Reprint from The Review of DIABETIC STUDIES Vol 12 No 3-4 2015/2016 Special Edition Genetics of Type 2 Diabetes

The Review of DIABETIC STUDIES

REVIEW

Genetic Determination of Serum Levels of Diabetes-Associated Adipokines

Dorit Schleinitz[1,2]

[1] *Integrated Research and Treatment Center AdiposityDiseases, University of Leipzig, Liebigstr. 21, 04103 Leipzig, Germany.*
[2] *Department of Medicine, University of Leipzig, 04103 Leipzig, Germany.*

Manuscript submitted August 30, 2015; accepted October 6, 2015

■ Abstract

Adipose tissue secretes an abundance of proteins. Some of these proteins are known as adipokines and adipose-derived hormones which have been linked with metabolic disorders, including type 2 diabetes, and even with cancer. Variance in serum adipokine concentration is often closely associated with an increase (obesity) or decrease (lipodystrophy) in fat tissue mass, and it is affected by age, gender, and localization of the adipose tissue. However, there may be genetic variants which, in consequence, influence the serum concentration of a certain adipokine, and thereby promote metabolic disturbances or, with regard to the "protective" allele, exert beneficial effects. This review focuses on the genetic determination of serum levels of the following adipokines: adiponectin, chemerin, leptin, progranulin, resistin, retinol binding protein 4, vaspin, adipsin, apelin, and omentin. The article reports on the latest findings from genome-wide association studies (GWAS) and candidate gene studies, showing variants located in/nearby the adipokine genes and other (non-receptor) genes. An extra chapter highlights adipokine-receptor variants. Epigenetic studies on adipokines are also addressed.

Keywords: type 2 diabetes · adipokine · ADIPOQ · SNP · chemerin · leptin · progranulin · resistin · RBP4 · vaspin

1. Introduction

In the last decades, the "static" role of adipose tissue as fat storage and mechanical protector has changed. Today, it is regarded as an endocrine organ secreting a multitude of metabolic active adipokines and adipose-derived hormones. The relationship between obesity and insulin resistance is complex, giving rise to a range of metabolic disorders, including type 2 diabetes (T2D), dyslipidemia, and coagulation disorders [1]. To date, over 300 proteins secreted from adipose tissue are known [2-5]. Multiple roles in metabolic and inflammatory responses are attributed to adipokines, which makes them interesting drug targets for the treatment of obesity or insulin resistance [6].

The secretion of adipokines seems to be tissue-specific, with some of them primarily secreted in visceral adipose tissue (VAT) and others in subcutaneous adipose tissue (SAT) [5, 7-9]. The difference in gene expression patterns between VAT and SAT points to genetic heterogeneity [10]. In most cases, the dysregulation of these bioactive proteins and their possible adverse effect on metabolism is associated with increasing fat mass at ectopic sites and/or the development of obesity. Also, a number of additional factors that impact on serum adipokine concentrations have to be taken into account. However, based on the known impact factors such as gender, body mass index (BMI), or fat mass there are still considerable large residuals in regression models. These residuals may result from lifestyle or other environmental factors. There may also be underlying genetic factors that promote metabolic disturbances or exert beneficial effects, as shown for retinol binding protein 4 (RBP4) [11-12].

Abbreviations:

ACTR3C	actin-related protein 3 homolog C (yeast)
ADARB2	adenosine deaminase RNA-specific B2
ADIPOQ	adiponectin
ADIPOR1/R2	adiponectin receptor 1/receptor 2
APLN	apelin
ARL15	ADP-ribosylation factor-like 15
ATG7	autophagy related 7
BMI	body mass index
C3AR1	complement component 3a receptor 1
CAP1	CAP, adenylate cyclase-associated protein 1
CDH13	cadherin 13
CFD	complement factor D; adipsin
CMIP	c-Maf-inducing protein
CMKLR1	chemerin chemokine-like receptor 1
CVD	cardiovascular disease
DTC	differentiated thyroid cancer
EDIL3	EGF-like repeats, discoidin I-like domain 3
EMSA	electrophoretic mobility shift assay
eQTL	expression quantitative trait loci
FER	fer (fps/fes related) tyrosine kinase
Glut 4	glucose transporter 4
GNL3	guanine nucleotide binding protein-like 3
GPR109A	hydroxycarboxylic acid receptor 2
GRP78	heat shock protein family A, member 5
GWAS	genome wide association study/studies
hK7	kallikrein 7
HNF1	hepatocyte nuclear factor 1 alpha
HOMA-IR	homeostasis model assessment for insulin resistance
IL-6	interleukin 6
IRS-1 or 2	insulin receptor substrate 1 or 2
ITLN1	omentin
KCNJ11	potassium channel, inwardly rectifying subfamily J, member 11
KNG1	kininogen
LD	linkage disequilibrium
LEP	leptin
LEPR	leptin receptor
LYPLAL1	lysophospholipase-like 1
MCEMP1	mast cell-expressed membrane protein 1
NDST4	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 4
PEPD	peptidase D
PDE3A	phosphodiesterase 3A, cGMP-inhibited
PGRN	progranulin
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
RARRES2	retinoic acid receptor responder (tazarotene induced) 2; chemerin
RBP4	retinol binding protein 4
RETN	resistin
SAT	subcutaneous adipose tissue
SNP	single nucleotide polymorphism
SORT1	sortilin 1
STRA6	stimulated by retinoic acid 6
T2D	type 2 diabetes
TRIB1	tribbles pseudokinase 1
TYW3/CRYZ	tRNA-yW synthesizing protein 3 homolog/zeta-crystallin
VAT	visceral adipose tissue
VEGFA	vascular endothelial growth factor A
WHR	waist-to-hip ratio

Family and twin studies also indicate a strong heritability for adipokines, suggesting that there are genetic factors that account for the variability in serum adipokine concentrations [13-14]. It is thus surprising that VAT and SAT distribution have not been regarded as traits in genome-wide association studies (GWAS) to date, except for the study by Fox *et al*., and irrespective of waist-to-hip ratio (WHR) [15]. Their inclusion could unravel adipokines that are directly involved in the regulation of fat distribution and subsequently in the development of T2D [16]. To date, it is not clear what comes first in the pathogenesis of T2D, adipose tissue dysfunction leading to imbalanced physiologic concentrations of adipokines or dysregulation of adipokines on a genetic basis promoting obesity and T2D (**Figure 1**). Finally, the genetics of adipokine receptors should not be underestimated as they are responsible for signal transduction in the target tissues.

This review aims to summarize human studies on T2D-related adipokines and genetic variants associated with the serum concentration of specific adipokines. In particular, the review considers the following three aspects: *i*) polymorphisms located in/nearby the adipokine gene and other (non-receptor) variants that associate with serum adipokine concentration, *ii*) genetic variation located in/nearby adipokine receptors that associate with serum adipokine concentrations, and *iii*) epigenetic mechanisms on adipokines discovered to date.

2. Genetic variants associated with serum adipokine concentration

2.1 Adiponectin (ADIPOQ)

Adiponectin is involved in the regulation of insulin sensitivity and glucose metabolism. A decrease in this adipokine is associated with deterioration in virtually all parameters of the metabolic syndrome, including T2D and cardiovascular disease (CVD) [17]. Variants of the *ADIPOQ* gene seem to cause substantial changes in adiponectin levels; this finding was replicated in independent study populations (see detailed review in Breitfeld *et al*., 2011) [17]. During the years following this discovery the data were supported by further studies (**Table 1**) [18-21]. Besides *ADIPOQ*, several other loci have been described to harbor variants that are associated with adiponectin levels, including:

- *ADP-ribosylation factor-like 15* (*ARL15*, rs4311394 C/T) [22]

- *Cadherin 13* (*CDH13*, rs3865188 A/T)
- Near *kininogen 1* (*KNG1*, rs11924390 C/T) [23]
- *Lysophospholipase-like 1* (*LYPLAL1*, rs3001032 C/T)
- *Guanine nucleotide binding protein-like 3* (*GNL3*, rs1108842 A/C)
- *Vascular endothelial growth factor A* (*VEGFA*, rs998584 C/A)
- *Tribbles pseudokinase 1* (*TRIB1*, rs2980879 T/A)
- *Phosphodiesterase 3A, cGMP-inhibited* (*PDE3A*, rs7955516 A/C)
- *Hydroxycarboxylic acid receptor 2* (*GPR109A*, rs601339 C/T)
- *c-Maf-inducing protein* (*CMIP*, rs2925979 T/C)
- *Peptidase D* (*PEPD*, rs731839 C/T) [21]
- *Fer (fps/fes related) tyrosine kinase* (*FER*, 10447248 A/G) (**Table 1**) [24]

Furthermore, in a Japanese population, the AA (TT) genotype of single nucleotide polymorphism (SNP) rs2805533 (A/G or T/C, respectively) in the *adenosine deaminase RNA-specific B2* (*ADARB2*) gene was associated with lower adiponectin levels, and with higher BMI, greater abdominal circumference, and higher triglyceride levels (**Table 1**) [25]. One of the largest non-GWA studies was conducted by Mather *et al*. who investigated seventy-seven tagging SNPs in *ADIPOQ* and its receptors *ADIPOR1* and *ADIPOR2* [26]. They found 13 *ADIPOQ* SNPs associated with baseline adiponectin concentrations in the Diabetes Prevention Program (DPP) cohort, four of which remained significantly associated with log adiponectin concentrations in a multivariable analysis including all 13 significant *ADIPOQ* SNPs:

- rs17366568 A/G
- rs1648707 A/C
- rs17373414 C/T
- rs1403696 C/T [26]

One year later, Peters *et al*. published a similar study, confirming the result obtained by Mather and colleagues [27]. They found nine tagSNPs significantly associated with serum adiponectin. However, these SNPs explain only <5% of the variance in serum adiponectin concentrations (**Table 1**). SNPs that were associated with adiponectin levels in the meta-analysis were summed up for each risk allele an individual possessed to form an allele score [27]. The allele score of three

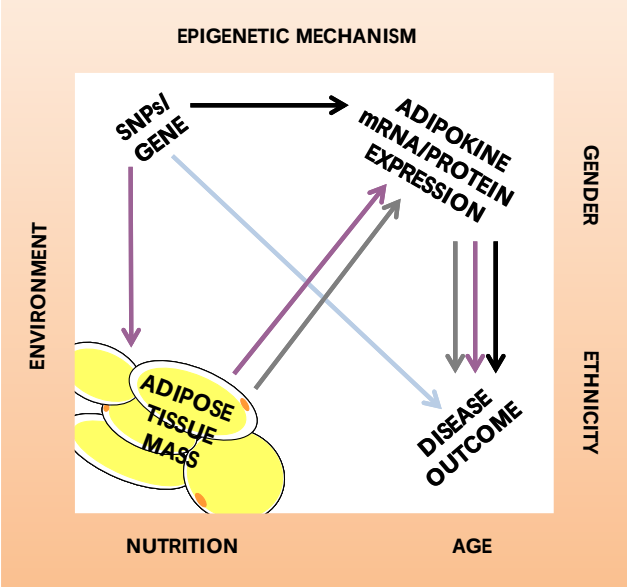

Figure 1. Genetics of adipokines and metabolic disease: cause and consequence. The figure illustrates different effect routes (arrows) impacting a disease outcome (e.g. T2D or obesity), including genetic information, adipose tissue mass, and secreted adipokines. These effects are influenced by multiple factors such as age, gender, nutrition, environment, ethnicity, and epigenetic mechanisms (illustrated by the framing space).

SNPs (rs12637534, rs16861209, rs17366568) was associated with T2D independently of serum adiponectin levels. None of the receptor SNPs was associated with serum adiponectin in this study [27]. Furthermore, rare population-specific mutations have been shown to account for ~17% of the variance in serum adiponectin concentrations (**Table 1**) [28-29].

2.2 Chemerin (RARRES2)

The initial report describing chemerin as an adipokine and elucidating its role in mouse and human white adipocyte differentiation and function was published by Goralski *et al*. in 2007 [30]. Circulating chemerin levels were positively correlated with HbA1c and HOMA-IR, and associated with metabolic syndrome phenotypes; they were also associated with chemerin-induced insulin resistance in primary human skeletal muscle cells [31-34]. Alterations in chemerin serum concentration are detectable in prediabetic states, and may thus reflect adipose tissue dysfunction as an early pathogenic event in T2D development [31].

Table 1. Variants found to be associated with serum adipokine concentrations

Adipokine/ *gene*	SNP-ID	SNP	Gene/ nearby gene	EA	ED	% variance	Reported in
Adiponectin/ *ADIPOQ*	$p < 10^{-8}$						
	rs3774261	A/G	*ADIPOQ*	G	↓	1.2% total, 2% cases, 0.9% controls [133]; < 5% [27]	[133], rev. [17]; [27]
	rs6444175	A/G	*ADIPOQ*	G	↓	n/a [22]; < 5% [27]	[22], rev. [17]; [27]
	rs266717	C/T	*ADIPOQ*	T	↑	n/a	[22], rev. [17]
	rs1426810	A/G	*ADIPOQ*	G	↑	n/a	[22], rev. [17]
	rs1648707	A/C	*ADIPOQ*	C	↓	n/a [20]; 7% attributed to *ADIPOQ* SNPs [26]; < 5% [27]	[22], rev. [17]; [26]; [27]
	rs17366568	A/G	*ADIPOQ*	A	↓	7% attributed to *ADIPOQ* SNPs [26]; <5% [27]	rev. [17]; [26]; [27]
	rs864265	G/T	*ADIPOQ*	T	↓	n/a [23], 3.2% offspring, 2.2% Filipino mothers	[23], [28], rev. [17]
	rs6810075	C/T	*ADIPOQ*	T	↑	n/a	[21]
	rs16861209	A/C	*ADIPOQ*	C	↓	< 5% [27]	[27]
	rs4311394	C/T	*ARL15*	C	↓	n/a	[22], rev. [17]
	rs3865188	A/T	*CDH13*	T	↓	n/a	[23]; [134]*, rev. [17]
	rs12922394	C/T	*CDH13*	T	↓	n/a	[19]
	rs11924390	C/T	*KNG1*	C	↓	with rs3865188 & rs864265 7.5% Filipino mothers, 8.9% offspring (ln-transformed ADIPOQ levels)	[23], rev. [17]
	rs3001032	C/T	*LYPLAL1*	T	↓	n/a	[21]
	rs1108842	A/C	*GNL3*	C	↑	n/a	[21]
	rs998584	C/A	*VEGFA*	C	↑	n/a	[21]
	rs2980879	T/A	*TRIB1*	T	↑	n/a	[21]
	rs7955516	A/C	*PDE3A*	C	↑	n/a	[21]
	rs601339	C/T	*GPR109A*	C	↑	n/a	[21]
	rs2925979	T/C	*CMIP*	T	↓	n/a	[21]
	rs731839	C/T	*PEPD*	C	↓	n/a	[21]
	$p > 10^{-8}$						
	rs2805533	C/T	*ADARB2*	T	↓	n/a	[25]
	rs10447248	A/G	*FER*	A	↓	1.3% NHS sample, 2.0% Italian sample	[24], rev. [17]
	rs822354	A/G	*ADIPOQ*	A	↑	1.1% NHS sample and 2.5% Italian sample	[24], rev. [17]
	rs17373414	C/T	*ADIPOQ*	C	↓	7% variability attributed to ADIPOQ SNPs [26]; <5% [27]	[26]; [27]
	rs1403696	C/T	*ADIPOQ*	T	↓	7% variability attributed to ADIPOQ SNPs	[26]
	rs12637534	A/G	*ADIPOQ*	G	↑	< 5%	[27]
	rs10937273	A/G	*ADIPOQ*	G	↓	< 5%	[27]; [137]
	rs822395	A/C	*ADIPOQ*	A	↓	< 5%	[27]
	Rare variants						
	rs117016164	A/G	*ETV5*	A	↓	n/a	[28], rev. [17]
	rs138773406	C/A (p.R221S)	*ADIPOQ*	A	↓	17.1% in offspring, 13.2% in Filipino mothers	[28]
	rs200573126	G/C (p.G45R)	*ADIPOQ*	C	↓	16-17% complete sample set; 62-63% families of linkage study	[29]
Chemerin/ *RARRES2*	$p < 10^{-8}$						
	rs7806429	A/G	*ACTR3C*	G	↑	2%	[36]
	$p > 10^{-8}$						
	rs2594989	C/T	*ATG7*	T	↑	n/a	[36]
	rs8027521	C/T	n/a	C	↑	n/a	[36]
	rs347344	C/T	*EDIL3*	n/a			[35]

Leptin/*LEP*	rs2167270	A/G	*LEP*	G	↓	n/a	[49], rev. [48]; [52]
	rs7799039	A/G	*LEP*	G	↓	n/a	[50], [51], rev. [48]; [52]
	rs1550805	C/T	*PI3K*	T	↑	n/a	[53]
	rs5219	G/A (p.E23K)	*KCNJ11*	A	↑	n/a	[54]#
Progranulin/ *PGRN*	rs646776	T/C	*CELSR2, PSRC1, SORT1*	C	↓	21.4%	[67]
	rs611917	A/G	*CELSR2, PSRC1, SORT1*	G	↓	n/a	[67]
Resistin/ *RETN*	$p < 10^{-8}$						
	rs34861192[a]	A/G	*RETN*	A	↑	37.9% with rs3745368	[82][a]
	rs3745368	A/G	*RETN*	G	↑	37.9% with rs34861192	[82]
	rs3931020	C/T	*TYW3/CRYZ*	C	↑	n/a	[85]
	rs13144478	A/T	*NDST4*	T	↑	n/a	[85]
	$p > 10^{-8}$						
	rs1862513[a,b,c]	C/G	*RETN*	G	↑	9.68 % [76]	[76][b]; [77][c]; [78]-[81]
	rs34124816[b]	A/C	*RETN*	A	↑	1.33 %	[76]
	rs3219177[c]	C/T	*RETN*	T	↑	n/a	[77]
	rs3745367[c]	G/A	*RETN*	A	↑[77;85]; ↓ [89]	n/a; 3.01% [89]	[77]; [85]; [89]
	rs4804765	G/T	*RETN*	T	↑	1.5% with rs1423096	[78]
	rs1423096	C/T	*RETN*	T	↑ [78]; ↓ [89]	1.5% with rs4804765 [78]; 15.44% [89]	[78]; [89]
	rs10401670	C/T	*RETN*	T	↑	n/a	[78]; [90]
Retinol binding protein 4/ *RBP4*	rs3758539	G/A	*RBP4*	A	↑	n/a	[95]
	rs10882273	A/G	*RBP4*	G	↓	n/a	[98]
	rs3758538	A/C	*RBP4*	C	↓	n/a	[98]
	rs17108993	C/G	*RBP4*	G	↓	n/a	[98]
Vaspin/ SERPINA12	$p < 10^{-8}$ - GWAS						
	rs11160190	C/T	*VASPIN/ SERPINA4*	C	↓	n/a	[103]
	rs6575436	T/A	*VASPIN*	A	↑	n/a	[103]
	rs4905203	C/G	*SERPINA11*	C	↓	n/a	[103]
	rs1956713	T/C	*SERPINA9*	C	↑	n/a	[103]
	rs1956721	C/T	*SERPINA11*	C	↓	n/a	[103]
	rs11621467	G/T	*SERPINA11/ SERPINA1*	G	↓	n/a	[103]
	$p < 10^{-8}$ – fine mapping of vaspin locus (for further variants please see [103])						
	rs8006968	T/A	*VASPIN*	T	↓	n/a	[103]
	rs7158068	A/G	*VASPIN*	A	↓	n/a	[103]
	rs10145558	T/C	*VASPIN*	C	↑	n/a	[103]
	rs1956709	T/C	*VASPIN*	C	↑	n/a	[103]
	rs12433651	T/C	*VASPIN*	C	↑	n/a	[103]
	rs2236240	G/A	*VASPIN*	A	↑	n/a	[103]
	rs2236242	A/T	*VASPIN*	T	↓	n/a	[103]
	rs3736803	C/T	*VASPIN*	C	↓	n/a	[103]
	Rare variants						
	rs61757459	C/T (p.R211X)	*VASPIN*	T	↓	n/a	[105]

Legend: Data for adiponectin partly adopted from Breitfeld *et al.* [17] and extended. Included are SNPs with the best statistical and/or functional evidence reported in the literature; further (LD) SNPs are discussed in the relevant references. *Abbreviations*: EA - effect allele, ED - effect direction serum level, rev - reviewed in. [a/b/c] SNPs in LD based on data in the cited study. SNP given for the genomic strand where the SNP's gene/nearby gene is located. This may deviate from the alleles reported in the publication. Percentage variance of adiponectin concentration belongs to the population cited in the study. * Discovery cohort. # Discrepancies between text and table in the publication cited.

Chemerin is coded by the *retinoic acid receptor responder (tazarotene induced) 2* (*RARRES2*) gene on chromosome 7q36.1. The study by Bozaoglu *et al*. revealed that serum chemerin levels are highly heritable (25%) in the San Antonio Family Heart Study comprising individuals of Mexican-American origin [35]. The GWAS was performed in 523 subjects and detected a SNP in the *EGF-like repeats and discoidin I-like domains 3* (*EDIL3*, rs347344 C/T) gene. The authors supported the role of *EDIL3* by showing that chemerin promotes angiogenesis in endothelial cells in a dose-dependent manner. Further loci were described as being associated with serum chemerin levels, with $p < 0.0001$ in that cohort, but the evidence for these associations still needs to be proven in replication or functional studies [35].

A recent genome-wide meta-analysis (n = 2,791) supported the high heritability estimates for serum chemerin levels, and revealed genetic variation near *RARRES2* to be involved in the regulation of the circulating serum chemerin concentrations [36]. The strongest evidence of association was for rs7806429 (A/G) in the *actin-related protein 3 homolog C (yeast)* (*ACTR3C*) gene, representing a cluster of SNPs in pairwise linkage disequilibrium (LD), which in addition associated moderately with *RARRES2* mRNA transcript levels in VAT. Albeit not significant at a genome-wide level, two other lead SNPs, rs2594989 (C/T) in *ATG7* and rs8027521 (C/T), and their LD partners might be worth investigating (**Table 1**) [36]. In this study, serum chemerin concentrations were also positively correlated with BMI and percentage body fat as well as with elevated fasting insulin, HOMA-IR, and $AUC_{glucose}$ which supports the findings of previous studies [36-38].

2.3 Leptin (LEP)

In the early 1970's, initially discovered as a monogenetic determined cause for obesity in mice [39-40], the *ob* gene product leptin was described as one of the first adipokines. It was named adipokine because the blood-circulating factor was found to have its main source in adipose tissue, and its structure and function were predicted to be cytokine-like [41-45]. Among the adipokines known to date, leptin and its receptor exhibit a unique feature: it is the only adipokine/adipokine receptor for which mutations are known to cause monogenic obesity in humans [46-47]. *LEP* genetics have been intensively studied in humans and livestock such as cattle and pigs (reviewed in [48], 2005).

Until 2005, the *LEP* polymorphism G>A at position 19 (now rs2167270 A/G) of the untranslated exon 1, and a variant in the promotor region, G(-2548)A (rs7799039 A/G), were the only variants in/nearby *LEP* which have been described as being associated with serum leptin levels (**Table 1**) [48-51]. Obese subjects, homozygous for the G-allele in one or other SNP, exhibit lower serum leptin levels than AG- or AA-allele carriers. The association of both SNPs with serum leptin levels was confirmed in a very recent study on differentiated thyroid cancer (DTC) [52].

In 2006, a study by Jamshidi *et al*. reported that SNP rs1550805 (C/T) in the *phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha* (*PI3K*) locus was significantly associated with serum leptin levels and body fat measures in a UK cohort of twin pairs and singletons [53]. Carriers of the T-allele had higher serum leptin levels. The authors speculated that the site marked by rs1550805 reflect a diminished ability on the part of PI3K to signal via insulin receptor substrate 1 or 2 (IRS-1 or IRS-2) in response to leptin [53]. This study is a good example of how genetic variants in downstream signal transducers might affect adipokine secretion by disturbed feedback mechanisms.

A significant association between plasma leptin and rs5219 (G/A, missense variant p.E23K) of *potassium channel, inwardly rectifying subfamily J, member* 11 (*KCNJ11*) was found in a population from Yucatan, Mexico [54]. Carriers of the A-allele exhibited higher serum leptin levels. *KCNJ11* is coding for a K_{ATP} channel KIR6.2 which is known to play a role in insulin secretion in pancreatic β-cells, and insulin and leptin signal transduction in the brain (**Table 1**) [55-59]. This polymorphism has been thoroughly investigated with regard to T2D and obesity in many populations (reviewed in detail in [60]). From a functional point of view, the Lys amino acid residue was shown to increase the probability of spontaneous K_{ATP} opening and decrease the potassium channel's sensitivity towards ATP-inhibitory activity, resulting in an inhibited insulin secretion in pancreatic beta-cells [60-61].

In the brain, in consequence, the A-allele of rs5219 may contribute to leptin resistance via feedback mechanisms that might be reflected in elevated leptin levels. However, this would be rather an indirect/downstream effect on serum leptin levels than an effect of polymorphisms directly acting on *LEP* gene transcription and protein expression, and the hypothesis is not yet proven. In contrast, in a recent but small study,

leptin levels were shown to be significantly lower in an adolescent group with T2D compared to a BMI-, age-, and gender-matched control group without T2D (74 in each group), with equal adiponectin levels in both groups [62].

2.4 Progranulin (PGRN)

Beside adipose tissue, progranulin is widely expressed in many epithelial cells, and impacts disease states in tumorigenesis, neurodegeneration, wound inflammatory response, and metabolic diseases [63-66]. It has been shown that progranulin levels are elevated in individuals with T2D, and correlate with visceral fat accumulation and macrophage infiltration into adipose tissue [66]. In 2010, Carrasquillo *et al*. identified rs646776 (T/C) near *sortilin 1* (*SORT1*) as a regulator of progranulin levels in human plasma of non-*GRN* mutation carriers [67]. They found that each copy of the minor C-allele decreased PGRN levels by ~15 % (**Table 1**). An association of the C-allele of this SNP with increased *SORT1* mRNA levels was detected in the liver, but not in the brain, and the link between sortilin and progranulin levels was investigated in a HeLa cell culture model [67-68]. *SORT1*-overexpressing cells showed a reduction in PGRN levels in the cell culture media. Knockdown of *SORT1* led to a significant increase in PGRN levels. A number of loss-of-function mutations in *PGRN* have also been described in families with dementia [69].

In case of tissue-specific mutations, it would be interesting to learn whether PGRN expressed from other sources such as adipose tissue could attenuate the deficits. However, it is necessary to consider that PGRN has multiple sources when investigating its genetics in relation to obesity or T2D. Therefore, the cell culture model for functional analyses should be chosen very carefully. In mice, ablation of *PGRN* prevented the animals from high-fat diet-induced insulin resistance, adipocyte hypertrophy, and obesity through blockade of IL-6, and insulin resistance induced by chronic administration of PGRN was suppressed by neutralizing IL-6 *in vivo* [70]. However, *PGRN* is a good example for an antagonistic, pleiotropic gene: excessive PGRN may favor the development of obesity and T2D, but insufficient PGRN levels may be harmful to the brain.

2.5 Resistin (RETN)

It has been proposed that resistin links obesity and diabetes, but the link is controversially discussed [71-74]. In 2003, Smith *et al*. showed that the G/G genotype of the *RETN* promoter SNP -180C/G (rs1862513) was associated with increased basal promotor activity in adipocytes and higher *RETN* mRNA levels in human SAT *in vivo* [75]. Also, *RETN* mRNA correlated positively with insulin resistance and liver fat. One year later, rs1862513 and a second promotor SNP, -537A/C (rs34124816) were investigated in a Korean population; it was shown that the A-allele of rs34124816 and the G-allele of rs1862513 were associated with higher plasma resistin concentrations [76]. The SNPs are in LD, and in functional studies, it was shown that the rs1862513 G-allele is specific for the binding of nuclear proteins from adipocytes and monocytes.

The association of the rs1862513 SNP and plasma resistin concentrations was replicated in a Finnish population and in a meta-analysis showing the same direction of association (**Table 1**) [77-78]. The putative causal role of the rs1862513 polymorphism has been confirmed by others, and further variants have been found (rs34861192 G/A, rs3745368 G/A) to associate with plasma resistin levels in an aged Japanese population [79-82]. These two variants accounted for 37.9% of the variance in plasma resistin level among all study participants (n = 3,133) [82]. Rs34861192 is in LD with rs1862513. However, in this study, plasma resistin levels appear to depend more on the rs34861192 genotype. The effect of rs1862513 seems to be mediated at the level of binding of the transcription factors (TF) Sp1 and Sp3 and promotor activity [79]. Based on a previous publication [83], the authors suggested that other transcription factors (such as SREBP1c) that bind to the resistin gene promoter in the vicinity of the rs34861192 polymorphism may play a greater role [82]. This may be a population-specific effect as rs34861192 is monomorphic in the Environmental Gene Project Centre d'Etude du Polymorphisme Humain (EGP-CEPH) Panel of the SNP database (dbSNP) [82].

Hivert *et al*. found a strong association of four tag SNPs (rs1477341 A/T, rs4804765 G/T, rs1423096 C/T, and rs10401670 C/T) on the 3' side of *RETN* with resistin levels, with all minor alleles associating with higher levels in the Framingham Offspring Study [78]. Rs4804765 and rs1423096 had independent associations with plasma resistin concentrations (1.5% of the variance in resistin levels in best-fitting model). Rs4804765 explained the association of the two other SNPs (rs1477341 and rs10401670) (**Table 1**). Interestingly, as stated by the authors, rs10401670 is located in the

second intron of the *mast cell-expressed membrane protein 1* (*MCEMP1*) gene that is mainly expressed by monocytes and mast cell lines [78, 84]. Since resistin is mainly expressed by macrophages that evolve from monocytes in adipose tissue, it would be interesting to know whether *MCEMP1* and its product are functionally influenced by rs10401670 or the SNPs in its 5' region, and whether this protein is involved in resistin and/or glucose metabolism [78].

A GWAS confirmed the association with the *RETN* locus (represented by rs3745367 G/A), and identified an association of the *tRNA-yW synthesizing protein 3 homolog/zeta-crystallin* (*TYW3/CRYZ*; represented by rs3931020 C/T) and *N-deacetylase/N-sulfotransferase (heparan glucosaminyl)* 4 (*NDST4*; represented by rs13144478 A/T) loci with circulating resistin levels [85]. In expression quantitative trait loci (eQTL) analyses, rs3931020 and its LD partner rs277369 T/C showed a significant *cis* association with *CRYZ* gene expression. Likewise, rs3931020 showed a significant but weaker *cis* association with *TYW3* gene expression. The authors speculated that the association of the SNP rs3931020 with circulating and mRNA resistin levels may be mediated by its effect in increasing *CRYZ* expression, which in turn, by stabilizing *RETN* mRNA, increases circulating resistin levels [85].

Zeta-crystallin is an NADPH-dependent quinone reductase that binds to adenine-uracil-rich elements in 3'-UTR of mRNAs. It may act as *trans*-acting factor in mRNA regulation [85-88]. The role of *TYW3* and *NDST4* is not yet clear [85]. Rs3745367 and rs1423096 have been replicated in a smaller GWAS in 2014 by Chung and colleagues. However, in contrast to Ukkola *et al*. and Qi *et al*., they found the relation with serum resistin concentrations to be inverse for the alleles [77, 85, 89]. A relationship between rs10401670 and serum resistin levels could be detected in 6- to 8-year-old boys (**Table 1**) [90].

2.6 Retinol binding protein 4 (RBP4)

Rbp4 was identified in adipocyte-specific *glucose transporter 4* (*Glut4*) knockout mice as an adipocyte-derived protein contributing to insulin resistance in obesity and T2D [91]. The liver was regarded as the main source for RBP4 until then, but in the insulin-resistant state, RBP4 production in adipose tissue is almost equivalent to that in the liver. RBP4 levels correlated with the degree of insulin resistance in subjects with obesity, impaired glucose tolerance, and T2D, and were also associated with anthropometric and metabolic measures such as BMI, WHR, serum triglyceride levels, and others [92].

RBP4 is a transporter for retinol in the circulation. It is important for a multitude of (metabolic) functions, including vision, gene transcription, immune system, bone metabolism, and others. *RBP4* is located at the chromosomal region 10q23-q24 which has been linked to the risk for T2D [93, 94]. The role of *RBP4* as a T2D candidate gene has been confirmed in several studies [11, 12]. A haplotype of 4 *RBP4* genetic variants (G-T-G-C; rs3758539 G/A, c.248+44T/C, rs12265684 G/C, and rs10882273 T/C) was shown to associate with higher visceral *RBP4* mRNA expression [12]. Munkhtulga *et al*. demonstrated in a Mongolian population that rs3758539 (-803 G/A) is associated with an increased risk of T2D, which supports the hypothesis that rs3758539 may be a causal variant (**Table 1**) [95]. It could be shown that diabetic patients who are homozygote for the A-allele exhibit significantly higher RBP4 serum levels. For the A-allele, the transcription efficiency of *RBP4* and the motif-binding efficiency of hepatocyte nuclear factor 1 alpha (HNF1) were increased in a hepatocarcinoma cell line [95].

These results are in contrast to the results obtained by Craig *et al*. and Kovacs *et al*., as in these studies the G-allele of the SNP was included in the haplotype [11-12]. However, the effect on transcription could not be observed in 3T3L1 cells. Therefore, the authors suggested clarifying the SNP function in clinical adipose tissue specimens or insulin-resistant 3T3L1 cells [95]. In 2010, a second study by Munkhtulga *et al*. carried out in adipocytes revealed that in a *RBP4* promotor assay in 3T3L1 cells the minor A-allele increased the promotor activity two to three times [96].

Associations of three more SNPs (+2333G/A (rs28383574), +5388C/T (rs7091052), and +8201T/A (rs386746636/rs7079946)) with serum RBP4 levels were found in a study performed in a Chinese population, but these associations were in strong LD to the rs3758539 variant, suggesting that they may simply tag the functional variant [97]. Furthermore, in a study population of 3,210 unrelated Han Chinese, reduced plasma RBP4 levels were significantly associated with the G-allele of rs10882273 A/G and the C-allele of rs3758538 A/C in the total cohort, and with the G-allele of rs17108993 C/G in a subgroup from Shanghai [98]. However, the genetic influence on plasma RBP4 levels seems to decline with age, suggesting that plasma RBP4 in the elderly may be regulated by environmental factors [99].

2.7 Vaspin (SERPINA12)

The visceral adipose tissue-derived serine protease inhibitor (vaspin, serpinA12) was detected in a rat model of T2D, and exhibits insulin-sensitizing properties [100]. *VASPIN* mRNA and protein expression have been associated with obesity and measures of insulin resistance/sensitivity [101]. Elevated vaspin levels were postulated to represent a compensatory mechanism protecting from insulin resistance in the context of obesity [102].

A GWAS was performed in 826 Sorbs from Germany, following the hypothesis that variability in serum vaspin concentrations has genetic components [103]. The following 6 SNPs were significantly associated with serum vaspin:

- rs11160190 C/T (between *VASPIN* and *SERPINA4*)
- rs6575436 T/A in *VASPIN*
- rs4905203 C/G
- rs1956713 T/C
- rs1956721 C/T
- rs11621467 G/T

The latter four are downstream polymorphisms, all of which could be replicated *in silico* in the KORA cohort (**Table 1**).

Fine mapping of the *VASPIN* locus by genotyping 26 tagging SNPs revealed several SNPs that were significantly associated ($p < 10^{-8}$) with serum VASPIN concentrations in a combined analysis including the Sorbs and the KORA cohorts (**Table 1**) [103]. However, none of the SNPs showing association with serum vaspin concentration with $p < 10^{-8}$ was associated with quantitative anthropometric and metabolic traits. Given that the SNP rs11160190 showing the strongest association with circulating vaspin maps 5' upstream of *VASPIN*, and that it is located within various transcription factor binding sites, there is an inevitable need for functional studies to prove the causality of this variant [103].

A functional study for vaspin SNPs was performed by Teshigawara *et al*. who showed that the A-allele of SNP rs77060950 C/A, predicting higher serum vaspin level in a Japanese population, was associated with higher luciferase activity [104]. Indeed, the transcription factor GATA, predicted for the site containing rs77060950, demonstrated a much stronger DNA protein complex by using the A-oligo instead of the C-oligo in the electrophoretic mobility shift assay (EMSA). Furthermore, serum vaspin concentrations tend to be lower in adults carrying a rare variant in *VASPIN*, rs61757459 C/T, predicting a premature stop codon (p.R211X) [105]. In consequence, this stop codon results in a truncated vaspin protein lacking four helices, multiple β-strands, and the integral reactive center loop.

2.8 Further adipokines

Adipsin (also called complement factor D (CFD)) is a serine protease with complement factor D activity. Its mRNA is highly induced during adipocyte differentiation, and its gene expression is profoundly altered in genetic and acquired obesity in mice studies [106-109]. In *adipsin*$^{-/-}$ mice, Lo *et al*. showed that this protein plays an important role in insulin secretion by the pancreatic β-cells. They also showed that adipsin is decreased in patients with T2D and β-cell failure [110]. The data by Lo *et al*. suggest that adipsin stimulates insulin secretion via actions of C3a on its receptor to improve glucose homeostasis *in vivo*. However, the dysregulation of adipsin expression may arise from certain genetic (like in *db/db* mice) or metabolic defects [110]. In this context, overfeeding studies in rats showed that the change in adipsin expression upon feeding a cafeteria diet was only minor. Similarly, human studies have shown that subjects with mild to moderate obesity did not have reduced levels of circulating adipsin [110-113].

Despite the fact that adipsin is an "old" adipokine, there are only a few studies linking genetic polymorphisms in any gene with serum adipsin levels. One study was conducted by Ukkola *et al*., but it should be interpreted with caution. The authors performed an overfeeding experiment in 12 pairs of young male monozygotic twins, and investigated a restriction fragment length polymorphism (RFLP) in *adipsin* (6.1 kb *Hinc II* polymorphism) [114]. The variant was associated with changes in body fat composition in response to the caloric surplus, but not with adipsin levels. However, the investigated sample size was low and participants were monozygotic twins, which resulted in a limited statistical power. Another publication reported on SNPs in CFD in age-related macular degeneration, but no association of rs3826945 (C/T) with plasma CFD concentrations was found [115].

Apelin (*APLN*) has pleiotropic effects on numerous organs and tissues, and appears to be a beneficial adipokine with anti-obesity and anti-diabetic features (reviewed in [116] and [117]). It exerts effects on the whole body metabolism at a level similar to adiponectin and leptin. The *APLN*

gene is located on the X chromosome. SNPs in/nearby *APLN* have been tested only in a few genotype-phenotype association studies, mainly in Asian populations [118-121]. In human primary adipocyte culture derived from 10 women (2 x CC, 4 x GC, 4 x GG), it was shown that carriers of the CC genotype from SNP rs3115757 C/G exhibit higher *APLN* mRNA and protein concentrations when cells were exposed to high glucose plus insulin [120]. However, this result was not evaluated statistically because of the small sample size. A recent study showed that rs3115758, which is in LD with rs3115757, is located in a miR-765 binding site in the 3'-UTR of *APLN* [122]. A reporter assay confirmed that the different alleles of rs3115758 interfered with miR-765 binding and modified *APLN* expression [122]. This was investigated in context with arterial stiffness, but remains to be investigated in adipocytes.

Omentin (*ITLN1*) was described in 2003 as a new adipokine secreted from omental adipose tissue (mRNA primarily expressed in the stromal vascular fraction) which enhances insulin-mediated glucose uptake in adipocytes and activates protein kinase Akt/PKB [123-125]. Decreased omentin levels are associated with increasing obesity and insulin resistance [126]. A missense variant Val109Asp (rs2274907 A>T, T representing the amino acid Val) was found by random sequencing, and investigated in patients with T2D and inflammatory bowel diseases [127]. However, no significant associations with clinical parameters could be detected. In patients suffering from psoriasis, serum omentin levels have been investigated in relation to the Val109Asp polymorphism, but no association was found, despite the fact that these patients exhibited lower serum omentin levels than the controls [128].

3. Adipokine receptors

Adipokines either act as autocrine or paracrine factors, or they circulate in the blood to be distributed to the target tissues. The study of their receptors is important as they can be targets for pharmacological treatment in obesity and T2D, and genetic variations in these receptors might codetermine the responsiveness and strength of adipokine signal transduction in the target tissues. For this purpose, pharmacogenomic studies are becoming more important [129]. Genetic variants in adipokine receptors may contribute to the regulation of serum adipokine levels through a feedback mechanism of downstream components which sense insufficient signal transduction activities or an overshoot in these activities. However, the identification of adipokine receptors is no minor undertaking: the receptors for many adipokines are not yet known, and depending on the receptor, they have been little investigated in genotype-phenotype association studies.

3.1 Adiponectin receptor 1 and 2 (ADIPOR1, ADIPOR2), cadherin 13 (CDH13)

Three receptors have been identified for adiponectin or high-molecular-weight (HMW) species of adiponectin so far: adiponectin receptor (ADIPOR) 1 and 2, located on chromosome 1 and 12, respectively, and cadherin 13 (CDH13) on chromosome 16 [130, 131]. All receptors have been thoroughly investigated in genetic association studies for T2D, insulin resistance, and related traits, but in most studies serum adiponectin measurements were not available for ADIPOR1 and 2. In 2009, Ling *et al*. found a SNP within *cadherin 13* (*CDH13*, rs7195409 A/G) to be associated with adiponectin levels [132]. However, the associated allele and the effect direction were not reported in the paper.

The *CDH13* SNP rs3865188 T/A was detected in a GWAS in Filipino women, with the T-allele associated with lower adiponectin levels [23]. It has been recently shown in male mice that there is a feedback regulation between adiponectin and T-cadherin which impacts on adiponectin levels in tissue and plasma via the regulation of the phosphatidylinositol-specific phospholipase C (PI-PLC) mediated T-cadherin cleavage [133].

In the GWAS by Ling *et al*., adiponectin levels were not associated with *ADPOR1* and *ADPOR2* SNPs [132]. The association of SNPs in the *CDH13* locus with plasma adiponectin levels was supported by further studies showing several signals depending on the investigated population, mainly Chinese and Japanese (**Table 2**) [134-137]. The *CDH13* promotor SNP rs12444338 G-allele was associated with increased promoter activity in a luciferase assay [134].

Cohen *et al*. investigated *ADIPOR1* and *ADIPOR2* polymorphisms in relation to serum adiponectin levels in a comparatively large study group of women [18]. None of the receptor SNPs was found to associate with adiponectin levels. *ADIPOR* SNPs have also been investigated in relation to cancer, but likewise in these cohorts, *ADIPOR* SNPs were not associated with circulating adiponectin levels [138].

Table 2. Adipokine receptor variants found to be associated with serum adipokine concentrations

Adipokine receptor / gene	SNP-ID	SNP	EA	ED	% variance	Reported in
Cadherin 13 / *CHD13*	rs3865188[a]	A/T	T	↓	n/a	[23]; [134]*, rev. [17]
	rs12596316	A/G	Minor (G)[#]	↓	n/a	[134]*, rev. [17]
	rs7193788[c]	A/G	Minor (G)[#] [134]; G [136]	↓ [134]; ↑ [136]	n/a	[134]*, rev. [17]; [136]
	rs3865185	A/T	Minor (T)[#]	↑	n/a	[134]*, rev. [17]
	rs3865186	A/G	Minor (A)[#]	↑	n/a	[134]*, rev. [17]
	rs3852724	A/C	Minor (C)[#]	↑	n/a	[134]*, rev. [17]
	rs12922394	C/T	T	↓	n/a	[21]
	rs12444338[a,b]	G/T	G	↑	n/a	[134][a]
	rs12051272[b]	G/T	G	↑	3.28% with rs4783244	[135][b]
	rs4783244[a,c]	G/T	G	↑	3.28 with rs12051272 [135]; 9.28% [136]; >4 % adiponectin & >6% HMW-adiponectin [137]	[135]; [136][c]; [137]
	rs8047711[c]	A/G	G	↑	n/a	[136]
Leptin receptor / *LEPR*	rs1137101	A/G p.Q223R	G	↓	n/a	[142]; [143]
	rs1137101	A/G p.Q223R	G	↑	41% (together with age, gender, cigarette smoking, CAD & obesity) [144]	[144]; [145]; [146]; [147]; [148]$_{men}$
	rs1137100	A/G p.K109R	G	↑ [147] ↓ [151]	n/a	[147]; [151]$_{women}$
	rs1805094	G/C p.K656N	C	↑	n/a	[148]$_{men}$
Apelin receptor / *APLN* or *APJ*	rs11544374	G/A	A	↑	n/a	[174][$]

Legend: Included are SNPs with the best statistical and/or functional evidence reported in the literature; further (LD) SNPs are discussed in the relevant references. [a/b/c] SNPs in LD based on data in the cited study. SNP given for the genomic strand where the SNP's gene/nearby gene is located: this might deviate from the alleles reported in the publication. Percentage variance of adiponectin concentration belongs to the population cited in the study. * Discovery cohort. [#] Assumed for investigated population in publication [134] based on NCBI SNP-database entries. [$] Limited by sample size. *Abbreviations*: EA – effect allele, ED – effect direction serum level, rev – reviewed in.

3.2 Chemerin chemokine-like receptor 1 (CMKLR1)

In contrast to the mechanisms previously proposed, recent data from rodents suggest that an agonist of the chemerin chemokine-like receptor 1 (CMKLR1) may be beneficial in the treatment of T2D. This suggestion is based on the observation that treatment with chemerin or its C-15 and C-19 terminal peptides causes an increased insulin-stimulated glucose uptake in wild-type rat and mouse epididymal adipocytes [139]. It seems that increased chemerin levels represent a compensatory mechanism in metabolic diseases. It has also been shown in mice that a disruption of the *CMKLR1* gene is associated with reduced adiposity, but the mice were glucose-intolerant and had a decreased glucose-stimulated insulin secretion [140]. Unfortunately, except for the *CMKLR1* intron variant rs1878022 A/G, which was found in a GWAS for the survival rate of patients with non-small cell lung cancer [141], no other "common" *CMKLR1* genetic variant has been investigated.

3.3 Leptin receptor (LEPR)

For the leptin receptor (LEPR), data exist on the association of polymorphisms in/nearby the gene with serum leptin levels in several populations, although they are contradictory. The p.Q223R (rs1137101 A/G) polymorphism in *LEPR* is the most investigated. While some studies reported an association of the variant coding for the glutamine ("Q") allele with higher plasma leptin serum levels [142, 143], others found that the arginine ("R") allele was associated with increased leptin levels (**Table 2**) [144-148]. At the amino acid level, this polymorphism leads to a change in

electric charge from neutral to positive in this position, and may thereby affect the functionality of the receptor and alter its signaling capacity. These changes need to be further clarified (summarized in [149]).

The study by Quinton *et al.* showed that in postmenopausal women carrying the R223-allele, the leptin-binding capacity to the soluble LEPR in plasma was lowered. It is unclear how the soluble form of the LEPR reflects the function of the transmembrane LEPR in various tissues, but it is speculated that subjects having this variant also have a form of leptin resistance [149-150].

Two other variants in *LEPR* are of interest, p.K109R (rs1137100 A/G) and p.K656N (rs1805094 G/C). In a young Dutch adult cohort with recorded weight gain over a period of ~7 years, leptin levels were increased in carriers of the p.K109R R-allele [147]. In contrast, leptin levels were found to be higher in *LEPR* p.K109K homozygote postmenopausal women who were overweight or obese, but with 82 study subjects in this group, the statistical power was limited [151].

In a Caucasian male population, carriers of the Asn656-allele had significantly higher levels of plasma leptin (**Table 2**) [148]. Another study revealed that in 132 men with obesity undergoing a polyunsaturated fatty acid-enriched hypocaloric diet, leptin levels were significantly decreased in the group homozygote for the Lys656-allele after 2 months of intervention [152]. However, this seems to be a long-term mediated effect as no effect of these three *LEPR* polymorphisms on the acute decline in leptin after 4 days of energy restriction was observed [153]. Interestingly, the *LEPR* genotype-serum leptin level association is often found in "diseased" groups (subjects with obesity or T2D) [142, 143, 151]. Unfortunately, many of the studies are statistically underpowered or not properly adjusted.

3.4 Sortilin 1 (SORT1)

SORT1 was described as a neuronal PGRN receptor that mediates PGRN endocytosis and delivery to lysosomes [154-156]. The receptor has been implicated in coronary artery disease via LDL metabolism in the liver [157, 158] (reviewed in [159]). It seems that the effect of SORT1/PGRN signal transduction in the brain is independent of the effects in the periphery. In the brain, Prudencio *et al.* identified a specific splicing enhancer element that regulates the inclusion of a sortilin exon cassette (Ex17b) which is normally not present in the mature *SORT1* mRNA [156]. The enhancer element is present in *Sort1* mRNA of mice and other species, but absent in primates that carry a premature stop codon within the Ex17b sequence. In the absence of the regulatory inhibitor, transactivation response region (TAR) DNA-binding protein-43 (TDP-43), Ex17b is included in the *SORT1* mRNA [156]. In humans, a truncated, nonfunctional, extracellularly released protein that binds to but does not internalize PGRN is generated, which is due to the stop codon in the Ex17b sequence [156]. Therefore, the authors proposed a potential mechanism linking mis-regulation of sortilin splicing with altered PGRN metabolism. Despite the association of the rs646776 variant near *SORT1* with serum PGRN levels (see section 2.4 above; **Table 1**) [67], no further variants in/nearby the receptor gene have been described as being associated with PGRN levels in the periphery to date.

3.5 CAP, adenylate cyclase-associated protein 1 (CAP1)

In 2014, Lee *et al.* discovered that adenylyl cyclase-associated protein 1 (CAP1) acts as receptor for resistin [160]. It could be shown that human resistin directly binds to CAP1 in monocytes and upregulates intracellular cAMP concentrations, PKA activity, and NF-κB-related transcription of inflammatory cytokines. No candidate gene or GWA study investigating *CAP1* polymorphisms and resistin serum levels has been performed to date.

3.6 Stimulated by retinoic acid 6 (STRA6)

The *stimulated by retinoic acid 6* (*STRA6*) encodes the receptor for the retinol/RBP4 complex, but it is not expressed in the liver [161]. These observations initiated studies leading to the identification of the novel RBP4 receptor-2 (RBPR2) in 2013 [162]. Polymorphisms in *RBPR2* have not been investigated so far. In *STRA6*, mutations have been identified. These mutations have two effects on vitamin A uptake: they either abolish vitamin A uptake activity of STRA6 from holo-RBP completely because STRA6 cell surface expression is lost, or vitamin A uptake activity is influenced by reduced STRA6 RBP binding activity [163].

In a South Indian population, three SNPs (rs974456 G/A, rs736118 G/A, rs4886578 G/A) were found to be associated with T2D, with the minor alleles appearing to be protective [164]. For rs736118, a polymorphism predicting an amino acid exchange from Met to Ile in the C-terminus of

STRA6 has been suggested to alter the trafficking and cell surface expression of the protein. However, the consequences of the receptor SNPs on serum RBP4 levels cannot be estimated as RBP4 was not measured in this study.

3.7 Kallikrein 7 (hK7), heat shock protein family A (Hsp70) member 5 (GRP78)

It is still not well understood how the extracellular vaspin signal is transduced into the cell [165]. Recently, circulating human kallikrein 7 (hK7) was identified as a protease target of vaspin. In an *in vitro* study, vaspin inhibited hK7 by the serpin mechanism with high specificity, suggesting that vaspin protects insulin from hK7-mediated degradation [166]. In mice, vaspin was shown to bind to cell-surface 78-kDa glucose-regulated protein (Grp78)/murine tumor cell DnaJ-like protein 1 (MTJ-1) complex under conditions of ER stress, causing vaspin transgenic mice to be protected from diet-induced obesity, glucose intolerance, and hepatic steatosis [167]. Furthermore, in endothelial cells vaspin was shown to bind to a GRP78/voltage-dependent anion channel complex after induction of ER stress, and to promote proliferation, to inhibit apoptosis, and to protect from vascular injuries in diabetes [168].

A *GRP78* polymorphism has been investigated in terms of risk for hepatocellular carcinoma (HCC) and onset of T2D peripheral neuropathy, but not in relation to vaspin concentration [169, 170]. However, the promoter SNP rs391957 C/T C-allele was associated with HCC risk and increased levels of *GRP78* mRNA and protein [169].

3.8 Complement component 3a receptor 1 (C3AR1), apelin receptor (APLNR) & omentin (ITLN1)

As mentioned in section 2, the data by Lo *et al*. suggest that adipsin stimulates insulin secretion via actions of C3a on its receptor C3aR1 [110]. In a candidate pathway-based GWAS in a Chinese population, a variant in the 3'-UTR of *C3AR1* (rs7842 A/G) was identified in an eQTL analysis to associate with C3AR1 expression levels and coronary artery disease [171]. In this study, carriers of the minor G-allele exhibited higher *C3AR1* expression levels in leukocytes. However, C3AR1-related measures, e.g. those of C3a and adipsin, have not been collected in this study.

The apelin receptor (APLNR or APJ) is a G protein-coupled receptor; its signaling is implicated in several pathologies, including heart disease, diabetes, obesity, and cancer (reviewed in [172]). A genetic variant (rs9943582 G/A) has been described to affect *APJ* mRNA transcription via modification of a specificity protein 1 (Sp1) transcription factor binding site [173]. It could also be shown that *APLN* is a transcriptional target of Sp1 via a Sp1 binding site in the 5'-flanking region of *APLN*. However, the relationship between the receptor SNP and serum apelin levels was not investigated [173]. To date, the rs11544374 G/A *APJ* polymorphism only was found to exert an effect on circulating apelin levels in childhood obesity (**Table 2**) [174]. Interestingly, obese subjects with impaired glucose metabolism only had lower apelin levels than controls. In the obese subgroup, carriers of the major G-allele had lower apelin levels [174]. However, the investigated sample size and so the statistical power was low (90 obese vs. 90 controls).

The situation is somehow different for omentin, also known as intelectin 1, as it is expressed as a lectin that binds galactofuranose, but also acts as a receptor for lactoferrin [175]. Human intelectin 1 is speculated to be attached to the epithelial cell membrane via glycosylphosphatidylinositol (GPI) as it has no putative transmembrane region [175, 176]. To date, no other molecules are known to act as a receptor for the adipokine omentin. The rs2274907 polymorphism remains the only genetic variant which has been investigated in the context of serum omentin levels.

4. Epigenetics

Evidently, adipokine epigenetic changes, which are not only limited to adipose tissue and are tightly controlled by nutrient factors, are involved in the development of obesity and related complications beginning early in life [177-180]. Genetic variants may contribute to this scenario as epigenetic mechanisms are influenced by insertion or removal of CpG/non-CpG sites. Also, SNPs may modify binding sites for DNA methyl transferases, histone packaging may be affected, and chromatin organization may be influenced [181, 182].

Methylated (me-)cytidines are susceptible to deamination. While deaminated non-methylated cytidines become uracils and are efficiently detected by DNA proofreading mechanisms, deamination of me-cytidine leads to the formation of thymin that is a regular DNA base [183]. In a recent paper investigating *LEP* and *ADIPOQ* methylation in paired SAT, VAT, and blood samples of 73 severely obese patients, fasting LDL-C levels were found to be positively correlated with *LEP* DNA methylation levels at certain CpG sites in blood

and SAT, and with *ADIPOQ* DNA methylation levels in SAT and VAT [178]. Furthermore, the authors reported that the association between LDL-C and *LEP* mRNA levels were partially dependent on *LEP* rs2167270 G/A genotype and DNA methylation level at CpG17. LDL-C levels were found to be negatively correlated with *LEP* mRNA levels in rs2167270 A-allele carriers only, and the correlation between *LEP* expression and LDL-C levels was no longer significant after adjusting Pearson's correlation coefficient for LEP-CpG17 DNA methylation levels [178].

A recent study by Putku *et al*. showed that the *CDH13* promoter harbors methylation quantitative trait loci (meQTLs) associated with cardiometabolic traits [184]. Four common variants (rs12443878 C/A, rs12444338 G/T, rs62040565 C/T, and rs8060301 A/T) exhibited effects on methylation levels of up to 3 CpG sites located 19-167,744 bp from the respective SNPs. SNP rs8060301 was also associated with high-molecular-weight adiponectin levels [184]. Rs8060301 is in LD with the previously described SNP rs4783244. Since rs8060301 is located at the strongest binding site of RNA polymerase II (Pol2) within the *CDH13* promoter, it is speculated that this SNP acts as a causal variant that directly affects gene expression driving the associations with metabolic phenotypes [184]. Finally, two rare *CDH13* promoter meQTLs were associated with HMW adiponectin (rs2239857 C/G, rs77068073 C/T).

Studies on epigenetic modifications in combination with SNP and mRNA expression data of other adipokines are sparse or limited by sample size. This may be due to the facts that environmental factors (including nutrition) across individuals are very heterogeneous, and target tissues (such as adipose tissue) are not easy to access. Furthermore, recent data by Rönn *et al*. suggests that the human DNA methylome in SAT changes considerably with age [185]. They also found BMI exerts effects on the degree of DNA methylation in human adipose tissue, proposing that obesity can mediate some of its effect through changes in the epigenome. Also, CpG sites showed differential DNA methylation in adipose tissue from subjects with T2D compared to controls [186]. Somewhat surprisingly, well-known adipokine/receptor genes were not found among the differentially methylated genes.

The relationship between genotype, methylation, and the mechanisms involved in the regulation of DNA methylation under certain conditions is still not clear [180]. In any case, the potential epigenetic modification should be taken into account when investigating the genetics of adipokines and adipokine receptors.

5. Concluding remarks

Surprisingly, despite a multitude of studies reporting statistical associations of genetic variants in adipokine genes with T2D, obesity, and related traits, little is known about the genetic determinants of serum adipokine concentrations. On the other hand, there are a lot of studies reporting correlations between serum adipokine concentrations and metabolic traits in small sample sets without investigating a genetic component. Likewise, a SNP is shown to either associate with the metabolic trait/outcome or the serum adipokine concentration, but not with both simultaneously, which would allow a causative chain to be generated. However, when reporting negative results for genetic association studies, it would be helpful to provide power calculations for the trait investigated in the cohort. This would enable that the plausibility of the study could be assessed. In any case, effective strategies will be necessary to study the genetics of adipokines.

GWAS are sparse in the field of the genetics of adipokines. This is mainly due to the lack of effective assays (e.g. ELISA) providing accurate and reliable measurements of circulating adipokines. Yet, there is good evidence from the recent reports that GWAS may indeed uncover novel adipokine regulators. Also, candidate gene studies may play an important role in the investigation of adipokine receptors or downstream signaling components. However, candidate gene strategies combined with deep sequencing of the tested genes/loci are more likely to identify rare variants affecting circulating adipokine levels. Either way, it will be necessary to have well-defined and well-characterized populations as well as valid adipokine measurements.

Another question is to what extent a genetic effect would be expected. In some cases, we may overestimate the genetic influence on serum adipokine levels compared to other factors such as increasing adipose tissue mass or aging. While reviewing the percentage variability in serum adipokine levels for which the genetic variants are responsible, it is obvious that in some cases (such as *ADIPOQ*), age, gender, and BMI have a higher proportion than the SNPs themselves (as shown in [26, 27]). In contrast to these considerations, data on chemerin and resistin suggest that serum adipokine levels have a high heritable component which supports the need to look for genetic vari-

ants determining serum adipokine levels [35, 36, 78].

Reviewing exact data was occasionally hampered by flaws in some studies, where SNP alleles were not reported, or tables and text have not been in agreement [54, 134]. Determining DNA strand specificity and reporting the respective minor and major alleles is easy for A/G, A/C, T/G, and T/C base exchanges. However, for A/T and G/C SNPs, it is sometimes difficult to define the correct direction of the effect as decisive information with regard to the assignment of DNA strand and alleles is frequently missing. Also, minor and major alleles can flip within and even between populations.

The strength of an association of a genetic variant with a trait also depends on the other genetic architecture of the individuals. The investigation of large admixed populations may result in the detection of variants with small effects because the scale of the population delivers sufficient statistical power. In contrast, comparatively large signals may be specific for a certain well-defined population, as shown in the paper by Asano *et al.* [82]. They found an effect of rs34861192 on serum resistin levels specific for the investigated Japanese population as this SNP is monomorphic in the EGP-CEPH Panel of dbSNP. This is also nicely demonstrated in the paper by Grarup *et al.* which is included in this RDS Special Edition [187].

There is a need for functional studies which will help to clarify the consequence of genetic polymorphisms that are statistically associated with serum adipokine levels and with the metabolic features of T2D. New techniques such as genome editing with the CRISPR/Cas system will enable efficient protocols to introduce specific genetic variants, monitor the consequence on gene and protein levels, and explain epigenetic effects [188]. There is no doubt that our knowledge of the genetic background of adipokines would lead to a better understanding of their regulatory mechanism. Considering the potential of adipokines as treatment agents, alternative, population-specific treatment strategies may be developed, targeting downstream components of the signaling pathways or other regulatory components, which may reduce side effects.

The pleiotropy of adipokines may add another aspect of complexity. In this regard, genetic variants associated with serum adipokine levels have been shown to be associated with numerous metabolic traits such as waist-to-hip ratio. This provides a unique opportunity to detect novel physiological relationships which help to understand the physiology of adipose tissue distribution and eventually the complex etiologies of metabolic diseases. The development of metabolic diseases is driven by a combination of multiple factors, including increased adipose tissue mass, genetic/epigenetic predisposition for elevated/reduced adipokine levels, and modified signal transduction at the receptors in the target tissues. The main challenge in the near future will be to uncover the causative chains behind the genetic associations.

Acknowledgments: I would like to thank my mentor and director of our group, Prof. Dr. Peter Kovacs, for his unlimited scientific and personal support, and the fruitful discussion and critical survey of this manuscript. Furthermore, I would like to thank PD Dr. Anke Tönjes and Dr. Jana Breitfeld for their excellent scientific work, and their agreement to include recent findings discovered by our group in this review.

Disclosures: The author is funded by a research grant from the Boehringer Ingelheim Foundation.

■ References

1. **Saltiel AR.** You are what you secrete. *Nat Med* 2001. 7(8):887-888.
2. **Lehr S, Hartwig S, Lamers D, Famulla S, Müller S, Hanisch FG, Cuvelier C, Ruige J, Eckardt K, Ouwens DM, Sell H, Eckel J.** Identification and validation of novel adipokines released from primary human adipocytes. *Mol Cell Proteomics* 2012. 11(1):M111.010504.
3. **Alvarez-Llamas G, Szalowska E, de Vries MP, Weening D, Landman K, Hoek A, Wolffenbuttel BH, Roelofsen H, Vonk RJ.** Characterization of the human visceral adipose tissue secretome. *Mol and Cell Proteomics* 2007. 6(4):589-600.
4. **Zhong J, Krawczyk SA, Chaerkady R, Huang H, Goel R, Bader JS, Wong GW, Corkey BE, Pandey A.** Temporal profiling of the secretome during adipogenesis in humans. *J Proteome Res* 2010. 9(10):5228-5238.
5. **Dahlman I, Elsen M, Tennagels N, Korn M, Brockmann B, Sell H, Eckel J, Arner P.** Functional annotation of the human fat cell secretome. *Arch Physiol Biochem* 2012. 118(3):84-91.
6. **Andrade-Oliveira V, Camara NO, Moraes-Vieira PM.** Adipokines as drug targets in diabetes and underlying disturbances. *J Diabetes Res* 2015. 2015:681612.
7. **Dusserre E, Moulin P, Vidal H.** Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochim Biophys Acta* 2000. 1500(1):88-96.
8. **Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S.** Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* 2007. 56(4):1010-1013.
9. **Yang X, Smith U.** Adipose tissue distribution and risk of metabolic disease: does thiazolidinedione-induced adipose tissue redistribution provide a clue to the answer? *Diabetologia*

2007. 50(6):1127-1139.
10. **Schleinitz D, Böttcher Y, Blüher M, Kovacs P.** The genetics of fat distribution. *Diabetologia* 2014. 57(7):1276-1286.
11. **Craig RL, Chu WS, Elbein SC.** Retinol binding protein 4 as a candidate gene for type 2 diabetes and prediabetic intermediate traits. *Mol Genet Metab* 2007. 90(3):338-344.
12. **Kovacs P, Geyer M, Berndt J, Klöting N, Graham TE, Böttcher Y, Enigk B, Tönjes A, Schleinitz D, Schön MR, Kahn BB, Blüher M, Stumvoll M.** Effects of genetic variation in the human retinol binding protein-4 gene (RBP4) on insulin resistance and fat depot-specific mRNA expression. Diabetes 2007. 56(12):3095-3100.
13. **Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Yakout SM, Sabico SB, Gibson GC, Chrousos GP, Kumar S.** Parent-offspring transmission of adipocytokine levels and their associations with metabolic traits. *Plos One* 2011. 6(4):e18182.
14. **Cesari M, Narkiewicz K, De Toni R, Aldighieri E, Williams CJ, Rossi GP.** Heritability of plasma adiponectin levels and body mass index in twins. *J Clin Endocrinol Metab* 2007. 92(8):3082-3088.
15. **Fox CS, Liu Y, White CC, Feitosa M, Smith AV, Heard-Costa N, Lohman K, GIANT Consortium, MAGIC Consortium, GLGC Consortium, et al.** Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. *Plos Genet* 2012. 8(5):e1002695.
16. **Blüher M, Mantzoros CS.** From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. *Metabolism* 2015. 64(1):131-145.
17. **Breitfeld J, Stumvoll M, Kovacs P.** Genetics of adiponectin. *Biochimie* 2012. 94(10):2157-2163.
18. **Cohen SS, Gammon MD, North KE, Millikan RC, Lange EM, Williams SM, Zheng W, Cai Q, Long J, Smith JR, Signorello LB, Blot WJ, Matthews CE.** ADIPOQ, ADIPOR1, and ADIPOR2 polymorphisms in relation to serum adiponectin levels and BMI in black and white women. *Obesity (Silver Spring)* 2011. 19(10):2053-2062.
19. **Ramya K, Ayyappa KA, Ghosh S, Mohan V, Radha V.** Genetic association of ADIPOQ gene variants with type 2 diabetes, obesity and serum adiponectin levels in south Indian population. *Gene* 2013. 532(2):253-262.
20. **Li P, Jiang R, Li L, Liu C, Yang F, Qiu Y.** Correlation of serum adiponectin and adiponectin gene polymorphism with metabolic syndrome in Chinese adolescents. *Eur J Clin Nutr* 2015. 69(1):62-67.
21. **Dastani Z, Hivert MF, Timpson N, Perry JR, Yuan X, Scott RA, et al.** Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. *Plos Genet* 2012. 8(3):e1002607.
22. **Richards JB, Waterworth D, O'Rahilly S, Hivert MF, Loos RJ, Perry JR, Tanaka T, Timpson NJ, Semple RK, Soranzo N, et al.** A genome-wide association study reveals variants in ARL15 that influence adiponectin levels. *Plos Genet* 2009. 5(12):e1000768.
23. **Wu Y, Li Y, Lange EM, Croteau-Chonka DC, Kuzawa CW, McDade TW, Qin L, Curocichin G, Borja JB, Lange LA, Adair LS, Mohlke KL.** Genome-wide association study for adiponectin levels in Filipino women identifies CDH13 and a novel uncommon haplotype at KNG1-ADIPOQ. *Hum Mol Genet* 2010. 19(24):4955-4964.
24. **Qi L, Menzaghi C, Salvemini L, De Bonis C, Trischitta V, Hu FB.** Novel locus FER is associated with serum HMW adiponectin levels. *Diabetes* 2011. 60(8):2197-201.
25. **Oguro R, Kamide K, Katsuya T, Akasaka H, Sugimoto K, Congrains A, Arai Y, Hirose N, Saitoh S, Ohishi M, Miura T, Rakugi H.** A single nucleotide polymorphism of the adenosine deaminase, RNA-specific gene is associated with the serum triglyceride level, abdominal circumference, and serum adiponectin concentration. *Exp Gerontol* 2012. 47(2):183-187.
26. **Mather KJ, Christophi CA, Jablonski KA, Knowler WC, Goldberg RB, Kahn SE, Spector T, Dastani Z, Waterworth D, Richards JB, et al.** Common variants in genes encoding adiponectin (ADIPOQ) and its receptors (ADIPOR1/2), adiponectin concentrations, and diabetes incidence in the Diabetes Prevention Program. *Diabet Med* 2012. 29(12):1579-1588.
27. **Peters KE, Beilby J, Cadby G, Warrington NM, Bruce DG, Davis WA, Davis TM, Wiltshire S, Knuiman M, McQuillan BM, Palmer LJ, Thompson PL, Hung J.** A comprehensive investigation of variants in genes encoding adiponectin (ADIPOQ) and its receptors (ADIPOR1/R2), and their association with serum adiponectin, type 2 diabetes, insulin resistance and the metabolic syndrome. *BMC Med Genet* 2013. 14:15.
28. **Croteau-Chonka DC, Wu Y, Li Y, Fogarty MP, Lange LA, Kuzawa CW, McDade TW, Borja JB, Luo J, AbdelBaky O, Combs TP, Adair LS, Lange EM, Mohlke KL.** Population-specific coding variant underlies genome-wide association with adiponectin level. *Hum Mol Genet* 2012. 21(2):463-471.
29. **Bowden DW, An SS, Palmer ND, Brown WM, Norris JM, Haffner SM, Hawkins GA, Guo X, Rotter JI, Chen YD, Wagenknecht LE, Langefeld CD.** Molecular basis of a linkage peak: exome sequencing and family-based analysis identify a rare genetic variant in the ADIPOQ gene in the IRAS Family Study. *Hum Mol Genet* 2010. 19(20):4112-4120.
30. **Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, Muruganandan S, Sinal CJ.** Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. *J Biol Chem* 2007. 282(38):28175-28188.
31. **Tönjes A, Fasshauer M, Kratzsch J, Stumvoll M, Blüher M.** Adipokine pattern in subjects with impaired fasting glucose and impaired glucose tolerance in comparison to normal glucose tolerance and diabetes. *Plos One* 2010. 5(11):e13911.
32. **Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, Mahaney MC, Rainwater DL, VandeBerg JL, MacCluer JW, Collier G, Blangero J, Walder K, Jowett JB.** Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. *J Clin Endocrinol Metab* 2009. 94(8):3085-3088.
33. **Sell H, Laurencikiene J, Taube A, Eckardt K, Cramer A, Horrighs A, Arner P, Eckel J.** Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary human skeletal muscle cells. *Diabetes* 2009. 58(12):2731-2740.
34. **Bobbert T, Schwarz F, Fischer-Rosinsky A, Maurer**

L, Möhlig M, Pfeiffer AF, Mai K, Spranger J. Chemerin and prediction of Diabetes mellitus type 2. *Clin Endocrinol (Oxf)* 2015. 82(6):838-843.
35. **Bozaoglu K, Curran JE, Stocker CJ, Zaibi MS, Segal D, Konstantopoulos N, Morrison S, Carless M, Dyer TD, Cole SA, et al.** Chemerin, a novel adipokine in the regulation of angiogenesis. *J Clin Endocrinol Metab* 2010. 95(5):2476-2485.
36. **Tönjes A, Scholz M, Breitfeld J, Marzi C, Grallert H, Gross A, Ladenvall C, Schleinitz D, Krause K, Kirsten H, et al.** Genome wide meta-analysis highlights the role of genetic variation in RARRES2 in the regulation of circulating serum chemerin. *Plos Genet* 2014. 10(12):e1004854.
37. **Ouwens DM, Bekaert M, Lapauw B, Van Nieuwenhove Y, Lehr S, Hartwig S, Calders P, Kaufman JM, Sell H, Eckel J, Ruige JB.** Chemerin as biomarker for insulin sensitivity in males without typical characteristics of metabolic syndrome. *Arch Physiol Biochem* 2012. 118(3):135-138.
38. **Li Y, Shi B, Li S.** Association between serum chemerin concentrations and clinical indices in obesity or metabolic syndrome: a meta-analysis. *Plos One* 2014. 9(12):e113915.
39. **Coleman DL, Hummel KP.** The influence of genetic background on the expression of the obese (ob) gene in the mouse. *Diabetologia* 1973. 9(4):287-293.
40. **Coleman DL.** Effects of parabiosis of obese with diabetes and normal mice. *Diabetologia* 1973. 9(4):294-298
41. **Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM.** Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994. 372(6505):425-432.
42. **Green ED, Maffei M, Braden VV, Proenca R, DeSilva U, Zhang Y, Chua SC Jr, Leibel RL, Weissenbach J, Friedman JM.** The human obese (OB) gene: RNA expression pattern and mapping on the physical, cytogenetic, and genetic maps of chromosome 7. *Genome Res* 1995. 5(1):5-12.
43. **Lönnqvist F, Arner P, Nordfors L, Schalling M.** Overexpression of the obese (ob) gene in adipose tissue of human obese subjects. *Nat Med* 1995. 1(9):950-953.
44. **Madej T, Boguski MS, Bryant SH.** Threading analysis suggests that the obese gene product may be a helical cytokine. *FEBS Lett* 1995. 373(1):13-18.
45. **Zhang F, Basinski MB, Beals JM, Briggs SL, Churgay LM, Clawson DK, DiMarchi RD, Furman TC, Hale JE, Hsiung HM, et al.** Crystal structure of the obese protein leptin-E100. *Nature* 1997. 387(6629):206-209.
46. **Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, et al.** Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997. 387(6636):903-908.
47. **Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, et al.** A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998. 392(6674):398-401.
48. **van der Lende T, Te Pas MF, Veerkamp RF, Liefers SC.** Leptin gene polymorphisms and their phenotypic associations. *Vitam Horm* 2005. 71:373-404.
49. **Hager J, Clement K, Francke S, Dina C, Raison J, Lahlou N, Rich N, Pelloux V, Basdevant A, Guy-Grand B, North M, Froguel P.** A polymorphism in the 5' untranslated region of the human ob gene is associated with low leptin levels. *Int J Obes Relat Metab Disord* 1998. 22(3):200-205.
50. **Mamme's O, Betoulle D, Aubert R, Giraud V, Tuzet S, Petiet A, Colas-Linhart N, Fumeron F.** Novel polymorphisms in the 5' region of the LEP gene. Association with leptin levels and response to low•calorie diet in human obesity. *Diabetes* 1998. 47(3):487-489.
51. **Mamme's O, Betoulle D, Aubert R, Herbeth B, Siest G, Fumeron F.** Association of the G-2548A polymorphism in the 5' region of the LEP gene with overweight. *Ann Hum Genet* 2000. 64(Pt 5):391-394.
52. **Marcello MA, Calixto AR, de Almeida JF, Martins MB, Cunha LL, Cavalari CA, Etchebehere EC, da Assumpção LV, Geloneze B, Carvalho AL, Ward LS.** Polymorphism in LEP and LEPR may modify leptin levels and represent risk factors for thyroid cancer. *Int J Endocrinol* 2015. 2015:173218.
53. **Jamshidi Y, Snieder H, Wang X, Pavitt MJ, Spector TD, Carter ND, O'Dell SD.** Phosphatidylinositol 3-kinase p85alpha regulatory subunit gene PIK3R1 haplotype is associated with body fat and serum leptin in a female twin population. *Diabetologia* 2006. 49(11):2659-2667.
54. **Hernandez-Escalante VM, Nava-Gonzalez EJ, Voruganti VS, Kent JW, Haack K, Laviada-Molina HA, Molina-Segui F, Gallegos-Cabriales EC, Lopez-Alvarenga JC, Cole SA, Mezzles MJ, Comuzzie AG, Bastarrachea RA.** Replication of obesity and diabetes-related SNP associations in individuals from Yucatan, Mexico. *Front Genet* 2014. 5:380.
55. **Gribble FM, Reimann F.** Sulphonylurea action revisited: the post-cloning era. *Diabetologia* 2003. 46(7):875-891.
56. **Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, et al.** Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* 2004. 350(18):1838-1849.
57. **Rorsman P.** The pancreatic beta cell as a fuel sensor: an electrophysiologist's viewpoint. *Diabetologia* 1997. 40(5):487-495.
58. **Spanswick D, Smith MA, Mirshamsi S, Routh VH, Ashford ML.** Insulin activates ATP-sensitive K+ channels in hypothalamic neurons of lean, but not obese rats. *Nat Neurosci* 2000. 3(8):757-758.
59. **Spanswick D, Smith MA, Groppi VE, Logan SD, Ashford ML.** Leptin inhibits hypothalamic neurons by activation of ATP-sensitive potassium channels. *Nature* 1997. 390(6659):521-525.
60. **Bonfanti DH, Alcazar LP, Arakaki PA, Martins LT, Agustini BC, de Moraes Rego FG, Frigeri HR.** ATP-dependent potassium channels and type 2 diabetes mellitus. *Clin Biochem* 2015. 48(7-8):476-482.
61. **Schwanstecher C, Meyer U, Schwanstecher M.** K(IR)6.2 polymorphism predisposes to type 2 diabetes by inducing overactivity of pancreatic beta-cell ATP-sensitive K(+) channels. *Diabetes* 2002. 51(3):875-879.
62. **Reinehr T, Woelfle J, Wiegand S, Karges B, Meissner T, Nagl K, Holl RW.** Leptin but not adiponectin is related to type 2 diabetes mellitus in obese adolescents. *Pediatr Diabetes* 2015. In press.
63. **Tangkeangsirisin W, Hayashi J, Serrero G.** PC cell-derived growth factor mediates tamoxifen resistance and promotes tumor growth of human breast cancer cells. *Cancer*

Res 2004. 64(5):1737-1743.
64. **Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, Hahn-Barma V, van der Zee J, Clot F, Bakchine S, et al.** Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain* 2008. 131(Pt 3):732-746.
65. **He Z, Bateman A.** Progranulin (granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis. *J Mol Med (Berl)* 2003. 81(10):600-612.
66. **Youn BS, Bang SI, Klöting N, Park JW, Lee N, Oh JE, Pi KB, Lee TH, Ruschke K, Fasshauer M, Stumvoll M, Blüher M.** Serum progranulin concentrations may be associated with macrophage infiltration into omental adipose tissue. *Diabetes* 2009. 58(3):627-636.
67. **Carrasquillo MM, Nicholson AM, Finch N, Gibbs JR, Baker M, Rutherford NJ, Hunter TA, DeJesus-Hernandez M, Bisceglio GD, Mackenzie IR, et al.** Genome-wide screen identifies rs646776 near sortilin as a regulator of progranulin levels in human plasma. *Am J Hum Genet* 2010. 87(6):890-897.
68. **Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, et al.** Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet* 2008. 40(2):189-197.
69. **Gijselinck I, Van Broeckhoven C, Cruts M.** Granulin mutations associated with frontotemporal lobar degeneration and related disorders: An update. *Hum Mutat* 2008. 29(12):1373-1386.
70. **Matsubara T, Mita A, Minami K, Hosooka T, Kitazawa S, Takahashi K, Tamori Y, Yokoi N, Watanabe M, Matsuo E, Nishimura O, Seino S.** PGRN is a key adipokine mediating high fat diet-induced insulin resistance and obesity through IL-6 in adipose tissue. *Cell Metab* 2012. 15(1):38-50.
71. **Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA.** The hormone resistin links obesity to diabetes. *Nature* 2001. 409(6818):307-312.
72. **Le Lay S, Boucher J, Rey A, Castan-Laurell I, Krief S, Ferre P, Valet P, Dugail I.** Decreased resistin expression in mice with different sensitivities to a high-fat diet. *Biochem Biophys Res Commun* 2001. 289(2):564-567.
73. **Janke J, Engeli S, Gorzelniak K, Luft FC, Sharma AM.** Resistin gene expression in human adipocytes is not related to insulin resistance. *Obes Res* 2002. 10(1):1-5
74. **Nagaev I, Smith U.** Insulin resistance and type 2 diabetes are not related to resistin expression in human fat cells or skeletal muscle. *Biochem Biophys Res Commun* 2001. 285(2):561-564.
75. **Smith SR, Bai F, Charbonneau C, Janderova L, Argyropoulos G.** A Promoter genotype and oxidative stress potentially link resistin to human insulin resistance. *Diabetes* 2003. 52(7):1611-1618.
76. **Cho YM, Youn BS, Chung SS, Kim KW, Lee HK, Yu KY, Park HJ, Shin HD, Park KS.** Common genetic polymorphisms in the promoter of resistin gene are major determinants of plasma resistin concentrations in humans. *Diabetologia* 2004. 47(3):559-565.
77. **Ukkola O, Kunnari A, Kesäniemi YA.** Genetic variants at the resistin locus are associated with the plasma resistin concentration and cardiovascular risk factors. *Regul Pept* 2008. 149(1-3):56-59.
78. **Hivert MF, Manning AK, McAteer JB, Dupuis J, Fox CS, Cupples LA, Meigs JB, Florez JC.** Association of variants in RETN with plasma resistin levels and diabetes-related traits in the Framingham Offspring Study. *Diabetes* 2009. 58(3):750-756.
79. **Osawa H, Yamada K, Onuma H, Murakami A, Ochi M, Kawata H, Nishimiya T, Niiya T, Shimizu I, Nishida W, Hashiramoto M, Kanatsuka A, Fujii Y, Ohashi J, Makino H.** The G/G genotype of a resistin single-nucleotide polymorphism at -420 increases type 2 diabetes mellitus susceptibility by inducing promoter activity through specific binding of Sp1/3. *Am J Hum Genet* 2004. 75(4):678-686.
80. **Azuma K, Oguchi S, Matsubara Y, Mamizuka T, Murata M, Kikuchi H, Watanabe K, Katsukawa F, Yamazaki H, Shimada A, Saruta T.** Novel resistin promoter polymorphisms: association with serum resistin level in Japanese obese individuals. *Horm Metab Res* 2004. 36(8):564-570.
81. **Osawa H, Tabara Y, Kawamoto R, Ohashi J, Ochi M, Onuma H, Nishida W, Yamada K, Nakura J, Kohara K, Miki T, Makino H.** Plasma resistin, associated with single nucleotide polymorphism -420, is correlated with insulin resistance, lower HDL cholesterol, and high-sensitivity C-reactive protein in the Japanese general population. *Diabetes Care* 2007. 30(6):1501-1506.
82. **Asano H, Izawa H, Nagata K, Nakatochi M, Kobayashi M, Hirashiki A, Shintani S, Nishizawa T, Tanimura D, Naruse K, Matsubara T, Murohara T, Yokota M.** Plasma resistin concentration determined by common variants in the resistin gene and associated with metabolic traits in an aged Japanese population. *Diabetologia* 2010. 53(2):234-246.
83. **Seo JB, Noh MJ, Yoo EJ, Park SY, Park J, Lee IK, Park SD, Kim JB.** Functional characterization of the human resistin promoter with adipocyte determination- and differentiation-dependent factor 1/sterol regulatory element binding protein 1c and CCAAT enhancer binding protein-alpha. *Mol Endocrinol* 2003. 17(8):1522-1533.
84. **Li K, Wang SW, Li Y, Martin RE, Li L, Lu M, Lamhamedi-Cherradi SE, Hu G, Demissie-Sanders S, Zheng J, Chung F, Oates T, Yao Z.** Identification and expression of a new type II transmembrane protein in human mast cells. *Genomics* 2005. 86(1):68-75.
85. **Qi Q, Menzaghi C, Smith S, Liang L, de Rekeneire N, Garcia ME, Lohman KK, Miljkovic I, Strotmeyer ES, Cummings SR, et al.** Genome-wide association analysis identifies TYW3/CRYZ and NDST4 loci associated with circulating resistin levels. *Hum Mol Genet* 2012. 21(21):4774-4780.
86. **Gonzalez P, Rao PV, Zigler JS Jr.** Organization of the human zeta-crystallin/quinone reductase gene (CRYZ). *Genomics* 1994. 21(2):317-324.
87. **Lapucci A, Lulli M, Amedei A, Papucci L, Witort E, Di Gesualdo F, Bertolini F, Brewer G, Nicolin A, Bevilacqua A, Schiavone N, Morello D, Donnini M, Capaccioli S.** zeta-Crystallin is a bcl-2 mRNA binding protein involved in bcl-2 overexpression in T-cell acute lymphocytic leukemia. *FASEB J* 2010. 24(6):1852-1865.
88. **Fernandez MR, Porte S, Crosas E, Barbera N, Farres J, Biosca JA, Pares X.** Human and yeast zeta-crystallins

bind AU-rich elements in RNA. *Cell Mol Life Sci* 2007. 64(11):1419-1427.

89. **Chung CM, Lin TH, Chen JW, Leu HB, Yin WH, Ho HY, Sheu SH, Tsai WC, Chen JH, Lin SJ, Pan WH.** Common quantitative trait locus downstream of RETN gene identified by genome-wide association study is associated with risk of type 2 diabetes mellitus in Han Chinese: a Mendelian randomization effect. *Diabetes Metab Res Rev* 2014. 30(3):232-240.
90. **Ortega L, Navarro P, Riestra P, Gavela-Perez T, Soriano-Guillen L, Garces C.** Association of resistin polymorphisms with resistin levels and lipid profile in children. *Mol Biol Rep* 2014. 41(11):7659-7664.
91. **Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, Kotani K, Quadro L, Kahn BB.** Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 2005. 436(7049):356-362.
92. **Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, Wason CJ, Oberbach A, Jansson PA, Smith U, Kahn BB.** Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *N Engl J Med* 2006. 354(24):2552-2563.
93. **Meigs JB, Panhuysen CI, Myers RH, Wilson PW, Cupples LA.** A genome-wide scan for loci linked to plasma levels of glucose and HbA1c in a community-based sample of Caucasian pedigrees: the Framingham Offspring Study. *Diabetes* 2002. 51(3):833-840.
94. **Duggirala R, Blangero J, Mitchell BD, Almasy L, O'Connell P, Stern MP.** Linkage of type 2 diabetes and age of diabetes onset to a genetic location on chromosome 10q in Mexican Americans (Abstract). *Diabetes* 1998. 47(Suppl 1):A170.
95. **Munkhtulga L, Nakayama K, Utsumi N, Yanagisawa Y, Gotoh T, Omi T, Kumada M, Erdenebulgan B, Zolzaya K, Lkhagvasuren T, Iwamoto S.** Identification of a regulatory SNP in the retinol binding protein 4 gene associated with type 2 diabetes in Mongolia. *Hum Genet* 2007. 120(6):879-888.
96. **Munkhtulga L, Nagashima S, Nakayama K, Utsumi N, Yanagisawa Y, Gotoh T, Omi T, Kumada M, Zolzaya K, Lkhagvasuren T, et al.** Regulatory SNP in the RBP4 gene modified the expression in adipocytes and associated with BMI. *Obesity (Silver Spring)* 2010. 18(5):1006-1014.
97. **Hu C, Jia W, Zhang R, Wang C, Lu J, Wu H, Fang Q, Ma X, Xiang K.** Effect of RBP4 gene variants on circulating RBP4 concentration and type 2 diabetes in a Chinese population. *Diabet Med* 2008. 25(1):11-18.
98. **Wu Y1, Li H, Loos RJ, Qi Q, Hu FB, Liu Y, Lin X.** RBP4 variants are significantly associated with plasma RBP4 levels and hypertriglyceridemia risk in Chinese Hans. *J Lipid Res* 2009. 50(7):1479-1486.
99. **Ribel-Madsen R, Friedrichsen M, Vaag A, Poulsen P.** Retinol-binding protein 4 in twins: regulatory mechanisms and impact of circulating and tissue expression levels on insulin secretion and action. *Diabetes* 2009. 58(1):54-60.
100. **Hida K, Wada J, Eguchi J, Zhang H, Baba M, Seida A, Hashimoto I, Okada T, Yasuhara A, Nakatsuka A, et al.** Visceral adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity. *Proc Natl Acad Sci U S A* 2005. 102(30):10610-10615.
101. **Klöting N, Berndt J, Kralisch S, Kovacs P, Fasshauer M, Schön MR, Stumvoll M, Blüher M.** Vaspin gene expression in human adipose tissue: association with obesity and type 2 diabetes. *Biochem Biophys Res Commun* 2006. 339(1):430-436.
102. **Youn BS, Klöting N, Kratzsch J, Lee N, Park JW, Song ES, Ruschke K, Oberbach A, Fasshauer M, Stumvoll M, Blüher M.** Serum vaspin concentrations in human obesity and type 2 diabetes. *Diabetes* 2008. 57(2):372-377.
103. **Breitfeld J, Tönjes A, Böttcher Y, Schleinitz D, Wiele N, Marzi C, Brockhaus C, Rathmann W, Huth C, Grallert H, et al.** Genetic variation in the vaspin gene affects circulating serum vaspin concentrations. *Int J Obes (Lond)* 2013. 37(6):861-866.
104. **Teshigawara S, Wada J, Hida K, Nakatsuka A, Eguchi J, Murakami K, Kanzaki M, Inoue K, Terami T, Katayama A, et al.** Serum vaspin concentrations are closely related to insulin resistance, and rs77060950 at SERPINA12 genetically defines distinct group with higher serum levels in Japanese population. *J Clin Endocrinol Metab* 2012. 97(7):E1202-E1207.
105. **Breitfeld J, Heiker JT, Böttcher Y, Schleinitz D, Tönjes A, Weidle K, Krause K, Kuettner EB, Scholz M, Kiess W, et al.** Analysis of a rare functional truncating mutation rs61757459 in vaspin (SERPINA12) on circulating vaspin levels. *J Mol Med (Berl)* 2013. 91(11):1285-1292.
106. **Cook KS, Groves DL, Min HY, Spiegelman BM.** A developmentally regulated mRNA from 3T3 adipocytes encodes a novel serine protease homologue. *Proc Natl Acad Sci U S A* 1985. 82(19):6480-6484.
107. **Cook KS, Min HY, Johnson D, Chaplinsky RJ, Flier JS, Hunt CR, Spiegelman BM.** Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve. *Science* 1987. 237(4813):402-405.
108. **Rosen BS, Cook KS, Yaglom J, Groves DL, Volanakis JE, Damm D, White T, Spiegelman BM.** Adipsin and complement factor D activity: an immune-related defect in obesity. *Science* 1989. 244(4911):1483-1487.
109. **Platt KA, Min HY, Ross SR, Spiegelman BM.** Obesity-linked regulation of the adipsin gene promoter in transgenic mice. *Proc Natl Acad Sci U S A* 1989. 86(19):7490-7494.
110. **Lo JC, Ljubicic S, Leibiger B, Kern M, Leibiger IB, Moede T, Kelly ME, Chatterjee Bhowmick D, Murano I, Cohen P, et al.** Adipsin is an adipokine that improves beta cell function in diabetes. *Cell* 2014. 158(1):41-53.
111. **Flier JS, Cook KS, Usher P, Spiegelman BM.** Severely impaired adipsin expression in genetic and acquired obesity. *Science* 1987. 237(4813):405-408.
112. **Napolitano A, Lowell BB, Damm D, Leibel RL, Ravussin E, Jimerson DC, Lesem MD, Van Dyke DC, Daly PA, Chatis P, et al.** Concentrations of adipsin in blood and rates of adipsin secretion by adipose tissue in humans with normal, elevated and diminished adipose tissue mass. *Int J Obes Relat Metab Disord* 1994. 18(4):213-218.
113. **Pomeroy C, Mitchell J, Eckert E, Raymond N, Crosby R, Dalmasso AP.** Effect of body weight and caloric restriction on serum complement proteins, including Factor D/adipsin: studies in anorexia nervosa and obesity. *Clin Exp Immunol* 1997. 108(3):507-515.
114. **Ukkola O, Chagnon M, Tremblay A, Bouchard C.** Genetic variation at the adipsin locus and response to long-

term overfeeding. *Eur J Clin Nutr* 2003. 57(9):1073-1078.
115. **Stanton CM, Yates JR, den Hollander AI, Seddon JM, Swaroop A, Stambolian D, Fauser S, Hoyng C, Yu Y, Atsuhiro K, et al.** Complement factor D in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2011. 52(12):8828-8834.
116. **Castan-Laurell I, Dray C, Attane C, Duparc T, Knauf C, Valet P.** Apelin, diabetes, and obesity. *Endocrine* 2011. 40(1):1-9.
117. **Bertrand C, Valet P, Castan-Laurell I.** Apelin and energy metabolism. *Front Physiol* 2015. 6:115.
118. **Zhang R, Hu C, Wang CR, Ma XJ, Bao YQ, Xu J, Lu JY, Qin W, Xiang KS, Jia WP.** Association of apelin genetic variants with type 2 diabetes and related clinical features in Chinese Hans. *Chin Med J (Engl)* 2009. 122(11):1273-1276.
119. **Zhao Q, Gu D, Kelly TN, Hixson JE, Rao DC, Jaquish CE, Chen J, Huang J, Chen CS, Gu CC, Whelton PK, He J.** Association of genetic variants in the apelin-APJ system and ACE2 with blood pressure responses to potassium supplementation: the GenSalt study. *Am J Hypertens* 2010. 23(6):606-613.
120. **Liao YC, Chou WW, Li YN, Chuang SC, Lin WY, Lakkakula BV, Yu ML, Juo SH.** Apelin gene polymorphism influences apelin expression and obesity phenotypes in Chinese women. *Am J Clin Nutr* 2011. 94(3):921-928.
121. **Zhu P, Lin F, Huang F, Huang Q, Li Q, Gao Z, Chen F.** Apelin and APLN single nucleotide polymorphisms and combined hypertension and central retinal artery stenosis in a Chinese population. *Clin Exp Hypertens* 2015. 37(4):280-287.
122. **Liao YC, Wang YS, Hsi E, Chang MH, You YZ, Juo SH.** MicroRNA-765 influences arterial stiffness through modulating apelin expression. *Mol Cell Endocrinol* 2015. 411:11-19.
123. **Yang RZ, Xu A, Pray J, Hu H, Jadhao S, Hansen BC, Shuldiner AR, McLenithan JC, Gong DW.** Cloning of omentin, a new adipocytokine from omental fat tissue in humans. *Diabetes* 2003. (Suppl 1):A1.
124. **Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, Shuldiner AR, Fried SK, McLenithan JC, Gong DW.** Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am J Physiol Endocrinol Metab* 2006. 290(8):E1253-E1261.
125. **Schäffler A, Neumeier M, Herfarth H, Fürst A, Schölmerich J, Büchler C.** Genomic structure of human omentin, a new adipocytokine expressed in omental adipose tissue. *Biochim Biophys Acta* 2005. 1732(1-3):96-102.
126. **de Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J, Ndubuizu K, Patil S, Schwartz A, Kligman M, Fried SK, Gong DW, Shuldiner AR, Pollin TI, McLenithan JC.** Omentin plasma levels and gene expression are decreased in obesity. *Diabetes* 2007. 56(6):1655-1661.
127. **Schäffler A, Zeitoun M, Wobser H, Buechler C, Aslanidis C, Herfarth H.** Frequency and significance of the novel single nucleotide missense polymorphism Val109Asp in the human gene encoding omentin in Caucasian patients with type 2 diabetes mellitus or chronic inflammatory bowel diseases. *Cardiovasc Diabetol* 2007. 6:3.
128. **Turan H, Yaykasli KO, Soguktas H, Yaykasli E, Aliagaoglu C, Erdem T, Karkucak M, Kaya E, Ucgun T, Bahadir A.** Omentin serum levels and omentin gene Val109Asp polymorphism in patients with psoriasis. *Int J Dermatol* 2014. 53(5):601-605.
129. **Everett JR.** Pharmacometabonomics in humans: a new tool for personalized medicine. *Pharmacogenomics* 2015. 16(7):737-754.
130. **Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, et al.** Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 2003. 423(6941):762-769.
131. **Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF.** T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci U S A* 2004. 101(28):10308-10313.
132. **Ling H, Waterworth DM, Stirnadel HA, Pollin TI, Barter PJ, Kesäniemi YA, Mahley RW, McPherson R, Waeber G, Bersot TP, Cohen JC, Grundy SM, Mooser VE, Mitchell BD.** Genome-wide linkage and association analyses to identify genes influencing adiponectin levels: the GEMS Study. *Obesity (Silver Spring)* 2009. 17(4):737-744.
133. **Matsuda K, Fujishima Y, Maeda N, Mori T, Hirata A, Sekimoto R, Tsushima Y, Masuda S, Yamaoka M, Inoue K, Nishizawa H, Kita S, Ranscht B, Funahashi T, Shimomura I.** Positive feedback regulation between adiponectin and T-cadherin impacts adiponectin levels in tissue and plasma of male mice. *Endocrinology* 2015. 156(3):934-946.
134. **Jee SH, Sull JW, Lee JE, Shin C, Park J, Kimm H, Cho EY, Shin ES, Yun JE, Park JW, et al.** Adiponectin concentrations: a genome-wide association study. *Am J Hum Genet* 2010. 87(4):545-552.
135. **Morisaki H, Yamanaka I, Iwai N, Miyamoto Y, Kokubo Y, Okamura T, Okayama A, Morisaki T.** CDH13 gene coding T-cadherin influences variations in plasma adiponectin levels in the Japanese population. *Hum Mutat* 2012. 33(2):402-410.
136. **Chung CM, Lin TH, Chen JW, Leu HB, Yang HC, Ho HY, Ting CT, Sheu SH, Tsai WC, Chen JH, Lin SJ, Chen YT, Pan WH.** A genome-wide association study reveals a quantitative trait locus of adiponectin on CDH13 that predicts cardiometabolic outcomes. *Diabetes* 2011. 60(9):2417-2423.
137. **Gao H, Kim YM, Chen P, Igase M, Kawamoto R, Kim MK, Kohara K, Lee J, Miki T, Ong RT, et al.** Genetic variation in CDH13 is associated with lower plasma adiponectin levels but greater adiponectin sensitivity in East Asian populations. *Diabetes* 2013. 62(12):4277-4283.
138. **Dhillon PK, Penney KL, Schumacher F, Rider JR, Sesso HD, Pollak M, Fiorentino M, Finn S, Loda M, Rifai N, Mucci LA, Giovannucci E, Stampfer MJ, Ma J.** Common polymorphisms in the adiponectin and its receptor genes, adiponectin levels and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2011. 20(12):2618-2627.
139. **Wargent ET, Zaibi MS, O'Dowd JF, Cawthorne MA, Wang SJ, Arch JR, Stocker CJ.** Evidence from studies in rodents and in isolated adipocytes that agonists of the chemerin receptor CMKLR1 may be beneficial in the treatment of type 2 diabetes. *PeerJ* 2015. 3:e753.
140. **Ernst MC, Haidl ID, Zuniga LA, Dranse HJ, Rourke JL, Zabel BA, Butcher EC, Sinal CJ.** Disruption of the chemokine-like receptor-1 (CMKLR1) gene is associated

with reduced adiposity and glucose intolerance. *Endocrinology* 2012. 153(2):672-682.

141. **Wu X, Ye Y, Rosell R, Amos CI, Stewart DJ, Hildebrandt MA, Roth JA, Minna JD, Gu J, Lin J, et al.** Genome-wide association study of survival in non-small cell lung cancer patients receiving platinum-based chemotherapy. *J Natl Cancer Inst* 2011. 103(10):817-825.
142. **Ben Ali S, Kallel A, Sediri Y, Ftouhi B, Feki M, Slimene H, Jemaa R, Kaabachi N.** LEPR p.Q223R Polymorphism influences plasma leptin levels and body mass index in Tunisian obese patients. *Arch Med Res* 2009. 40(3):186-190.
143. **Furusawa T, Naka I, Yamauchi T, Natsuhara K, Kimura R, Nakazawa M, Ishida T, Nishida N, Eddie R, Ohtsuka R, Ohashi J.** The serum leptin level and body mass index in Melanesian and Micronesian Solomon Islanders: focus on genetic factors and urbanization. *Am J Hum Biol* 2011. 23(4):435-444.
144. **Oliveira Rd, Cerda A, Genvigir FD, Sampaio MF, Armaganijan D, Bernik MM, Dorea EL, Hirata MH, Hinuy HM, Hirata RD.** Leptin receptor gene polymorphisms are associated with adiposity and metabolic alterations in Brazilian individuals. *Arg Bras Endocrinol Metabol* 2013. 57(9):677-684.
145. **Chagnon YC, Wilmore JH, Borecki IB, Gagnon J, Perusse L, Chagnon M, Collier GR, Leon AS, Skinner JS, Rao DC, Bouchard C.** Associations between the leptin receptor gene and adiposity in middle-aged Caucasian males from the HERITAGE family study. *J Clin Endocrinol Metab* 2000. 85(1):29-34
146. **Suriyaprom K, Tungtrongchitr R, Thawnasom K.** Measurement of the levels of leptin, BDNF associated with polymorphisms LEP G2548A, LEPR Gln223Arg and BDNF Val66Met in Thai with metabolic syndrome. *Diabetol Metab Syndr* 2014. 6(1):6.
147. **van Rossum CT, Hoebee B, van Baak MA, Mars M, Saris WH, Seidell JC.** Genetic variation in the leptin receptor gene, leptin, and weight gain in young Dutch adults. *Obes Res* 2003. 11(3):377-386.
148. **Masuo K, Straznicky NE, Lambert GW, Katsuya T, Sugimoto K, Rakugi H, Socratous F, Hastings J, Lambert EA, Ogihara T, Esler MD.** Leptin-receptor polymorphisms relate to obesity through blunted leptin-mediated sympathetic nerve activation in a Caucasian male population. *Hypertens Res* 2008. 31(6):1093-1100.
149. **Quinton ND, Lee AJ, Ross RJ, Eastell R, Blakemore AI.** A single nucleotide polymorphism (SNP) in the leptin receptor is associated with BMI, fat mass and leptin levels in postmenopausal Caucasian woman. *Hum Genet* 2001. 108(3):233-236.
150. **Stefan N, Vozarova B, Del Parigi A, Ossowski V, Thompson DB, Hanson RL, Ravussin E, Tataranni PA.** The Gln223Arg polymorphism of the leptin receptor in Pima Indians: influence on energy expenditure, physical activity and lipid metabolism. *Int J Obes Relat Metab Disord* 2002. 26(12):1629-1632.
151. **Wauters M, Mertens I, Chagnon M, Rankinen T, Considine RV, Chagnon YC, Van Gaal LF, Bouchard C.** Polymorphisms in the leptin receptor gene, body composition and fat distribution in overweight and obese women. *Int J Obes Relat Metab Disord* 2001. 25(5):714-720.
152. **de Luis DA, Aller R, Izaola O, Gonzalez Sagrado M, Conde R, de la Fuente B, Primo D.** Effect of Lys656Asn polymorphism of leptin receptor gene on cardiovascular risk factors and serum adipokine levels after a high polyunsaturated fat diet in obese patients. *J Clin Lab Anal* 2014. In press.
153. **Mars M, van Rossum CT, de Graaf C, Hoebee B, De Groot LC, Kok FJ.** Leptin responsiveness to energy restriction: genetic variation in the leptin receptor gene. *Obes Res* 2004. 12(3):442-444.
154. **Hu F, Padukkavidana T, Vaegter CB, Brady OA, Zheng Y, Mackenzie IR, Feldman HH, Nykjaer A, Strittmatter SM.** Sortilin-mediated endocytosis determines levels of the frontotemporal dementia protein, progranulin. *Neuron* 2010. 68(4):654-667.
155. **Carrasquillo MM, Nicholson AM, Finch N, Gibbs JR, Baker M, Rutherford NJ, Hunter TA, DeJesus-Hernandez M, Bisceglio GD, Mackenzie IR, et al.** Genome-wide screen identifies rs646776 near sortilin as a regulator of progranulin levels in human plasma. *Am J Hum Genet* 2010. 87(6):890-897.
156. **Prudencio M, Jansen-West KR, Lee WC, Gendron TF, Zhang YJ, Xu YF, Gass J, Stuani C, Stetler C, Rademakers R, Dickson DW, Buratti E, Petrucelli L.** Misregulation of human sortilin splicing leads to the generation of a nonfunctional progranulin receptor. *Proc Natl Acad Sci U S A* 2012. 109(52):21510-21515.
157. **Kjolby M, Andersen OM, Breiderhoff T, Fjorback AW, Pedersen KM, Madsen P, Jansen P, Heeren J, Willnow TE, Nykjaer A.** Sort1, encoded by the cardiovascular risk locus 1p13.3, is a regulator of hepatic lipoprotein export. *Cell Metab* 2010. 12(3):213-223.
158. **Musunuru K, Strong A, Frank-Kamenetsky M, Lee NE, Ahfeldt T, Sachs KV, Li X, Li H, Kuperwasser N, Ruda VM, et al.** From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. *Nature* 2010. 466(7307):714-719.
159. **Coutinho MF, Bourbon M, Prata MJ, Alves S.** Sortilin and the risk of cardiovascular disease. *Rev Port Cardiol* 2013. 32(10):793-799.
160. **Lee S, Lee HC, Kwon YW, Lee SE, Cho Y, Kim J, Lee S, Kim JY, Lee J, Yang HM, Mook-Jung I, Nam KY, Chung J, Lazar MA, Kim HS.** Adenylyl Cyclase-Associated Protein 1(CAP1) is a Receptor for Human Resistin and Mediates Inflammatory Actions of Human Monocytes. *Cell Metab* 2014. 19(3):484-497.
161. **Kawaguchi R, Yu J, Honda J, Hu J, Whitelegge J, Ping P, Wiita P, Bok D, Sun H.** A membrane receptor for retinol binding protein mediates cellular uptake of vitamin A. *Science* 2007. 315(5813):820-825.
162. **Alapatt P, Guo F, Komanetsky SM, Wang S, Cai J, Sargsyan A, Rodríguez Díaz E, Bacon BT, Aryal P, Graham TE.** Liver retinol transporter and receptor for serum retinol-binding protein (RBP4). *J Biol Chem* 2013. 288(2):1250-1265.
163. **Kawaguchi R, Yu J, Wiita P, Honda J, Sun H.** An essential ligand-binding domain in the membrane receptor for retinol-binding protein revealed by large-scale mutagenesis and a human polymorphism. *J Biol Chem* 2008. 283(22):15160-15168.
164. **Nair AK, Sugunan D, Kumar H, Anilkumar G.** Case-control analysis of SNPs in GLUT4, RBP4 and STRA6: association of SNPs in STRA6 with type 2 diabetes in a South Indian population. *Plos One* 2010. 5(7):e11444.
165. **Heiker JT.** Vaspin (serpinA12) in obesity, insulin resistance, and inflammation. *J Pept Sci* 2014. 20(5):299-306.

166. **Heiker JT, Klöting N, Kovacs P, Kuettner EB, Sträter N, Schultz S, Kern M, Stumvoll M, Blüher M, Beck-Sickinger AG.** Vaspin inhibits kallikrein 7 by serpin mechanism. *Cell Mol Life Sci* 2013. 70(14):2569-2583.
167. **Nakatsuka A, Wada J, Iseda I, Teshigawara S, Higashio K, Murakami K, Kanzaki M, Inoue K, Terami T, Katayama A, et al.** Vaspin is an adipokine ameliorating ER stress in obesity as a ligand for cell-surface GRP78/MTJ-1 complex. *Diabetes* 2012. 61(11):2823-2832.
168. **Nakatsuka A, Wada J, Iseda I, Teshigawara S, Higashio K, Murakami K, Kanzaki M, Inoue K, Terami T, Katayama A, et al.** Visceral adipose tissue-derived serine proteinase inhibitor inhibits apoptosis of endothelial cells as a ligand for the cell-surface GRP78/voltage-dependent anion channel complex. *Circ Res* 2013. 112(5):771-780.
169. **Zhu X, Zhang J, Fan W, Wang F, Yao H, Wang Z, Hou S, Tian Y, Fu W, Xie D, et al.** The rs391957 variant cis-regulating oncogene GRP78 expression contributes to the risk of hepatocellular carcinoma. *Carcinogenesis* 2013. 34(6):1273-1280.
170. **Jia Y, Tong Y, Min L.** Significance of functional GRP78 polymorphisms in predicting the onset of type 2 diabetic peripheral neuropathy in Chinese population. *Neurol Res* 2015. 37(8):683-687.
171. **Xu C, Yang Q, Xiong H, Wang L, Cai J, Wang F, Li S, Chen J, Wang C, Wang D, et al.** Candidate pathway-based genome-wide association studies identify novel associations of genomic variants in the complement system associated with coronary artery disease. *Circ Cardiovasc Genet* 2014. 7(6):887-894.
172. **Chapman NA, Dupre DJ, Rainey JK.** The apelin receptor: physiology, pathology, cell signalling, and ligand modulation of a peptide-activated class A GPCR. *Biochem Cell Biol* 2014. 92(6):431-440.
173. **Hata J, Matsuda K, Ninomiya T, Yonemoto K, Matsushita T, Ohnishi Y, Saito S, Kitazono T, Ibayashi S, Iida M, Kiyohara Y, Nakamura Y, Kubo M.** Functional SNP in an Sp1-binding site of AGTRL1 gene is associated with susceptibility to brain infarction. *Hum Mol Genet* 2007. 16(6):630-639.
174. **Kotanidou EP, Kalinderi K, Kyrgios I, Efraimidou S, Fidani L, Papadopoulou-Alataki E, Eboriadou-Petikopoulou M, Galli-Tsinopoulou A.** Apelin and G212A apelin receptor gene polymorphism in obese and diabese youth. *Pediatr Obes* 2015. 10(3):213-219.
175. **Akiyama Y, Oshima K, Kuhara T, Shin K, Abe F, Iwatsuki K, Nadano D, Matsuda T.** A lactoferrin-receptor, intelectin 1, affects uptake, sub-cellular localization and release of immunochemically detectable lactoferrin by intestinal epithelial Caco-2 cells. *J Biochem* 2013. 154(5):437-448.
176. **Suzuki YA, Shin K, Lönnerdal B.** Molecular cloning and functional expression of a human intestinal lactoferrin receptor. *Biochemistry* 2001. 40(51):15771-15779.
177. **Shen W, Wang C, Xia L, Fan C, Dong H, Deckelbaum RJ, Qi K.** Epigenetic modification of the leptin promoter in diet-induced obese mice and the effects of N-3 polyunsaturated fatty acids. *Sci Rep* 2014. 4:5282.
178. **Houde AA, Legare C, Biron S, Lescelleur O, Biertho L, Marceau S, Tchernof A, Vohl MC, Hivert MF, Bouchard L.** Leptin and adiponectin DNA methylation levels in adipose tissues and blood cells are associated with BMI, waist girth and LDL-cholesterol levels in severely obese men and women. *BMC Med Genet* 2015. 16:29.
179. **Houde AA, Legare C, Hould FS, Lebel S, Marceau P, Tchernof A, Vohl MC, Hivert MF, Bouchard L.** Cross-tissue comparisons of leptin and adiponectin: DNA methylation profiles. *Adipocyte* 2014. 3(2):132-140.
180. **Houde AA, Hivert MF, Bouchard L.** Fetal epigenetic programming of adipokines. *Adipocyte* 2013. 2(1):41-46.
181. **Zhi D, Aslibekyan S, Irvin MR, Claas SA, Borecki IB, Ordovas JM, Absher DM, Arnett DK.** SNPs located at CpG sites modulate genome-epigenome interaction. *Epigenetics* 2013. 8(8):802-806.
182. **Visser M, Palstra RJ, Kayser M.** Allele-specific transcriptional regulation of IRF4 in melanocytes is mediated by chromatin looping of the intronic rs12203592 enhancer to the IRF4 promoter. *Hum Molr Genet* 2015. 24(9):2649-2661.
183. **Jeltsch A.** Molecular enzymology of mammalian DNA methyltransferases. *Curr Top Microbiol Immunol* 2006. 301:203-225.
184. **Putku M, Kals M, Inno R, Kasela S, Org E, Kozich V, Milani L, Laan M.** CDH13 promoter SNPs with pleiotropic effect on cardiometabolic parameters represent methylation QTLs. *Hum Genet* 2015. 134(3):291-303.
185. **Rönn T, Volkov P, Gillberg L, Kokosar M, Perfilyev A, Jacobsen AL, Jorgensen SW, Brons C, Jansson PA, Eriksson KF, et al.** Impact of age, BMI and HbA1c levels on the genome-wide DNA methylation and mRNA expression patterns in human adipose tissue and identification of epigenetic biomarkers in blood. *Hum Mol Genet* 2015. 24(13):3792-3813.
186. **Nilsson E, Jansson PA, Perfilyev A, Volkov P, Pedersen M, Svensson MK, Poulsen P, Ribel-Madsen R, Pedersen NL, Almgren P, et al.** Altered DNA methylation and differential expression of genes influencing metabolism and inflammation in adipose tissue from subjects with type 2 diabetes. *Diabetes* 2014. 63(9):2962-2976.
187. **Grarup N, Moltke I, Albrechtsen A, Hansen T.** Diabetes in population isolates: lessons from Greenland. *Rev Diabet Stud* 2015. 12(3-4):330-347.
188. **Mali P, Yang L, Esvelt KM, Aach J, Guell M, DiCarlo JE, Norville JE, Church GM.** RNA-guided human genome engineering via Cas9. *Science* 2013. 339(6121):823-826.

