Genes Nutr (2015) 10:1
DOI 10.1007/s12263-014-0449-8

RESEARCH PAPER

Role of genetic variants in *ADIPOQ* in human eating behavior

Kerstin Rohde · Maria Keller · Annette Horstmann · Xuanshi Liu · Fabian Eichelmann · Michael Stumvoll · Arno Villringer · Peter Kovacs · Anke Tönjes · Yvonne Böttcher

Received: 13 August 2014 / Accepted: 29 November 2014 / Published online: 27 December 2014

Abstract The beneficial effects of adiponectin and its negative correlation with BMI are well described. Adiponectin serum levels are altered in eating disorders such as anorexia nervosa, bulimia nervosa or binge eating. Here, we tested the hypothesis that (1) adiponectin serum levels correlate with human eating behavior factors and (2) that genetic variants of the *ADIPOQ* locus influence both serum levels and eating behavior. We analyzed 11 SNPs within *ADIPOQ* and in the 5′ UTR and measured serum adiponectin levels in 1,036 individuals from the German Sorbs population. The German version of the three-factor eating questionnaire (FEV) was completed by 548 Sorbs. For replication purposes, we included an independent replication cohort from Germany ($N = 350$). In the Sorbs, we observed positive correlations of restraint with adiponectin serum levels ($P = 0.001$; $r = 0.148$) which, however, did not withstand adjustment for covariates ($P = 0.083$; $r = 0.077$). In addition, four SNPs were nominally associated with serum adiponectin levels (all $P < 0.05$). Of these, two variants (rs3774261; rs1501229, all $P < 0.05$) were also related to disinhibition. Furthermore, three variants were exclusively associated with hunger (rs2036373, $P = 0.049$) and disinhibition (rs822396; rs864265, all $P < 0.05$). However, none of these associations withstood Bonferroni corrections for multiple testing (all $P > 9.3 \times 10^{-4}$). In our replication cohort, we observed similar effect directions at rs1501229 for disinhibition and hunger. A meta-analysis resulted in nominal statistical significance $P = 0.036$ (Z score 2.086) and $P = 0.017$ (Z score 2.366), respectively. Given the observed relationship of the SNPs with adiponectin levels and eating behavior, our data support a potential role of adiponectin in human eating behavior. Whether the relationship with eating behavior is mediated by the effects of circulating adiponectin warrants further investigations.

Keywords Adiponectin serum levels · Genetics · Eating behavior · Human studies

Kerstin Rohde and Maria Keller have contributed equally.

K. Rohde · M. Keller · A. Horstmann · X. Liu · F. Eichelmann · M. Stumvoll · P. Kovacs · Y. Böttcher (✉)
IFB Adiposity Diseases, University of Leipzig, Liebigstraße 21, 04103 Leipzig, Germany
e-mail: yvonne.boettcher@medizin.uni-leipzig.de

K. Rohde
e-mail: Kerstin.Rohde@medizin.uni-leipzig.de

A. Horstmann · A. Villringer
Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

X. Liu
Bioinformatics Group, Department of Computer Science, University of Leipzig, Leipzig, Germany

M. Stumvoll · A. Tönjes
Department of Medicine, University of Leipzig, Leipzig, Germany

A. Villringer
Clinic of Cognitive Neurology, University of Leipzig, Leipzig, Germany

Introduction

Human circulating adiponectin is a well-described adipocytokine exerting anti-inflammatory (Yokota et al. 2000) and insulin-sensitizing effects (Yamauchi et al. 2001; Berg et al. 2001). An inverse relationship to obesity and BMI with beneficial effects for insulin sensitivity was shown (Arita et al. 1999; Cnop et al. 2003). Adiponectin serum

levels may be influenced by nutritional compounds as well as physical activity, environmental components and gender (Henneman et al. 2010; Antoniades et al. 2009; Mantzoros et al. 2006). In particular, a 1.5-fold higher concentration in women compared to men was described (Heid 2006). Besides several other loci such as *ARL15* (ADP-ribosylation factor-like 15 gene locus) (Richards et al. 2009), the strongest genetic determinants influencing circulating adiponectin concentrations were identified within the *ADIPOQ* locus (adiponectin gene locus) (Ling et al. 2009; Heid et al. 2010; Richards et al. 2009).

Physiologic effects of adiponectin are mainly mediated by binding to one of its two receptor isoforms (AdipoR1 and AdipoR2) (Zhao et al. 2005) consequently activating signaling cascades such as adenosine monophosphate-activated protein kinase (AMPK) (Yamauchi et al. 2002), and PPARα transcription factor (peroxisome proliferator-activated receptor alpha) or NF-κB (nuclear factor 'kappa-light-chain-enhancer' of activated B cells) (Thundyil et al. 2012). AdipoR1 is most abundantly expressed in skeletal muscle and highly affine for globular adiponectin, while AdipoR2 binds full-length and globular adiponectin and is predominantly expressed in liver (Yamauchi et al. 2003). AdipoR1 and AdipoR2 are also expressed in human adipocytes (Rasmussen et al. 2006; Fasshauer et al. 2004; Li et al. 2007). Circulating adiponectin was shown to be involved in enhanced glucose uptake via GLUT4 (glucose transporter 4) (Ceddia et al. 2005; Mao et al. 2006), as well as in enhanced fatty acid uptake and oxidation in skeletal muscle in animal models (Tomas et al. 2002; Yoon 2006). Adiponectin-dependent AMPK activation may demonstrate a link to beneficial effects of this adipokine on metabolic and cardiovascular systems (Kahn et al. 2005). However, beside these important aspects of adiponectin in peripheral tissues, less is known about its central effects in brain. One study demonstrated that adiponectin administration stimulated the AMPK activation in the arcuate hypothalamus influencing food uptake and energy expenditure (Kubota et al. 2007). While elevated adiponectin levels were present in serum and cerebrospinal fluid during fasting state in mice, these levels were normalized after refeeding, suggesting that adiponectin might influence food intake via central mechanism in the brain (Kubota et al. 2007). One may argue whether similar central effects exist in humans (Pan et al. 2006; Kos et al. 2006). Consistent with potential central effects, human adiponectin levels were also shown to be altered in eating disorders such as anorexia nervosa, binge eating disorder and bulimia nervosa (reviewed in, e.g., Bou Khalil and El Hachem 2014). In particular, many studies demonstrated elevated adiponectin serum levels in female patients affected with anorexia nervosa (Modan-Moses et al. 2007; Pannacciulli et al. 2003; Terra et al. 2013), while binge eating disorder was related to decreased circulating adiponectin (Monteleone et al. 2003; Carnier et al. 2012). It is worth noting that inconsistent data exist for patients suffering from bulimia nervosa (Housova et al. 2005; Tagami et al. 2004; Monteleone et al. 2003). Taken together, besides its well-known effects in terms of obesity, type 2 diabetes and related metabolic conditions adiponectin seems to be involved in food intake and energy expenditure as well as in the pathophysiology of eating disorders.

Here, we tested the hypothesis that adiponectin serum levels correlate with human eating behavior factors measured by the German version of the three-factor eating questionnaire (Fragebogen zum Essverhalten—FEV). Further, we analyzed whether genetic variation in the *ADIPOQ* locus influences adiponectin serum levels and the eating behavior factors restraint, disinhibition and hunger.

Materials and methods

Subjects

The Sorbs cohort is a self-contained population from eastern Germany which was extensively phenotyped for a wide range of anthropometric and metabolic phenotypes including weight, height, waist-to-hip-ratio (WHR) and a 75-g oral glucose tolerance test (OGTT) and standardized questionnaires for individual medical history and family histories (Veeramah et al. 2011). A total of 1,036 subjects with mean age of 48 ± 16 years and mean BMI 26.9 ± 4.9 kg/m^2 were included. A total of 548 Sorbs completed the FEV (Pudel and Westenhöfer 1989), the German version of the TFEQ (Stunkard and Messick 1985) as described elsewhere (Gast et al. 2013). Total adiponectin serum levels were measured in the Sorbs population. All subjects gave written informed consent, and the study was approved by the ethics committee of the University of Leipzig. The main characteristics of the Sorbs are summarized in Table 1.

The replication cohort is an independent German population described elsewhere (Gast et al. 2013). A total of 350 individuals were included in the analysis (mean age of 27 ± 5 years and mean BMI of 27.0 ± 6.2 kg/m^2; Table 1). Phenotyping included anthropometric measurements (BMI, weight, height) and human eating behavior factors measured using the FEV (Pudel and Westenhöfer 1989). The local ethics committee of the University of Leipzig approved the study.

Genetic analysis of the *ADIPOQ* locus

Eleven *ADIPOQ* SNPs (single nucleotide polymorphisms) within the *ADIPOQ* gene and the 5′ UTR (5′ untranslated

Table 1 Main characteristics of the study populations

	Sorbs			Replication cohort		
	Total	Male	Female	Total	Male	Female
N total	1,036	418	618	350	189	152
Age	48 ± 16	48 ± 17	48 ± 16	27 ± 5	27 ± 5	27 ± 5
BMI (kg/m^2)	26.9 ± 4.9	27.2 ± 4.0	26.8 ± 5.5	27.0 ± 6.2	26.9 ± 5.8	27.1 ± 6.7
Serum adiponectin (μg/ml)	16.6 ± 5.5	14.5 ± 5.1	18.0 ± 5.3	n.a.	n.a.	n.a.

Data are presented as mean ± SD

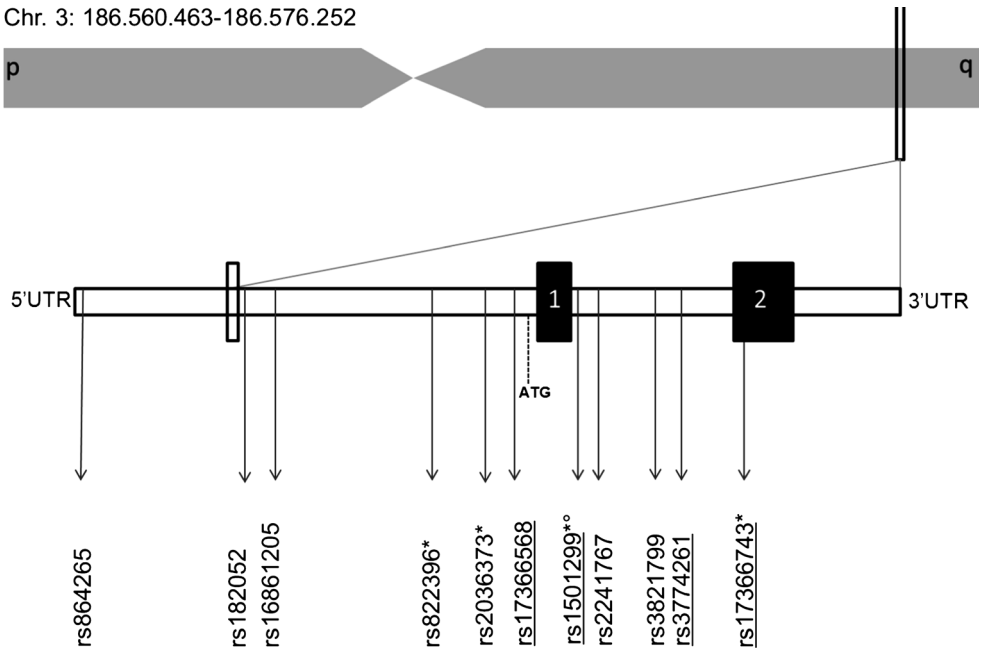

Fig. 1 Gene structure of the *ADIPOQ* gene (not scaled) and its location on Chromosome 3. *Filled boxes* present coding exons, *unfilled* indicate non-coding exons. ATG: translation start; *asterisk* SNPs de novo genotyped in this study. Genotype data for the other SNPs were extracted from previous analysis (Tönjes et al. 2009). *Underlined* SNPs were significantly associated with adiponectin serum levels in the Sorbs. *Circle* SNPs remain significant with disinhibition and hunger after meta-analysis

region) were analyzed. Of these, genotypes for seven SNPs (rs864265; rs182052; rs16861205; rs17366568; rs2241767; rs3821799; rs3774261) were extracted from Affymetrix Genome-Wide Human SNP data (Affymetrix Inc., Santa Clara, CA, USA) earlier described by Tönjes et al. (2009). Four additional tagging variants (rs822396; rs1501229; rs2036373; rs17366743) were selected from the HapMap database ($r^2 > 0.8$, minor allele frequency (MAF) < 0.05) and individually genotyped (Fig. 1). De novo genotyping of rs822396; rs1501229; rs2036373; and rs17366743 was performed using TaqMan® SNP Genotyping Assay (Applied Biosystems by Life-Technologies Carlsbad, CA, USA). Fluorescence was detected by an ABI 7500 Real-Time PCR system. All SNPs were in Hardy–Weinberg equilibrium (all $P > 0.05$) except rs822396 in the Sorbs. To avoid genotyping errors, a random selection (~5 %) of the sample was re-genotyped; all genotypes matched the initially designated genotypes. Water was used as a no template control (NTC).

Measurement of circulating serum adiponectin

Total adiponectin serum levels in the Sorbs were measured using a high-sensitivity human adiponectin ELISA (Bio-Vendor; Heidelberg; Germany) using antibodies specific for human adiponectin according to manufacturers' instructions. Serum samples were collected after an overnight fast.

Statistics

Non-normally distributed data were logarithmically transformed to approximate a normal distribution. Linear

Table 2 Adiponectin serum levels in T2D and obesity in the Sorbs

	T2D		Obesity		
	Yes	No	Lean	Overweight	Obese
N total	103	845	360	369	220
Serum adiponectin (μg/ml)	15.5 ± 5.9	16.6 ± 5.1	17.5 ± 5.0	15.8 ± 5.1	16.1 ± 5.4
P value	**0.047**[a] (adjusted for BMI: 0.330)		**4.2×10^{-8}**[b]; **0.001**[c]		

Circulating adiponectin levels in μg/ml are presented as mean ± SD. *P* values were calculated using unpaired *t* tests

[a] T2D yes versus no; [b] lean versus overweight; [c] lean versus obese

regression models adjusted for age, gender and BMI (except for BMI) were employed to test for genetic association with BMI, eating behavior factors (restraint, disinhibition and hunger) and serum adiponectin levels. Additive model of inheritance was tested. Individuals with type 2 diabetes (T2D) were excluded from the genetic association analysis for eating behavior factors and adiponectin serum levels. Linear regression analyses adjusted for age, gender and BMI were used to assess the relationship between eating behavior and serum adiponectin levels. To correct for multiple testing, we applied Bonferroni correction as suggested at: http://www.quantitativeskills.com/sisa/calculations/bonfer.htm (alpha niveau 0.05; number of tests/phenotypes = 55) and lowered the significance threshold to $P < 9.3 \times 10^{-4}$. All *P* values $> 9.3 \times 10^{-4}$ but ≤ 0.05 were considered to be of nominal statistical significance. All *P* values are provided without the Bonferroni correction. SPSS statistics version 20.0.1 (SPSS, Inc.; Chicago, IL) was used for all statistical analyses. Meta-analyses were performed using METAL (Willer et al. 2010).

Results

Circulating adiponectin levels in the Sorbs

As expected, adiponectin serum levels were negatively correlated with BMI ($P = 4.5 \times 10^{-5}$; $r = -0.141$, Table 2). A strong positive correlation of serum adiponectin with the eating behavior factor restraint was observed ($P = 0.001$, $r = 0.148$), which, however, did not withstand adjustment for covariates such as age, gender and BMI ($P = 0.083$; $r = 0.077$).

ADIPOQ SNPs associated with adiponectin serum levels and human eating behavior phenotypes

We observed nominal associations between four intragenic SNPs (rs1501229; rs17366743; rs17366568; and rs3774261) and circulating adiponectin levels in the Sorbs (all $P < 0.05$, Table 3). The strongest relationship was detected at rs3774261 (Table 3), an intronic variant with minor allele carriers conferring increased serum adiponectin levels ($P = 0.006$; $\beta = 0.693$).

Of these four variants, two SNPs were also nominally related to disinhibition (rs1501229 and rs3774261, Table 3). Minor allele carriers of these two variants showed both elevated serum adiponectin levels and increased disinhibition scores. In addition, we observed a third SNP (rs2036373) exerting a nominal association with hunger (Table 3). Two further variants, rs822396 and rs864265, were exclusively related to disinhibition. However, none of these associations withstood Bonferroni corrections for multiple testing (all $P > 9.3 \times 10^{-4}$). No relationship between the variants and BMI was observed.

Replication analysis in an independent German cohort

Two variants (rs3774261 and rs1501229) conferring the strongest relationships to both, adiponectin serum levels and the eating behavior factor disinhibition in the Sorbs, were taken forward to replication analyses in an independent German cohort. None of the variants were related to eating behavior factors (Table 4, all $P > 0.05$). Nonetheless, we observed similar effect directions for rs1501229 as in the Sorbs showing elevated disinhibition scores in minor allele carriers. We did not find similar effect directions between the Sorbs and the replication cohort for rs3774261.

Meta-analyses

A sample size-weighted meta-analysis for rs1501229 and rs3774261 including the results from the two study populations (Sorbs and German cohort) resulted in nominal statistical significance at rs1501229 with disinhibition and hunger (combined $P_{\text{disinhibition}} = 0.0369$ (*Z* score 2.086); $P_{\text{hunger}} = 0.01798$ (*Z* score 2.366) Table 5).

Table 3 Association analysis of *ADIPOQ* genetic variants with adiponectin levels and eating behavior factors in the Sorbs

SNP	Genotype *N*	Gender M/F	BMI kg/m^2	Adiponectin μg/ml	Restraint *N* = 548	Disinhibition *N* = 548	Hunger *N* = 547
rs864265	T/T *N* = 12	6/6	27.2 ± 4.2	16.44 ± 4.74	7.38 ± 4.08	2.63 ± 2.00	2.94 ± 1.48
	T/G *N* = 178	70/108	26.8 ± 4.7	16.75 ± 5.17	8.09 ± 4.48	4.01 ± 2.70	3.58 ± 2.77
	G/G *N* = 642	256/386	26.4 ± 4.7	16.56 ± 5.13	7.84 ± 5.03	4.45 ± 3.05	4.03 ± 2.82
P value			n.s.	n.s.	n.s.	**0.015**[a]	n.s.
rs182052	A/A *N* = 154	62/92	26.9 ± 4.7	16.18 ± 4.99	7.75 ± 4.75	3.88 ± 2.81	3.59 ± 2.50
	A/G *N* = 396	160/236	26.3 ± 4.7	16.88 ± 5.12	7.67 ± 4.83	4.47 ± 3.18	4.12 ± 3.00
	G/G *N* = 284	113/171	26.5 ± 4.6	16.43 ± 5.22	8.22 ± 5.04	4.30 ± 2.77	3.76 ± 2.63
P value			n.s.	n.s.	n.s.	n.s.	n.s.
rs16861205	A/A *N* = 3	1/2	28.2 ± 11.8	17.62 ± 3.40	10.00 ± 0.00	5.00 ± 0.00	0.00 ± 0.00
	A/G *N* = 135	50/85	26.9 ± 5.3	16.00 ± 5.02	7.75 ± 4.83	4.55 ± 3.25	3.90 ± 3.22
	G/G *N* = 697	283/414	26.4 ± 4.5	16.70 ± 5.15	7.90 ± 4.92	4.27 ± 2.93	3.92 ± 2.71
P value			n.s.	n.s.	n.s.	n.s.	n.s.
rs17366568	A/A *N* = 12	3/9	22.5 ± 3.4	17.52 ± 4.52	6.61 ± 4.26	3.67 ± 3.71	3.94 ± 2.46
	A/G *N* = 175	73/102	26.5 ± 4.6	15.81 ± 5.28	7.61 ± 4.83	4.32 ± 3.22	3.61 ± 2.90
	G/G *N* = 649	259/390	26.6 ± 4.7	16.78 ± 5.08	7.98 ± 4.93	4.32 ± 2.89	3.98 ± 2.77
P value			n.s.	**0.027**[a]	n.s.	n.s.	n.s.
rs2241767	G/G *N* = 2	0/2	27.2 ± 2.6	18.71 ± 5.08	12.00 ± 0.00	2.00 ± 0.00	1.00 ± 0.00
	G/A *N* = 86	37/49	26.0 ± 4.3	16.84 ± 5.89	8.37 ± 4.52	4.69 ± 3.20	3.76 ± 2.59
	A/A *N* = 747	298/449	26.6 ± 4.8	16.57 ± 5.03	7.81 ± 4.94	4.26 ± 2.94	3.91 ± 2.80
P value			n.s.	n.s.	n.s.	n.s.	n.s.
rs3821799	T/T *N* = 138	54/84	26.2 ± 5.1	17.23 ± 5.53	6.99 ± 4.75	4.92 ± 2.95	4.31 ± 3.04
	T/C *N* = 408	172/236	26.4 ± 4.4	16.49 ± 4.88	8.17 ± 5.09	4.14 ± 2.88	3.79 ± 2.69
	C/C *N* = 289	110/179	26.9 ± 4.9	16.41 ± 5.27	7.87 ± 4.64	4.27 ± 3.09	3.90 ± 2.78
P value			n.s.	n.s.	n.s.	n.s.	n.s.
rs3774261	A/A *N* = 94	36/58	26.0 ± 5.0	17.85 ± 5.20	7.46 ± 5.04	4.89 ± 2.92	4.17 ± 2.92
	A/G *N* = 396	164/232	26.4 ± 4.4	16.61 ± 5.00	8.07 ± 5.16	4.34 ± 2.87	3.92 ± 2.81
	G/G *N* = 347	136/211	26.8 ± 5.0	16.22 ± 5.21	7.80 ± 4.56	4.10 ± 3.09	3.81 ± 2.74
P value			n.s.	**0.006**[a]	n.s.	**0.019**[a]	n.s.
rs822396	G/G *N* = 56	21/35	26.40 ± 4.67	17.57 ± 4.95	7.89 ± 4.4	3.49 ± 2.6	3.61 ± 2.6
	A/G *N* = 288	117/171	26.95 ± 4.77	16.71 ± 4.81	8.06 ± 5.0	4.19 ± 2.9	3.86 ± 2.8
	A/A *N* = 553	218/335	26.21 ± 4.58	16.48 ± 5.27	7.84 ± 4.9	4.52 ± 3.1	3.61 ± 2.6
P value			n.s.	n.s.	n.s.	**0.036**[a]	n.s.
rs1501229	T/T *N* = 70	30/40	25.60 ± 4.63	17.70 ± 5.12	7.24 ± 5.35	4.81 ± 2.70	3.78 ± 2.68
	G/T *N* = 387	154/233	26.55 ± 4.51	16.80 ± 4.90	8.13 ± 5.10	4.51 ± 2.95	3.96 ± 2.95
	G/G *N* = 434	172/262	26.52 ± 4.76	16.31 ± 5.29	7.88 ± 4.61	4.13 ± 3.10	4.52 ± 2.92
P value			n.s.	**0.010**[a]	n.s.	**0.016**[a]	n.s.
rs2036373	G/G *N* = 2	1/1	32.30 ± 12.45	17.83 ± 2.53	8.00 ± 7.1	4.25 ± 3.18	2.00 ± 0.00
	G/T *N* = 75	38/37	26.87 ± 4.42	16.50 ± 5.99	7.87 ± 4.8	4.87 ± 3.03	4.67 ± 3.09
	T/T *N* = 811	313/498	26.43 ± 4.64	16.65 ± 5.01	7.92 ± 4.	4.32 ± 3.01	3.85 ± 2.79
P value			n.s.	n.s.	n.s.	n.s.	**0.049**[a]
rs17366743	C/C *N* = 0						
	C/T *N* = 39	18/21	27.30 ± 3.27	14.96 ± 4.84	8.91 ± 5.72	4.77 ± 3.52	3.59 ± 2.58
	T/T *N* = 855	339/516	26.43 ± 4.71	16.71 ± 5.12	7.88 ± 4.86	4.31 ± 2.98	3.92 ± 2.81
P value			n.s.	**0.036**[a]	n.s.	n.s.	n.s.

Data are presented as mean ± SD

n.s. non-significant ($P > 0.05$)

[a] *P* values (additive model of inheritance) were calculated using linear regression analysis, adjusted for age, gender and ln BMI

Table 4 Replication analyses in an independent German cohort

SNP	Genotype *N*	Gender M/F	Age years	BMI kg/m^2	Restraint	Disinhibition	Hunger
rs1501229	T/T $N = 36$	23/13	26 ± 4.0	28.3 ± 6.7	7.51 ± 5.02	6.47 ± 2.86	6.03 ± 3.50
	G/T $N = 121$	65/56	27 ± 5.3	27.0 ± 6.6	5.46 ± 4.13	6.17 ± 3.21	5.82 ± 3.32
	G/G $N = 156$	87/69	27 ± 5.0	26.8 ± 5.8	6.37 ± 4.56	6.09 ± 3.21	5.14 ± 3.38
P value			n.s.	n.s.	n.s.	n.s.	n.s.
rs3774261	A/A $N = 56$	33/23	26 ± 4.3	28.0 ± 6.9	7.53 ± 4.59	6.20 ± 2.73	5.82 ± 3.54
	A/G $N = 133$	74/59	27 ± 5.5	26.8 ± 6.2	5.43 ± 4.23	6.02 ± 3.22	5.62 ± 3.34
	G/G $N = 123$	67/56	26.5 ± 4.8	27.0 ± 5.9	6.36 ± 4.65	6.38 ± 3.32	5.34 ± 3.46
P value			n.s.	n.s.	n.s.	n.s.	n.s.

Data are presented as mean ± SD. *P* values (additive model of inheritance) were calculated using linear regression analysis, adjusted for age, gender and ln BMI.

n.s. non-significant ($P > 0.05$)

Table 5 Meta-analysis for Sorbs and German replication cohort

SNP	Minor allele	Sorbs			German cohort			Combined		
		P value	*β*	SE	*P* value	*β*	SE	*P* value	*Z* score	Direction
		Disinhibition								
rs1501229	T	**0.016**	0.429	0.178	0.781	0.067	0.239	**0.03696**	2.086	++
rs3774261	A	**0.019**	0.412	0.175	0.431	−0.177	0.225	0.1762	1.352	+−
		Restraint								
rs1501229	T	0.800	−0.078	0.307	0.852	0.069	0.369	0.9275	−0.091	−+
rs3774261	A	0.893	−0.041	0.307	0.360	0.318	0.347	0.6483	0.456	−+
		Hunger								
rs1501229	T	0.097	0.296	0.178	0.084	0.487	0.281	**0.01798**	2.366	++
rs3774261	A	0.389	0.152	0.176	0.378	0.236	0.267	0.2217	1.222	++

P values were calculated based on effect sizes from linear regression model using additive inheritance model. Significant *P* values < 0.05 are presented in bold. All data are adjusted for age, gender and ln BMI. All analyses were standardized to the minor allele

Discussion

The present study mainly supports the well-known relationship between genetic variants in the *ADIPOQ* gene locus and adiponectin serum levels. Beyond this, we observed two variants conferring increased adiponectin levels along with increased eating behavior scores which, however, did not withstand correction for multiple testing. Moreover, we found circulating adiponectin correlated with the eating behavior factor restraint in the German Sorbs.

ADIPOQ locus and adiponectin serum levels

In the Sorbs, we found mean circulating adiponectin levels of 16.62 ± 5.10 µg/ml. In line with others describing significant differences between male and female adiponectin serum levels (Heid 2006) which is most likely caused by enriched testosterone levels in men inhibiting the secretion of high molecular weight (HMW) adiponectin from adipocytes (Xu et al. 2005; Wang et al. 2008), we found ~19 % higher serum levels in women compared to men. Many studies described genetic variants in the *ADIPOQ* locus to be associated with reduced adiponectin levels in T2D, obesity and impaired insulin sensitivity (Vasseur 2002; Comuzzie et al. 2001; Ramya et al. 2013; Peters et al. 2013; Kadowaki 2006). Consistently, in the Sorbs, adiponectin serum levels are negatively correlated with BMI. The *ADIPOQ* gene locus was shown to be a major locus influencing plasma adiponectin levels with genome-wide significance (Heid 2006; Ling et al. 2009). Several studies identified rs17366568 upstream the transcription start site showing strongest associations to adiponectin serum concentration (Heid 2006; Peters et al. 2013; Cohen et al. 2011; Mather et al. 2012). In line with this, the same variant was nominally associated with circulating adiponectin in the Sorbs (*P* value = 0.027). Consistently with other studies, we observed three other markers influencing adiponectin serum levels (Ramya et al. 2013).

ADIPOQ locus and eating behavior

Beside its well-described role in endocrine metabolism and cardiovascular function in peripheral tissues as well as the reported autocrine effects on adipocytes (Wu et al. 2003), adiponectin confers also central effects on energy expenditure or food intake (Kubota et al. 2007; Qi et al. 2004; Kadowaki et al. 2008). It was recently shown that adiponectin is also expressed in brain (Rodriguez-Pacheco et al. 2007; Psilopanagioti et al. 2009) and is functionally active (Rodriguez-Pacheco et al. 2007). In addition, several studies reported intracerebral injection (Hoyda et al. 2009a; Iwama et al. 2009; Park et al. 2011) and most importantly expression of adiponectin receptors in the brain (Hoyda et al. 2009b; Dadson et al. 2011). Further, it was shown that peripherally administered adiponectin is able to cross the blood–brain barrier and binds similarly to leptin neuronal targets in the hypothalamus (Thundyil et al. 2012; Qi et al. 2004; Kubota et al. 2007). In the present study, we observed several SNPs in the *ADIPOQ* gene locus which were nominally associated with human eating behavior factors such as disinhibition and hunger (Pudel and Westenhöfer 1989) as well as with adiponectin levels themselves. Minor allele carrier shows elevated adiponectin serum levels along with increased disinhibition scores which indicate the tendency to frequently overeat. It is of note, however, that none of these nominal associations withstands correction for multiple testing. Moreover, although we observed a positive correlation of restraint with adiponectin serum levels, no significant relationship of eating behavior factors and adiponectin concentrations was observed. Comparing low versus high adiponectin level groups results in significantly higher restraint scores in the high adiponectin group; however, these data do not withstand adjustment for gender (data not shown). Nevertheless, albeit non-significant, our data are in line with the hypothesis that adiponectin activates AMPK-mediated signaling via adiponectin receptor binding in the hypothalamus as demonstrated in animal models (Kubota et al. 2007; Minokoshi et al. 2008). This may result in overeating or increased hunger feelings. Since adiponectin levels can be further influenced by nutritional compounds, increased food intake may in turn serve as a positive feedback process (Mantzoros et al. 2006). However, this mechanism seems to be accompanied by decreased energy expenditure that may ultimately lead together with overeating to increased body weight (Kubota et al. 2007; Minokoshi et al. 2008). In contrast, Qi et al. (2004) reported a temporary loss in body weight after adiponectin injection into lateral-cerebral ventricles without decreased food intake in mice. The authors concluded that higher energy expenditure resulted in the weight loss, which was further supported by increased brown adipose tissue UCP-1 (uncoupling protein-1) mRNA expression. It is still not yet clarified how adiponectin acts in the human brain, because animal studies are not fully comparable with humans and adiponectin in human cerebrospinal fluid is 1000-fold lower than serum levels (Pan et al. 2006; Kos et al. 2006). Further studies are warranted to better understand whether adiponectin acts directly through beneficial effects in peripheral tissues or indirectly by activating AMPK that may lead to altered food intake or energy expenditure.

Our study is limited at several aspects. In particular, in regard to our association results for eating behavior factors, it needs to be acknowledged that the TFEQ from Stunkard and Messick (1985) provides several restrictions. While the questionnaire identifies the three factors restraint, disinhibition and hunger, the subscale disinhibition was most consistently reported to be related with increased BMI and obesity as well as with higher energy intake (Bryant et al. 2008). It was demonstrated (Dykes et al. 2003; French et al. 1994) that disinhibition is strongly related to overeating without hunger feelings in certain situational circumstances which otherwise correlates with a high amount of food intake. Conflicting results, however, were reported for the relationship between restraint and BMI (Dykes et al. 2003; French et al. 1994), while in individuals with high restraint scores both increased and decreased energy intakes were observed (Bellisle et al. 2004; French et al. 1994). Moreover, since the questionnaire does not allow to drawing any conclusions in terms of energy intake, our data can only be interpreted in terms of eating behavior dimensions which are related to energy intake.

Therefore, our data need to be interpreted with caution. Despite the fact that the identified associations did not withstand Bonferroni correction, in concert with the well-known effects of SNPs on adiponectin concentrations, we suggest that genetic variants in *ADIPOQ* may potentially play a role in eating behavior which may be mediated via influencing the serum adiponectin levels. However, we are well aware that our data would not allow drawing these conclusions without including larger studies necessary to confirm the observed effects. Moreover, the sample size of the independent replication cohort is small, which is most likely one reason for the non-significant association results. Moreover, the small sample size may also lead to false-positive results. Since effects of gender and age on eating behavior are well recognized (Hays and Roberts 2008; Provencher et al. 2003; Jastreboff et al. 2014; Dakanalis et al. 2013), the large difference in age between the two cohorts in concert with the differential gender ratio may be one reason to explain the observed discrepancies in eating behavior scores. In addition to the reported other limitations, differences in eating behavior scores may have prevented us from identifying statistically significant SNP

effects. Further, we have no serum adiponectin levels available in the replication cohort.

Taken together, in addition to the known relationship between genetic variation in the *ADIPOQ* gene locus and adiponectin serum levels, our data suggest a potential correlation with human eating behavior factors. This may indicate potentially regulatory mechanisms in the brain in regard to beneficial effects of adiponectin. Whether the association with eating behavior is mediated by adiponectin levels or vice versa warrants further investigations.

Acknowledgments We thank all those who participated in the studies. This work was supported by grants from the German Diabetes Association (to Y.B., A.T. and P.K.) and from the DDS Foundation to Y.B. Y.B. was further supported by a research grant from the IFB AdiposityDiseases ADI-K50D, K7-45 and by a research fellowship from the EFSD (European Foundation for the Study of Diabetes). P.K. was supported by ADI-K60E and K7-57. A.H. was supported by a research grant from the IFB AdiposityDiseases ADI-K50F, projects ADI-K7-53 and ADI-K7-54. IFB AdiposityDiseases is supported by the Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01EO1001. K.R. is funded by a research grant from the Boehringer Ingelheim Foundation. A.T., A.H., M.S.; A.V. and P.K. were further supported by a grant from Deutsche Forschungsgemeinschaft, the SFB 1052/1: "Obesity mechanisms" (projects C1 to A.T., A05 to A.H., A1 to M.S. and A.V., B03 to P.K.). X.L. was funded by a research grant from the Deutsche Forschungsgemeinschaft BO 3147/4-1 to Y.B.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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