61. <https://doi.org/10.1038/oby.2007.512>.
- [7] Schmid SM, Hallschmid M, Jauch-Chara K, Born J, Schultes B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *J Sleep Res* 2008;17:331–4. <https://doi.org/10.1111/j.1365-2869.2008.00662.x>.
- [8] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004;141:846–50.
- [9] Collings PJ, Ball HL, Santorelli G, West J, Barber SE, McEachan RR, et al. Sleep Duration and Adiposity in Early Childhood: Evidence for Bidirectional Associations from the Born in Bradford Study. *Sleep* 2017;40. <https://doi.org/10.1093/sleep/zsw054>.
- [10] Stunkard, A.J., Harris, J.R., Pedersen, N.L., & McClearn GE. The body-mass index of twins who have been reared apart. *N Engl J Med* 1990;322:1483–7.
- [11] Watson NF, Buchwald D, Vitiello M V., Noonan C, Goldberg J. A Twin Study of Sleep Duration and Body Mass Index. *J Clin SLEEP Med* 2010;6:11–7.

- [12] Watson NF, Harden KP, Buchwald D, Vitiello M V, Pack AI, Weigle DS, et al. Sleep duration and body mass index in twins: a gene-environment interaction. 2012;35:597–603. <https://doi.org/10.5665/sleep.1810>.
- [13] Heath, A.C., Kendler. K.S., Eaves., L.J., & Martin. NG. Evidence for Genetic Influences on Sleep Disturbance and Sleep Pattern in Twins. *Sleep* 1990;13:318–35.
- [14] Partinen M, et al. Genetic and environmental determination of human sleep. *Sleep* 1990;6:179–85.
- [15] Dudbridge F. Power and Predictive Accuracy of Polygenic Risk Scores. *PLoS Genet* 2013;9. <https://doi.org/10.1371/journal.pgen.1003348>.
- [16] Jones SE, Tyrrell J, Wood AR, Beaumont RN, Ruth KS, Tuke MA, et al. Genome-Wide Association Analyses in 128,266 Individuals Identifies New Morningness and Sleep Duration Loci. *PLoS Genet* 2016;12:e1006125. <https://doi.org/10.1371/journal.pgen.1006125>.
- [17] Garfield V, Fatemifar G, Dale C, Smart M, Bao Y, Llewellyn CH, et al. Assessing potential shared genetic aetiology between body mass index and sleep duration in 142,209 individuals. *Genet Epidemiol* 2019;43. <https://doi.org/10.1002/gepi.22174>.
- [18] Hasler G, Buysse DJ, Klaghofer R, Gamma A, Ajdacic V, Eich D, et al. The association between short sleep duration and obesity in young adults: a 13-year prospective study. *Sleep* 2004;27:661–6.
- [19] Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep* 2005;28:1289–96.
- [20] de Magalhães JP, Curado J, Church GM. Meta-analysis of age-related gene expression profiles identifies common signatures of aging. *Bioinformatics* 2009;25:875–81. <https://doi.org/10.1093/bioinformatics/btp073>.
- [21] VAN DEN BERG JF, VAN ROOIJ FJA, VOS H, TULEN JHM, HOFMAN A, MIEDEMA HME, et al. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons*. *J Sleep Res* 2008;17:295–302. <https://doi.org/10.1111/j.1365-2869.2008.00638.x>.
- [22] A. Sadeh, J. Alster, D. Urbach PL. Actigraphically based automatic bedtime sleep-wake scoring: Validity and clinical applications. *J Ambul Monit* 1989;2:209–16.
- [23] Hyde M, O’Driscoll DM, Binette S, Galang C, Tan SK, Verginis N, et al. Validation of actigraphy for determining sleep and wake in children with sleep disordered breathing. *J Sleep Res* 2007;16:213–6. <https://doi.org/10.1111/j.1365-2869.2007.00588.x>.

- [24] Spruyt K, Gozal D, Dayyat E, Roman A, Molfese DL. Sleep assessments in healthy school-aged children using actigraphy: concordance with polysomnography. *J Sleep Res* 2011;20:223–32. <https://doi.org/10.1111/j.1365-2869.2010.00857.x>.
- [25] Belanger M-E, Bernier A, Paquet J, Simard V, Carrier J. Validating actigraphy as a measure of sleep for preschool children. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* 2013;9:701–6. <https://doi.org/10.5664/jcsm.2844>.
- [26] Steinsbekk S, Belsky D, Guzey IC, Wardle J, Wichstrøm L. Polygenic Risk, Appetite Traits, and Weight Gain in Middle Childhood: A Longitudinal Study. *JAMA Pediatr* 2016;170:e154472. <https://doi.org/10.1001/jamapediatrics.2015.4472>.
- [27] Sadeh A, Sharkey KM, Carskadon MA. Activity-based sleep-wake identification: an empirical test of methodological issues. *Sleep* 1994;17:201–7.
- [28] Cole TJ, Freeman J V, Preece MA. Body mass index reference curves for the UK, 1990. *Arch Dis Child* 1995;73. <https://doi.org/10.1136/adc.73.1.25>.
- [29] Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, et al. Consensus Statement of the American Academy of Sleep Medicine on the Recommended Amount of Sleep for Healthy Children: Methodology and Discussion. *J Clin Sleep Med* 2016;12:1549–61. <https://doi.org/10.5664/jcsm.6288>.
- [30] Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010;42:937–48. <https://doi.org/10.1038/ng.686>.
- [31] Liu J, Zhang A, Li L. Sleep duration and overweight/obesity in children: Review and implications for pediatric nursing. *J Spec Pediatr Nurs* 2012;17:193–204. <https://doi.org/10.1111/j.1744-6155.2012.00332.x>.
- [32] Tyrrell J, Wood AR, Ames RM, Yaghoobkar H, Beaumont RN, Jones SE, et al. Gene–obesogenic environment interactions in the UK Biobank study. *Int J Epidemiol* 2017;dyw337. <https://doi.org/10.1093/ije/dyw337>.
- [33] Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518:197–206. <https://doi.org/10.1038/nature14177>.
- [34] Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? *Epidemiology* 2008;19:838–45. <https://doi.org/10.1097/EDE.0b013e318187a7b0>.
- [35] Biddle DJ, Robillard R, Hermens DF, Hickie IB, Glozier N, Buysse DJ, et al. Accuracy of self-reported sleep parameters compared with actigraphy in young people with

mental ill-health. *Sleep Health* 2015;1:214–20.
<https://doi.org/10.1016/j.sleh.2015.07.006>.

Table 1. *Sample characteristics in TESS, at age 6*

	Mean (SD)/N (%)
Age (years)	6.01 (0.16)
BMI (kg/m ²)	15.35 (1.23)
BMI-SDS	-0.22 (0.83)
Sex	
Boys	246 (54.42)
Girls	206 (45.58)
Weight status	
Underweight	52 (11.50)
Normal weight	382 (84.51)
Overweight/obese	18 (3.98)
Total sleep time (hours)	9.59 (0.76)

Note. BMI= body mass index.

Table 2. *SNPs included in the BMI GRS*

Chr	Nearest Gene	rs	Alleles	BMI-		
				Increasing Allele	Frequency of BMI- Increasing Allele	GWAS Effect- Size for BMI
1	NEGR1	rs2568958	A/G	A	60%	0.13
	TNNI3K	rs1514177	C/G	G	43%	0.07
	PTBP2	rs11165643	C/T	T	63%	0.06
	SEC16B	rs10913469	C/T	C	21%	0.21
2	TMEM18	rs7567570	C/T	C	82%	0.31
	ADCY3, RBJ	rs10182181	A/G	G	51%	0.14
	FANCL	rs887912	A/G	A	29%	0.10
3	CADM2	rs7640855	A/G	A	20%	0.10
	ETV5	rs7647305	C/T	C	79%	0.12
4	SLC39A8	rs13107325	C/T	T	8%	0.19
5	FLJ35779	rs2112347	G/T	T	65%	0.10
	ZNF608	rs6864049	A/G	G	55%	0.07
6	TFAP2B	rs2206277	A/G	A	18%	0.13
9	LRRN6C	rs1412235	C/G	C	31%	0.11
	LMX1B	rs867559	A/G	G	21%	0.24
11	STK33, RPL27A	rs4929949	C/T	C	52%	0.06
	BDNF	rs6265	A/G	G	52%	0.18
	MTCH2	rs10838738	A/G	G	34%	0.05
12	BCDIN3, FAIM2	rs7138803	A/G	A	36%	0.12
13	MTIF3	rs1475219	C/T	C	20%	0.09
14	PRKD1	rs11847697	C/T	T	3%	0.17
	NRXN3	rs10150332	C/T	C	23%	0.13
15	MAP2K5	rs2241423	A/G	G	78%	0.13
16	GPRC5B	rs12446554	G/T	G	87%	0.17
	SH2B1	rs4788102	A/G	A	39%	0.15
	FTO	rs9939609	A/T	A	36%	0.38
18	MC4R	rs921971	C/T	C	28%	0.21
19	KCTD15	rs29941	C/T	C	67%	0.06
	ZC3H4, TMEM160	rs3810291	A/G	A	68%	0.09

Note. BMI=body mass index, Chr=chromosome, GWAS=genome-wide association studies. Alleles are reported from the forward strand. The nearest gene is reported for the locus identified in the BMI GWAS by the GIANT consortium (Speliotes et al., 2010). GWAS effect sizes are the per-allele change in BMI estimated in meta-analysis of BMI GWAS by the GIANT consortium.