

## REVIEW

**ZBTB16 and Metabolic Syndrome: a Network Perspective****O. ŠEDA<sup>1</sup>, L. ŠEDO VÁ<sup>1,2</sup>, J. VČELÁK<sup>3</sup>, M. VAŇKOVÁ<sup>3</sup>, F. LIŠKA<sup>1</sup>, B. BENDLOVÁ<sup>3</sup>**

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**Summary**

Metabolic syndrome is a prevalent, complex condition. The search for genetic determinants of the syndrome is currently undergoing a paradigm enhancement by adding systems genetics approaches to association studies. We summarize the current evidence on relations between an emergent new candidate, zinc finger and BTB domain containing 16 (ZBTB16) transcription factor and the major components constituting the metabolic syndrome. Information stemming from studies on experimental models with altered *Zbtb16* expression clearly shows its effect on adipogenesis, cardiac hypertrophy and fibrosis, lipid levels and insulin sensitivity. Based on current evidence, we provide a network view of relations between ZBTB16 and hallmarks of metabolic syndrome in order to elucidate the potential functional links involving the ZBTB16 node. Many of the identified genes interconnecting ZBTB16 with all or most metabolic syndrome components are linked to immune function, inflammation or oxidative stress. In summary, ZBTB16 represents a promising pleiotropic candidate node for metabolic syndrome.

**Key words**

Metabolic syndrome • Systems biology • Pleiotropy • Animal models

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**Introduction**

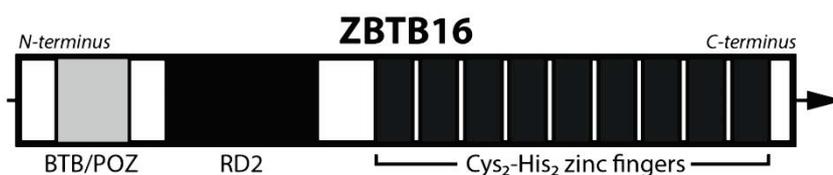
Metabolic syndrome is a prevalent condition with a worldwide surge of both incidence and prevalence (Aguilar *et al.* 2015). The syndrome is defined by presence of at least three out of five clinical criteria [elevated waist circumference, elevated triglycerides (or treatment), reduced high-density lipoprotein cholesterol (or treatment), elevated blood pressure (or treatment) and elevated fasting glucose (or treatment)] are diagnosed as having the condition (Alberti *et al.* 2009). Distinct cut-points are set for all criteria, except elevated waist circumference, which must rely on population and country-specific definitions. All individual constituents of metabolic syndrome are multifactorial traits with substantial heritable and environmental components. The genetic architecture of the syndrome is complex and usually involves numerous gene-gene, nutrigenetic and pharmacogenetic interactions (Seda *et al.* 2005c). Therefore, the identification of genetic determinants of metabolic syndrome in the general human population is complicated by numerous factors that cannot be easily controlled (Bureau *et al.* 2015). Despite over 1000 highly significant associations ( $P < 5 \times 10^{-8}$ ) of DNA polymorphisms with individual components of metabolic syndrome or the complete metabolic syndrome being currently inventoried in the NHGRI-EBI Catalog of Published Genome-Wide Association Studies (<http://www.ebi.ac.uk/gwas>, accessed on May 30<sup>th</sup>, 2017), we are still far from attaining a clinically utilizable algorithm for genetic risk assessment and prediction.

Systems genetic approaches are gaining ground in analysis of complex diseases, identifying not only single polymorphisms, but rather nodes within networks and pathways crucial for disease onset and pathogenesis (Civelek and Lusis 2014). One of the emergent genes with mounting evidence for its implication in metabolic syndrome is promyelocytic leukemia zinc finger.

## PLZF / ZBTB16

Promyelocytic leukemia zinc finger (PLZF), also known by the HUGO Gene Nomenclature Committee approved name ZBTB16 (zinc finger and BTB domain containing 16), was initially discovered in humans as a cause of retinoic acid-resistant acute promyelocytic leukemia in the form of fusion protein PLZF-RAR $\alpha$  associated with the t(11;17)(q23;q21) translocation (Grignani *et al.* 1998). ZBTB16 is expressed in numerous tissues and well conserved in mammals. Human and mouse/rat ZBTB16 proteins show 97%/96% identity over 673 aminoacid residues of the protein, respectively. Within its C-terminus, this transcription factor contains nine Cys<sub>2</sub>-His<sub>2</sub> type zinc fingers that facilitate sequence-specific DNA binding to its target genes (Li *et al.* 1997, Suliman *et al.* 2012). There is a repressor domain RD2 which interacts with ETO co-repressor (Melnick *et al.* 2000) and a N-terminal BTB/POZ (bric a brac-tramtrack-broad complex, poxvirus and zinc-finger)

multimerization/repression domain (Ahmad *et al.* 1998) as shown in Figure 1. As a member of the POK (POZ and Krüppel zinc finger (ZF)) family of proteins, ZBTB16 induces epigenetic changes, including histone modifications and DNA methylation, thus regulating the chromatin state (Puszyk *et al.* 2013). ZBTB16 also interacts, through its three N-terminal zinc-finger motifs, with nuclear receptors, in particular with retinoic acid receptor (RAR)  $\alpha$ , blocking the RAR-RXR heterodimerization necessary for retinoic acid signaling (Martin *et al.* 2003). As a multifaceted signaling hub for number of cellular processes, ZBTB16 is a target of several post-translational modifications, including ubiquitination (Sobieszczuk *et al.* 2010), phosphorylation (Costoya *et al.* 2008), acetylation (Guidez *et al.* 2005) and sumoylation, i.e. activation of SUMO molecules (Kang *et al.* 2003). The regulators of PLZF activity include CBP/p300 acetyltransferase, sirtuin 1 and histone deacetylase 3 (McConnell *et al.* 2015, Puszyk *et al.* 2013). PLZF also robustly responds to glucocorticoids (Fahnenstich *et al.* 2003, Chen *et al.* 2014). Although traditionally viewed as a repressor acting through recruitment of nuclear receptor corepressors 1 and 2 and histone deacetylases, more recent findings describe a possibility of dynamic change of PLZF to an activator through interferon-triggered phosphorylation (Ozato 2009).



**Fig. 1.** Schematic representation of major domains of the ZBTB16 protein. BTB/POZ, bric a brac-tramtrack-broad complex, poxvirus and zinc-finger; RD2, repressor domain.

## ZBTB16 as a pleiotropic factor

The disruption of *Zbtb16* in mice by gene targeting revealed that the protein acts as a transcriptional repressor of *Hox* genes, via a process of chromatin remodeling, in the modulation of both embryonic limb patterning and apoptosis (Barna *et al.* 2000, Barna *et al.* 2002, Barna *et al.* 2005, Ivins *et al.* 2003). The crucial role of ZBTB16 in the limb development was further supported by data from human (Fischer *et al.* 2008) and rat studies (Liska *et al.* 2016, Liska *et al.* 2009). Contrasting with the loss-of function mutations in the knock-out mouse and human, the *Zbtb16* mutation responsible for the morphological aberration in the

polydactylous rat strain (PD/Cub) model of limb development (Kren 1975) and metabolic syndrome (Sedova *et al.* 2000, Seda *et al.* 2005a) was found to comprise 2,964-bp deletion in intron 2 of the gene, removing several deeply conserved noncoding elements (Liska *et al.* 2009). ZBTB16 is also involved in regulation of self-renewal and differentiation of distinct type of stem cells (Liu *et al.* 2016); maintenance of spermatogenesis (Costoya *et al.* 2004), osteo- and chondrogenesis of mesenchymal stem cells (Ikeda *et al.* 2005, Liu *et al.* 2011), regulation of hematopoietic stem cell quiescence and formation of specialized natural killer T cells. The relevance of ZBTB16 for cancer and immune system function (Suliman *et al.* 2012), stem cell self-

renewal (Liu *et al.* 2016) as well as hematopoiesis (Maeda 2016) has been reviewed extensively earlier and is beyond the scope of the current review. Below we summarize the current evidence on relations between ZBTB16 and the major components constituting the metabolic syndrome. Finally, we have queried the Ingenuity Pathway Analysis database (content version 33559992) for entities connecting *Zbtb16* to single or multiple hallmarks of metabolic syndrome in order to elucidate the potential functional network links involving the ZBTB16 node (Fig. 2).

### ZBTB16 and adipose tissue

ZBTB16 was identified as a potent anti-adipogenic factor in a large comparative epigenomic analysis of murine and human adipogenesis (Mikkelsen *et al.* 2010). The overexpression of *Zbtb16* in L1 cells was sufficient to repress adipogenesis, evidenced by reduced lipid content and diminished markers of terminal differentiation. Conversely, RNAi-mediated knockdown of *Zbtb16* enhanced L1 adipogenesis (Mikkelsen *et al.* 2010). The importance of *Zbtb16* in adipogenesis and obesity was corroborated by a study showing that *Zbtb16* overexpression in brown adipocytes led to the induction of components of the thermogenic program, including genes involved in fatty acid oxidation, glycolysis and mitochondrial function (Plaisier *et al.* 2012). Enhanced *Zbtb16* expression also increased mitochondrial number, as well as the respiratory capacity and uncoupling. These effects were accompanied by decreased triglyceride content and increased carbohydrate utilization in brown adipocytes (Plaisier *et al.* 2012). In a study focusing on the role of diacylglycerol acyltransferase-1 (DGAT1) in synthesis of triacylglycerols and intramuscular fat deposition, *Zbtb16* was substantially downregulated in *Dgat1*-transgenic mice favoring intramuscular fat deposition (Ying *et al.* 2017). Natural variation in *Zbtb16* mRNA levels in multiple tissues across a panel of >100 mouse strains was inversely correlated with body weight and body fat content (Plaisier *et al.* 2012). In our network scan we identified 32 entities interconnecting *Zbtb16* and obesity, for 18 of which there is evidence of relation to at least one more metabolic syndrome component (Fig. 2).

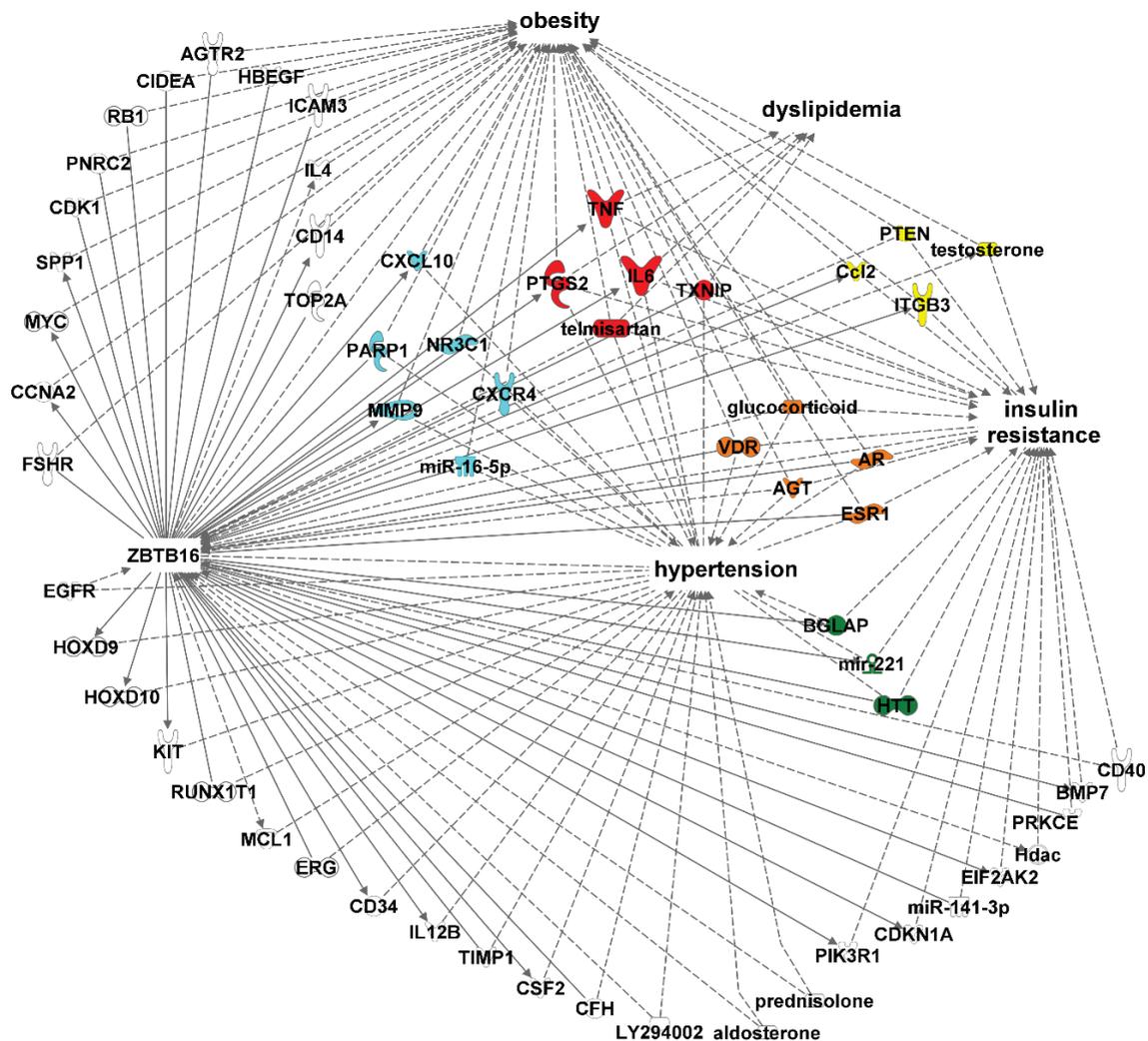
### ZBTB16 and cardiovascular traits

ZBTB16 has been suggested as a candidate for

congenital heart disease based on biallelic loss-of-expression in RNAseq analyses of surgically repaired subjects suffering from congenital heart disease (McKean *et al.* 2016). There are multiple lines of evidence pointing to possible contribution of ZBTB16 to the pathogenesis of hypertension, cardiac hypertrophy, and cardiac fibrosis. First, in renal epithelial cells, ZBTB16 is a part of the negative feedback regulation of mineralocorticoid action. Aldosterone induces ZBTB16 which in turn suppresses expression of beta- and gamma- epithelial sodium channel (ENaC) subunits, limiting thus sodium reabsorption (Naray-Fejes-Toth *et al.* 2008). Second, direct interaction of the ZBTB16 with AT2 angiotensin receptor induces expression of phosphatidylinositol-3 kinase p85 $\alpha$  subunit (p85 $\alpha$  PI3K). This pathway may explain missing cardiac hypertrophic response in mice deficient in AT2. Third, direct interaction of ZBTB16 with (pro)renin receptor (Ahmed *et al.* 2011, Shamansurova *et al.* 2016) leads to increased expression of p85 $\alpha$  PI3K, the same target as in the AT2 cascade (Funke-Kaiser *et al.* 2010). Moreover, renin stimulation has proliferative and antiapoptotic effects on rat cardiomyocytes that are completely dependent on ZBTB16 function. This pathway may therefore be connected to cardiac hypertrophy and/or fibrosis associated with hypertension (Scheffe *et al.* 2006). We have previously established a SHR-*Lx* congenic strain that carries a mutated *Zbtb16* gene of PD/Cub origin (Sedova *et al.* 2000) on the SHR genetic background within a 1.4 Mbp differential segment of chromosome 8 (Seda *et al.* 2005b). The SHR-*Lx* congenic subline exhibits decreased blood pressure and amelioration of left ventricular hypertrophy when compared to SHR controls (Liska *et al.* 2014). Sequence analysis of genes isolated within the SHR-*Lx* genome revealed an intronic deletion of a putative enhancer in *Zbtb16* gene as the most promising candidate. Accordingly, cardiac expression of *Zbtb16* in the PD5 subline (with deletion) was significantly reduced compared to SHR (without deletion) (Liska *et al.* 2014). In a subsequent study, we generated a null *Plzf* allele in the SHR using transcription activator-like effector nuclease-mediated gene targeting to assess *in vivo* effects of *Plzf* on metabolic and cardiac traits (Liska *et al.* 2017). The SHR-*Plzf*<sup>+/-</sup> (heterozygotes were used due to semilethality of the *Plzf*<sup>-/-</sup> knockout on SHR background) rats versus wild-type controls showed reduced cardiomyocytes hypertrophy and interstitial fibrosis and their left ventricular mass index was also significantly smaller despite no differences in blood

pressure (Liska *et al.* 2017). There were four chemical entities (aldosterone, glucocorticoids, prednisolone and telmisartan), single microRNA (miR-16-5p) and

27 protein-coding genes interconnecting ZBTB16 and hypertension (Fig. 2).



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**Fig. 2.** Network of relations between entities (genes, chemicals) connecting *Zbtb16* to single or multiple components of metabolic syndrome built using Ingenuity Pathway Analysis software. The presented relationships are based on Ingenuity Knowledge Base evidence from human, rat and mice studies; the use of capital letters in the gene name labels in the integrative scheme does not necessarily implicate the existence of human-based data. Entities interconnecting *Zbtb16* with all components of metabolic syndrome are shown in **red**: tumor necrosis factor alpha (*TNFA*), interleukin 6 (*IL6*) and prostaglandin-endoperoxide synthase 2 (*PTGS2*) and thioredoxin interacting protein (*TXNIP*); entities interconnecting *Zbtb16* with hypertension, insulin resistance and obesity are shown in **orange**: vitamin D receptor (*VDR*), angiotensinogen (*AGT*), androgen receptor (*AR*), estrogen receptor 1 (*ESR1*); entities interconnecting *Zbtb16* with hypertension, and obesity are shown in **turquoise**: C-X-C motif chemokine ligand 10 (*CXCL10*), poly(ADP-ribose) polymerase 1 (*PARP1*), nuclear receptor subfamily 3 group C member 1 (*NR3C1*), matrix metalloproteinase 9 (*MMP9*), C-X-C motif chemokine receptor 4 (*CXCR4*), miR-16-5p; entities interconnecting *Zbtb16* with insulin resistance and obesity are shown in **yellow**: phosphatase and tensin homolog (*PTEN*), C-C motif chemokine ligand 2 (*CCL2*), integrin subunit beta 3 (*ITGB3*); entities interconnecting *Zbtb16* with insulin resistance and hypertension are shown in **green**: bone gamma-carboxyglutamate protein (*BGLAP*), huntingtin (*HTT*), microRNA 221 (*mir-221*). The genes with evidence of connection to single metabolic syndrome component are: angiotensin II receptor type 2 (*AGTR2*), bone morphogenetic protein 7 (*BMP7*), cyclin A2 (*CCNA2*), CD14 molecule (*CD14*), CD34 molecule (*CD34*), cyclin dependent kinase 1 (*CDK1*), cyclin dependent kinase inhibitor 1A (*CDKN1A*), complement factor H (*CFH*), cell death-inducing DFFA-like effector a (*CIDEA*), epidermal growth factor receptor (*EGFR*), eukaryotic translation initiation factor 2 alpha kinase 2 (*EIF2AK2*), ERG, ETS transcription factor (*ERG*), follicle stimulating hormone receptor (*FSHR*), heparin binding EGF like growth factor (*HBEGF*), homeobox D10 (*HOXD10*), homeobox D9 (*HOXD9*), intercellular adhesion molecule 3 (*ICAM3*), interleukin 12B (*IL12B*), interleukin 4 (*IL4*), KIT proto-oncogene receptor tyrosine kinase (*KIT*), BCL2 family apoptosis regulator (*MCL1*), v-myc avian myelocytomatosis viral oncogene homolog (*MYC*), phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*), proline rich nuclear receptor coactivator 2 (*PNRC2*), protein kinase C epsilon (*PRKCE*), RB transcriptional corepressor 1 (RB1), RUNX1 translocation partner 1 (*RUNX1T1*), secreted phosphoprotein 1 (*SPP1*), TIMP metalloproteinase inhibitor 1 (*TIMP1*), topoisomerase (DNA) II alpha (*TOP2A*).

## ZBTB16 and lipid metabolism

The SHR-*Plzf*<sup>+/-</sup> targeted model mentioned above displayed significantly reduced levels of triacylglycerols and cholesterol, both in plasma and in liver. Hepatic *Plzf* expression is induced in db/db and diet-induced obese mice, which exhibit severe hepatic steatosis (Chen *et al.* 2014). Conversely, SHR-*Lx* congenic strain carrying the 3kb-deletion in an intron of *Zbtb16* exhibits more pronounced dyslipidemia than the SHR – higher serum LDL cholesterol after challenge by high sucrose diet and higher triacylglycerols concentration after dexamethasone administration (Seda *et al.* 2005b). In an experiment, during which mice were given a single oral dose of synthetic triacylglycerols composed of one single fatty acid, *Zbtb16* gene was among the top genes upregulated in the heart by all of the five different treatments used in the study (Georgiadi *et al.* 2012). Moreover, while the majority of genes responding to fatty acid treatment were regulated in a PPAR-alpha-dependent manner, induction of *Zbtb16* was completely independent of PPAR alpha (Georgiadi *et al.* 2012). As evident from Figure 2, dyslipidemia was connected to *Zbtb16* via four genes (and a drug telmisartan) forming the “core nodes”, i.e. interconnecting *Zbtb16* to all metabolic syndrome components: tumor necrosis factor alpha (*TNFα*), interleukin 6 (*IL6*) and prostaglandin-endoperoxide synthase 2 (*PTGS2*) and thioredoxin interacting protein (*TXNIP*).

## ZBTB16 and carbohydrate metabolism/insulin sensitivity

PLZF is a downstream effector for PGC-1-controlled gluconeogenesis and at the same time PLZF negatively regulates the insulin signaling pathway by decreasing the phosphorylation of IRS1, Akt, and FoxO1 in normal mice (Chen *et al.* 2014). Liver-specific knockdown of PLZF relieved hyperglycemia in db/db mice and led to decreased insulin levels, improved glucose and pyruvate tolerance and insulin sensitivity (Chen *et al.* 2014). We showed earlier that SHR-*Lx* congenic strain carrying the 3kb-deletion in an intron of *Zbtb16* displays higher sensitivity to dexamethasone-induced insulin resistance of the skeletal muscle when compared to SHR controls (Seda *et al.* 2005b). Furthermore, there is a significant deterioration of glucose tolerance and increase of triacylglycerols

concentration after administration of all-trans retinoic acid in SHR-*Lx*, but not in SHR (Krupkova *et al.* 2009, Krupkova *et al.* 2014). The SHR-*Plzf*<sup>+/-</sup> targeted model exhibited lower levels of serum insulin and significantly increased sensitivity of adipose and muscle tissue to insulin action when compared with wild-type controls and were more tolerant to glucose during oral glucose tolerance test (Liska *et al.* 2017).

## ZBTB16 and GWAS

Despite the evidence gathered in the above-mentioned studies, ZBTB16 has not been so far associated with any metabolic syndrome-related traits in human genome-wide association studies (GWAS). However, polymorphisms within and near ZBTB16 showed significant associations to other complex traits, including diisocyanate-induced occupational asthma (Yucesoy *et al.* 2015), susceptibility to non-glioblastoma glioma (Kinnersley *et al.* 2015), gestational age at birth in premature rupture of membrane-initiated deliveries (Bacelis *et al.* 2016) and behavioral traits (Sonuga-Barke *et al.* 2008), documenting the wide-range of action of the gene over several major biological systems. There are several possible reasons for the current lack of GWAS-based evidence for the role of ZBTB16 in metabolic syndrome. The effects of ZBTB16 polymorphisms might be too subtle to be detected using the statistical models with strict multiple comparison correction; even more likely is the possibility that the effect is contextual in nature as documented previously for distinct genomic backgrounds or environmental (diet, medication) conditions in the experimental models (Seda *et al.* 2002, Seda *et al.* 2008).

## ZBTB16 and metabolic syndrome – a network perspective

The data summarized in this review provide ample evidence of involvement of ZBTB16 in processes underlying pathogenesis of practically all major constituents of metabolic syndrome. While the information from experimental models with altered *Zbtb16* expression clearly shows its effect on adipogenesis, cardiac hypertrophy and fibrosis, lipid levels and insulin sensitivity, the underlying mechanisms remain mostly elusive. Among the identified nodes interconnecting ZBTB16 with all or most metabolic syndrome components there are many genes linked to

immune function, inflammation or oxidative stress, i.e. processes frequently associated with the onset and pathogenesis of the metabolic syndrome itself (Rani *et al.* 2016). Other putative nodes include e.g. osteocalcin (bone gamma-carboxyglutamate protein, BGLAP), implicated in both cardiovascular risk and type 2 diabetes (Magni *et al.* 2016), androgen and estrogen receptors, but also huntingtin (Hult *et al.* 2011) and microRNAs mir-16 and mir-222. The presented network view of ZBTB16 interactions within the frame of metabolic syndrome thus provides a compendium of testable hypotheses for future

functional studies.

### Conflict of Interest

There is no conflict of interest.

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