

REVIEW

Recent progress in the use of genetics to understand links between type 2 diabetes and related metabolic traits

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Abstract

Genome-wide association studies have identified genetic variants associated with increased risk of type 2 diabetes. The aim of this review is to highlight some of the insights into the mechanism underlying type 2 diabetes provided by genetic association studies.

Introduction

Type 2 diabetes is caused by defective insulin secretion in the presence of insulin resistance. It usually occurs in late adulthood and is associated with high body mass index (BMI). Genome-wide association studies (GWASs) have identified more than 200 genetic variants associated with metabolic traits, including 65 loci associated with type 2 diabetes (Figure 1) [1-17]. This number is increasing as larger meta-analyses of GWASs are performed. For most of the variants the precise gene involved and its biological role in type 2 diabetes is unknown. Nevertheless, some genetic variants have provided interesting insights into the links between metabolic traits and disease. We discuss several examples in this review (Table 1).

Genetic studies highlight the differences between glucose homeostasis in the general population and risk of type 2 diabetes

GWASs have identified 36 variants associated with normal variation in fasting glucose levels [14,18,19]. We might have expected these variants to be associated with type 2 diabetes with effect sizes proportional to their effects on fasting glucose in the normal range, but this relationship is not clear. Several genetic variants have proportionally larger effects on fasting or stimulated

glucose in the normal range compared with their effects on type 2 diabetes risk, and vice versa [14,17]. Three variants stand out: those in *GCK*, *MTN1RB* and *G6PC2*, which have the strongest effect on fasting glucose but no effect (*G6PC2*) or small effects (*GCK* and *MTN1RB*) on risk of type 2 diabetes (Figure 2). Arguably the most interesting is the variant at *G6PC2*. This gene encodes glucose-6-phosphatase that functions in glucose transport and sensing. Variants lying in the intronic region of this gene, but of no obvious function, are associated with fasting glucose and insulin secretion but not type 2 diabetes. The allele associated with increased fasting glucose is also, paradoxically, associated with improved response to an oral glucose challenge [20]. In contrast, *TCF7L2* is most strongly associated with type 2 diabetes, but has a relatively limited effect on fasting glucose in the normal range. These findings suggest that there are differences in the genes and mechanisms that influence normal physiological glucose levels compared with the beta cell dysfunction and pathophysiological glucose levels seen in type 2 diabetes.

Insights into the relationship between circadian rhythm and type 2 diabetes

Genetic studies have revealed that polymorphisms in the *MTN1RB* gene influence the risk of type 2 diabetes and glucose control in the non-diabetic population. *MTN1RB* encodes one of two distinct receptors through which melatonin exerts its effect [21]. Melatonin is a circulating hormone that regulates circadian rhythm. The *MTN1RB* receptor is expressed in human islets [22,23]. Increased nocturnal levels of melatonin coincide with decreased insulin levels. There is evidence from animal studies that if the central and peripheral circadian rhythms, including the melatonin pathway, are disrupted, the risk of metabolic disorders and type 2 diabetes is increased [24,25]. The association between *MTN1RB* genetic variation and glucose control appears to be driven by a primary effect on insulin secretion [23]. The variants in *MTN1RB* are also associated with alterations to *MTN1RB* gene expression in human islet samples - the type 2 diabetes risk and

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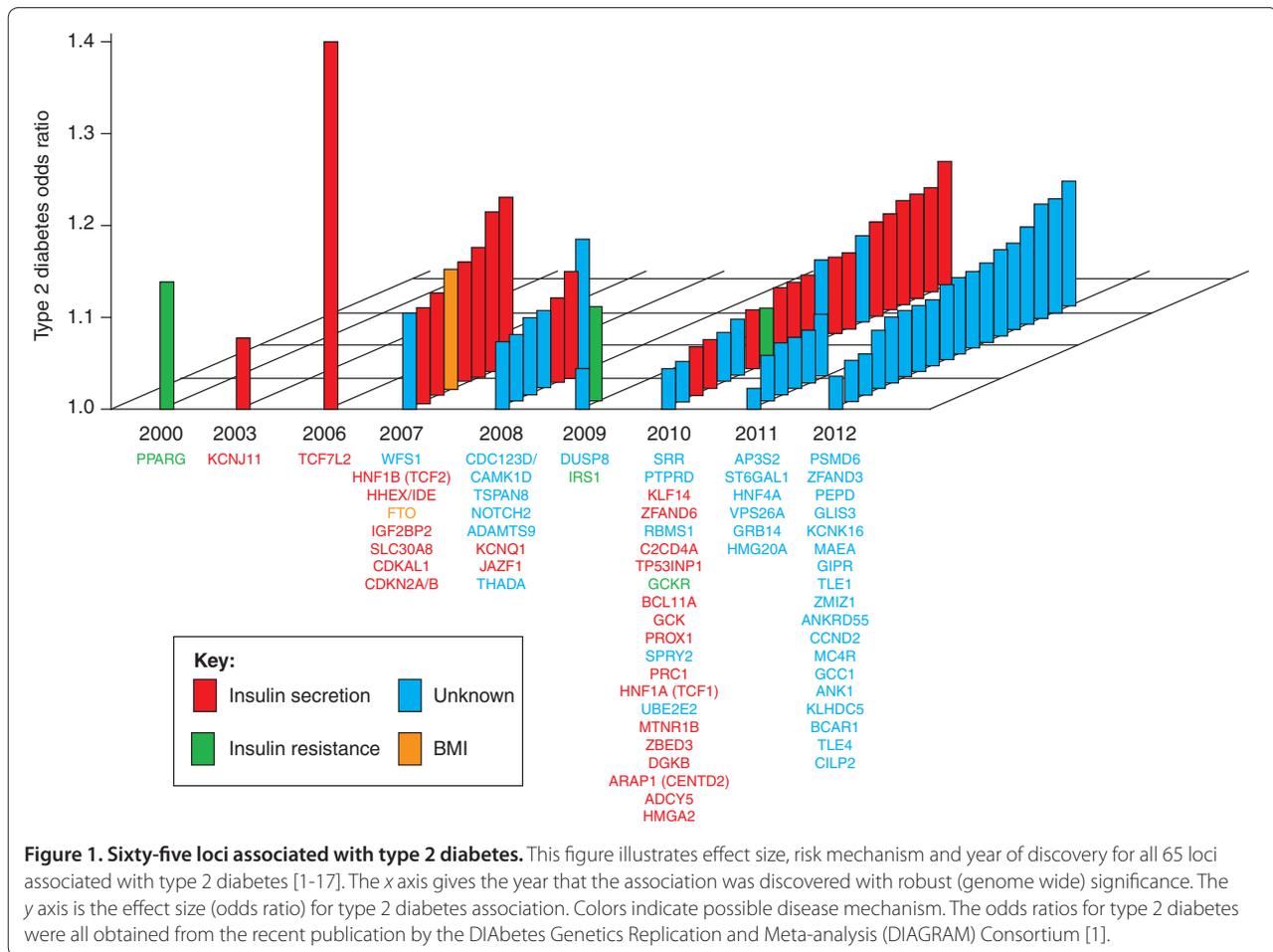


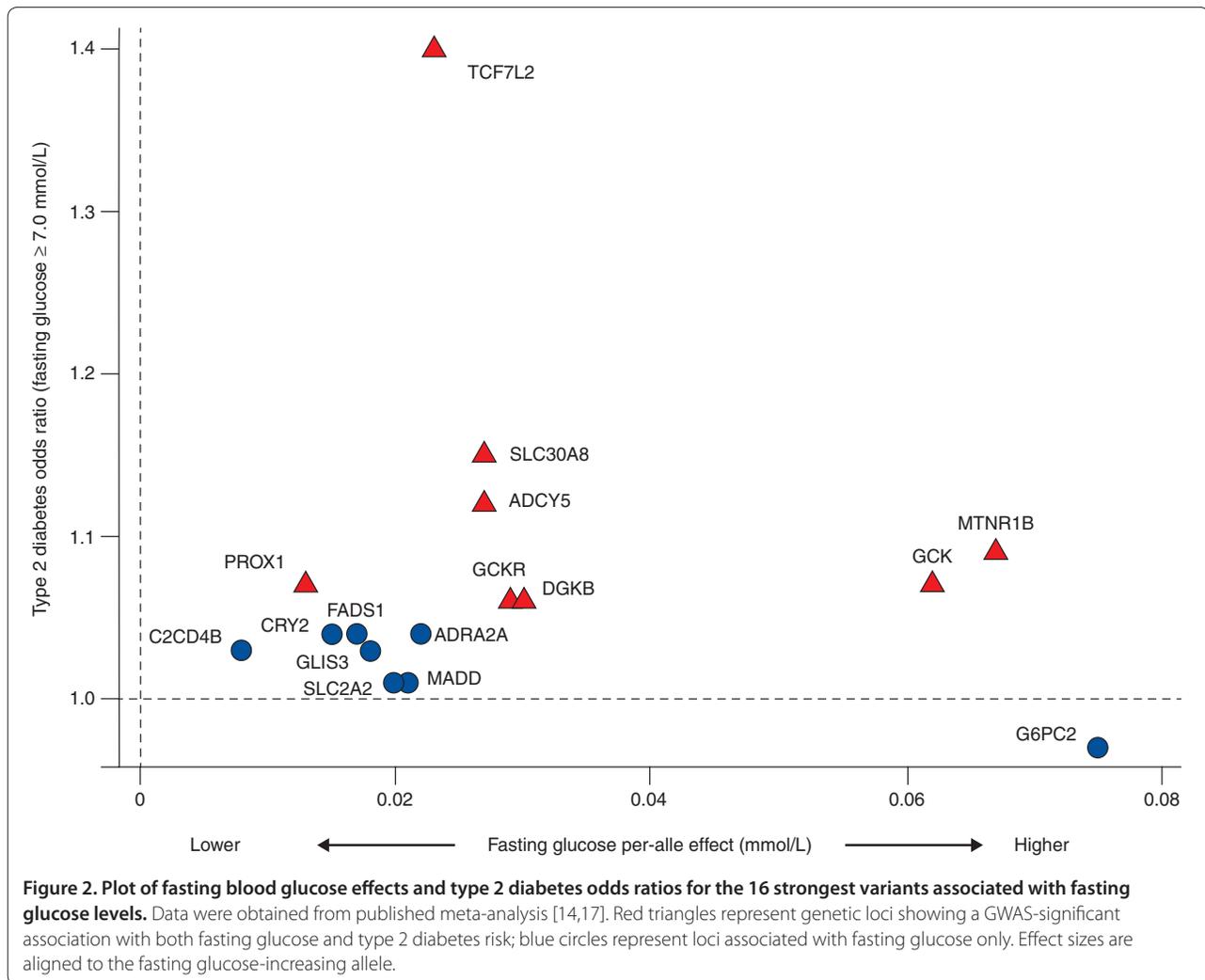
Table 1. Evidence for links between diabetes and related metabolic traits from genetic studies

Primary trait	Secondary trait	Loci	Result	Reference(s)
Fasting glucose in the normal range	Type 2 diabetes	<i>GCK</i> and <i>MTNR1B</i>	Variants at these loci have the strongest effects on fasting glucose but relatively small effects on risk of type 2 diabetes	[14,18,20]
		<i>G6PC2</i>	Fasting glucose increasing allele is paradoxically associated with improved response to an oral glucose challenge	
Circadian rhythm	Insulin secretion	<i>MTNR1B</i>	Variants in the melatonin receptor <i>MTNR1B</i> are associated with increased fasting glucose, impairment of insulin secretion from the pancreatic beta cell, and increased risk of type 2 diabetes	[2,23,26]
Inflammatory marker CRP	Obesity and metabolic syndrome phenotypes	<i>CRP</i>	<i>CRP</i> has no causal effect on obesity and development of insulin resistance and type 2 diabetes, suggesting inflammation is not causally linked to obesity	[28,44]
BMI	Circulating CRP	<i>FTO</i>	Obesity causally affects the circulating levels of CRP	[28]
SHBG levels	Type 2 diabetes	<i>SHBG</i>	Raised circulating SHBG levels reduce the risk of type 2 diabetes	[35,36]
Birth weight	Type 2 diabetes	<i>CDKAL1</i> , <i>HHEX/IDE</i> and <i>ADCY5</i>	Genetic variants that influence birth weight also influence type 2 diabetes risk	[40-42]

BMI, body mass index; CRP, C-reactive protein; SHBG, sex hormone binding globulin.

glucose raising allele is associated with increased *MTNR1B* expression [23]. A large-scale exon sequencing study of the *MTNR1B* locus in more than 7,000 Europeans revealed 36 very rare variants (minor allele frequency <0.1%) associated with type 2 diabetes risk [26].

Four of these rare variants caused complete loss of melatonin binding and signaling capabilities [26]. It is not clear why rare reduced function mutations are associated with increased type 2 diabetes risk and a common allele that increases *MTNR1B* gene expression is also



associated with increased risk. One suggestion is that the increased expression could be the result of the absence of negative feedback regulatory events under conditions of impaired melatonin receptor signaling [26].

Insights into the relationship between obesity, inflammation and diabetes

Genetic studies have provided important insights into the relationships between obesity, inflammation and diabetes. Obesity is associated with a multitude of adverse metabolic traits, including insulin resistance, non-alcoholic fatty liver disease, hyperglycemia, hypertension and dyslipidemia. One intriguing association is that between inflammation and obesity, but the causal direction is unknown. GWASs have identified genetic variants associated with obesity, and variants associated with inflammation. Variants in the *FTO* gene are associated with obesity and variants in the *C-reactive protein (CRP)* gene are associated with *C-reactive protein (CRP)* levels - an inflammatory marker synthesized by the liver. *FTO*

associates with multiple metabolic phenotypes to the extent expected based on its association with BMI and the correlations between BMI and secondary metabolic phenotypes [27]. These associations include *FTO* versus circulating CRP levels [28]. In contrast *CRP* genetic variants are not associated with obesity [28]. These findings suggest that inflammatory markers, particularly CRP, do not causally influence the risk of obesity. This finding provides evidence that the subclinical inflammatory profile associated with obesity is more likely to be secondary to adiposity rather than causal. The causal effect of obesity on inflammatory markers is likely to be driven by adipocytes that are a key expresser of inflammatory molecules [29-31].

Insights into the relationship between circulating sex hormone binding globulin levels and type 2 diabetes

Recent genetic studies have highlighted a possible causal role for lower sex hormone binding globulin (SHBG) levels

Table 2. Evidence of links between SHBG and sex hormones and insulin resistance/type 2 diabetes from non-genetic studies

Study	Primary perturbation	Effect on insulin secretion/resistance	Reference(s)
Evidence that SHBG is upstream of type 2 diabetes			
Prospective studies	Altered levels of sex hormones	Increased risk of type 2 diabetes	[34]
PCOS in women	Elevation in levels of androgens	Increased risk of non-insulin-dependent diabetes mellitus	[45]
Randomized controlled trial	Androgen supplementation in men with low testosterone levels	Increased insulin sensitivity	[46]
Animal model (male mouse)	Lack of androgen receptor	Insulin resistance	[47]
Animal model (female rat)	Treatment with testosterone after oophorectomy	Insulin resistance	[48]
Evidence that SHBG is downstream of type 2 diabetes			
<i>In vitro</i> study	Incubation of hepatoblastoma cell line with IGF-I	Decreased SHBG levels	[49]
Animal model (mouse) and <i>in vitro</i> study	Increased fasting glucose	Downregulation of <i>SHBG</i> expression	[50]
Intervention study	Insulin lowering interventions in non-diabetic men and women (without PCOS)	Increased SHBG levels	[51,52]
Study of obese women with PCOS	Increase insulin levels	Reduced serum SHBG levels	[53]

IGF-1, insulin-like growth factor I; PCOS, polycystic ovarian syndrome; SHBG, sex hormone binding globulin.

and increased risk of type 2 diabetes. This evidence comes from studies of genetic variation in the *SHBG* gene.

SHBG, a plasma transport protein that is mainly produced by the liver, binds to sex hormones: estradiol, and with higher affinity to testosterone. It was assumed that SHBG plays one role only, which is regulation of free sex hormone bioavailability to target tissues. However, several physiologic roles have been suggested for SHBG through its multiple interactions with its receptor; these roles include modification of sex hormone uptake and cell proliferation [32-34]. The multiple interactions between SHBG and its receptors in various target tissues suggest that the role is more complex than the simple transport of sex hormones in serum.

A number of observational epidemiological studies have demonstrated associations between type 2 diabetes and androgens (primarily testosterone), estrogens (estradiol) and SHBG [34] that cannot be explained by adiposity. It is controversial whether SHBG is a cause or consequence of these conditions. The non-genetic evidence that suggests reduced SHBG levels increase the risk of type 2 diabetes, and the evidence that points to reverse causation, are summarized in Table 2.

Two Mendelian randomization analyses, using genetic variants at the *SHBG* locus, have provided evidence that raised circulating SHBG levels reduce the risk of type 2 diabetes [35,36]. In both studies, the effects of SHBG variants on risk of type 2 diabetes were consistent with those predicted by the effect of the SNPs on SHBG levels and the correlation between SHBG levels and type 2 diabetes.

Insights into the relationship between birth weight and type 2 diabetes

Numerous epidemiological studies have shown that reduced birth weight is associated with impaired glucose tolerance and type 2 diabetes. There are two hypotheses proposed to explain the association between birth weight and type 2 diabetes. (a) The fetal programming hypothesis proposes that poor intra-uterine nutrition will not only cause small, thin babies, but also programs the development of risk factors of disease, such as type 2 diabetes in adults [37,38]. (b) The fetal insulin hypothesis suggests that fetal genetics influencing insulin secretion and action have a direct effect on small, thin babies and their increased risk of type 2 diabetes [39]. Maternal genes such as *GCK* and *TCF7L2* can indirectly, through their effect on intra-uterine glucose levels, influence fetal growth [40,41]. The hypothesis suggests that the glucose raising variants in mothers increase the birth weight of offspring because the fetal pancreas is exposed to more glucose and therefore secretes more insulin. In contrast, the genetic variants at *CDKAL1*, *HHEX/IDE* and *ADCY5* loci are associated with birth weight through fetal genotype independently of maternal genotype [40-43]. Variants at the *CDKAL1*, *HHEX/IDE* and *ADCY5* loci are all associated with insulin secretion and their association with birth weight suggests the mechanism starts in prenatal life. The association of three type 2 diabetes loci, *CDKAL1*, *HHEX/IDE* and *ADCY5*, with birth weight is consistent with the fetal insulin hypothesis. The assessment of the role of the remaining 62 type 2 diabetes loci with birth weight could elucidate whether type 2

diabetes loci in addition to *CDKAL1*, *HHEX/IDE* and *ADCY5* also influence prenatal growth.

Limitations of genetic association studies

The genetic links between type 2 diabetes and metabolic traits have highlighted possible new biological pathways. Nevertheless, genetic association studies have some limitations. One caveat is that the variant discovered by GWASs may not be the actual causal variant but just linked to it on a chromosome (linkage disequilibrium). Indeed, the causal variant could be in a nearby gene or non-genic region. The other limitation is that the variants discovered to be associated with complex traits explain a very small proportion of individual variation in disease risk or trait levels. These small effect sizes have compromised the disease predictive value of common genetic variants. One explanation is that common diseases such as type 2 diabetes are caused not only by many common variants with small effect but also by rare variants with larger effect that would not be detected in a GWAS. With the advent of high-throughput platforms and methods, full sequencing of samples could make it feasible to assess structural variants and rare variants and discover more of the heritable component to type 2 diabetes.

Summary

In summary, we have presented a number of examples of how genetics helps us understand the complex associations between type 2 diabetes and many other metabolic traits, including glucose homeostasis, circadian rhythm, SHBG, inflammation and birth weight.

GWASs, which do not rely on a prior understanding of disease biology, have resulted in remarkable progress in our understanding of the genetic underpinnings of type 2 diabetes in the last 5 years. We anticipate that advances in technology and resources, including very large sample sizes such as the 500,000 individuals available in the UK Biobank, will lead to even more progress in understanding the highly complex genetic and non-genetic risk factors for metabolic diseases.

Abbreviations

BMI, body mass index; CRP, C-reactive protein; GWAS, genome-wide association study; SHBG, sex hormone binding globulin; SNP, single nucleotide polymorphism.

Competing interests

The authors declare that they have no competing interests.

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References

1. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, Prokopenko I, Kang HM, Dina C, Esko T, Fraser RM, Kanoni S, Kumar A, Lagou V, Langenberg C, Luan J, Lindgren CM, Müller-Nurasyid M, Pechlivanis S, Rayner NW, Scott LJ, Wiltshire S, Yengo L, Kinnunen L, Rossin EJ, Raychaudhuri S, Johnson AD, Dimas AS, *et al.*: Large-scale association analysis provides insights into the genetic

architecture and pathophysiology of type 2 diabetes. *Nat Genet* 2012, **44**:981-990.

2. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJ, Manning AK, Jackson AU, Aulchenko Y, Potter SC, Erdos MR, Sanna S, Hottenga JJ, Wheeler E, Kaakinen M, Lyssenko V, Chen WM, Ahmadi K, Beckmann JS, Bergman RN, Bochud M, Bonnycastle LL, Buchanan TA, Cao A, Cervino A, Coin L, Collins FS, Crisponi L, de Geus EJ, *et al.*: Variants in *MTNR1B* influence fasting glucose levels. *Nat Genet* 2009, **41**:77-81.
3. Zeggini E, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney AS, Wellcome Trust Case Control Consortium (WTCCC), McCarthy MI, Hattersley AT, *et al.*: Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 2007, **316**:1336-1341.
4. Altschuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES: The common *PPARG* γ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 2000, **26**:76-80.
5. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Hattagadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K: Variant of transcription factor 7-like 2 (*TCF7L2*) gene confers risk of type 2 diabetes. *Nat Genet* 2006, **38**:320-323.
6. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P: A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 2007, **445**:881-885.
7. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, *et al.*: A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* 2007, **316**:1341-1345.
8. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altschuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskiran MR, Tuomi T, *et al.*: Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 2007, **316**:1331-1336.
9. Sandhu MS, Weedon MN, Fawcett KA, Wasson J, Debenham SL, Daly A, Lango H, Frayling TM, Neumann RJ, Sherva R, Blech I, Pharoah PD, Palmer CN, Kimber C, Tavendale R, Morris AD, McCarthy MI, Walker M, Hitman G, Glaser B, Permutt MA, Hattersley AT, Wareham NJ, Barroso I: Common variants in *WFS1* confer risk of type 2 diabetes. *Nat Genet* 2007, **39**:951-953.
10. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsson KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, *et al.*: Two variants on chromosome 17 confer prostate cancer risk, and the one in *TCF2* protects against type 2 diabetes. *Nat Genet* 2007, **39**:977-983.
11. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, *et al.*: Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet* 2008, **40**:638-645.
12. Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proença C, Bacot F, Balkau B, Belisle A, Borch-Johnsen K, Charpentier G, Dina C, Durand E, Elliott P, Hadjadj S, Järvelin MR, Laitinen J, Lauritzen T, Marre M, Mazur A, Meyre D, Montpetit A, Pisinger C, Posner B, Poulsen P, Pouta A, Prentki M,

- Ribel-Madsen R, Ruokonen A, Sandbaek A, *et al.*: **Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia.** *Nat Genet* 2009, **41**:1110-1115.
13. Kong A, Steinthorsdottir V, Masson G, Thorleifsson G, Sulem P, Besenbacher S, Jonasdottir A, Sigurdsson A, Kristinsson KT, Jonasdottir A, Frigge ML, Gylfason A, Olason PI, Gudjonsson SA, Sverrisson S, Stacey SN, Sigurgeirsson B, Benediktsson KR, Sigurdsson H, Jonsson T, Benediktsson R, Olafsson JH, Johannsson OT, Hreidarsson AB, Sigurdsson G; DIAGRAM Consortium, Ferguson-Smith AC, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K, *et al.*: **Parental origin of sequence variants associated with complex diseases.** *Nature* 2009, **462**:868-874.
14. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Mägi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, *et al.*: **New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk.** *Nat Genet* 2010, **42**:105-116.
15. Kooner JS, Saleheen D, Sim X, Sehmi J, Zhang W, Frossard P, Been LF, Chia KS, Dimas AS, Hassanali N, Jafar T, Jowett JB, Li X, Radha V, Rees SD, Takeuchi F, Young R, Aung T, Basit A, Chidambaram M, Das D, Grundberg E, Hedman AK, Hydrie ZI, Islam M, Khor CC, Kowlessur S, Kristensen MM, Liju S, Lim WY, *et al.*: **Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci.** *Nat Genet* 2011, **43**:984-989.
16. Yamauchi T, Hara K, Maeda S, Yasuda K, Takahashi A, Horikoshi M, Nakamura M, Fujita H, Grarup N, Cauchi S, Ng DP, Ma RC, Tsunoda T, Kubo M, Watada H, Maegawa H, Okada-Iwabu M, Iwabu M, Shojima N, Shin HD, Andersen G, Witte DR, Jørgensen T, Lauritzen T, Sandbaek A, Hansen T, Ohshige T, Omori S, Saito I, Kaku K, *et al.*: **A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at UBE2E2 and C2CD4A-C2CD4B.** *Nat Genet* 2010, **42**:864-868.
17. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu G, Willer CJ, Raychaudhuri S, McCarroll SA, Langenberg C, Hofmann OM, Dupuis J, Qi L, Segrè AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, *et al.*: **Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis.** *Nat Genet* 2010, **42**:579-589.
18. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan J, Mägi R, Strawbridge RJ, Rehnberg E, Gustafsson S, Kanoni S, Rasmussen-Torvik LJ, Yengo L, Lecoeur C, Shungin D, Sanna S, Sidore C, Johnson PC, Jukema JW, Johnson T, Mahajan A, Verweij N, Thorleifsson G, Hottenga JJ, Shah S, Smith AV, Sennblad B, Gieger C, Salo P, Perola M, *et al.*: **Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways.** *Nat Genet* 2012, **44**:991-1005.
19. Saxena R, Hivert MF, Langenberg C, Tanaka T, Pankow JS, Vollenweider P, Lyssenko V, Bouatia-Naji N, Dupuis J, Jackson AU, Kao WH, Li M, Glazer NL, Manning AK, Luan J, Stringham HM, Prokopenko I, Johnson T, Grarup N, Boesgaard TW, Lecoeur C, Shrader P, O'Connell J, Ingelsson E, Couper DJ, Rice K, Song K, Andreasen CH, Dina C, Köttgen A, *et al.*: **Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge.** *Nat Genet* 2010, **42**:142-148.
20. Ingelsson E, Langenberg C, Hivert MF, Prokopenko I, Lyssenko V, Dupuis J, Mägi R, Sharp S, Jackson AU, Assimes TL, Shrader P, Knowles JW, Zethelius B, Abbasi FA, Bergman RN, Bergmann A, Berne C, Boehnke M, Bonnycastle LL, Bornstein SR, Buchanan TA, Bumpstead SJ, Böttcher Y, Chines P, Collins FS, Cooper CC, Dennison EM, Erdos MR, Ferrannini E, Fox CS, *et al.*: **Detailed physiologic characterization reveals diverse mechanisms for novel genetic Loci regulating glucose and insulin metabolism in humans.** *Diabetes* 2010, **59**:1266-1275.
21. Pandi-Perumal SR, Trakht I, Srinivasan V, Spence DW, Maestroni GJ, Zisapel N, Cardinali DP: **Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways.** *Prog Neurobiol* 2008, **85**:335-353.
22. Muhlbauer E, Peschke E: **Evidence for the expression of both the MT1- and in addition, the MT2-melatonin receptor, in the rat pancreas, islet and beta-cell.** *J Pineal Res* 2007, **42**:105-106.
23. Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spégel P, Bugliani M, Saxena R, Fex M, Pulizzi N, Isomaa B, Tuomi T, Nilsson P, Kuusisto J, Tuomilehto J, Boehnke M, Althuler D, Sundler F, Eriksson JG, Jackson AU, Laakso M, Marchetti P, Watanabe RM, Mulder H, Groop L: **Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion.** *Nat Genet* 2009, **41**:82-88.
24. Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J: **Obesity and metabolic syndrome in circadian Clock mutant mice.** *Science* 2005, **308**:1043-1045.
25. Bach AG, Muhlbauer E, Peschke E: **Adrenoceptor expression and diurnal rhythms of melatonin and its precursors in the pineal gland of type 2 diabetic goto-kakizaki rats.** *Endocrinology* 2010, **151**:2483-2493.
26. Bonnefond A, Clément N, Fawcett K, Yengo L, Vaillant E, Guillaume JL, Dechaume A, Payne F, Roussel R, Czernichow S, Hercberg S, Hadjadj S, Balkau B, Marre M, Lantier O, Langenberg C, Bouatia-Naji N; Meta-Analysis of Glucose and Insulin-Related Traits Consortium (MAGIC), Charpentier G, Vaxillaire M, Rocheleau G, Wareham NJ, Sladek R, McCarthy MI, Dina C, Barroso I, Jockers R, Froguel P: **Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes.** *Nat Genet* 2012, **44**:297-301.
27. Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, Ebrahim S, Shields B, Zeggini E, Weedon MN, Lindgren CM, Lango H, Melzer D, Ferrucci L, Paolisso G, Neville MJ, Karpe F, Palmer CN, Morris AD, Elliott P, Jarvelin MR, Smith GD, McCarthy MI, Hattersley AT, Frayling TM: **Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI.** *Diabetes* 2008, **57**:1419-1426.
28. Timpson NJ, Nordestgaard BG, Harbord RM, Zacho J, Frayling TM, Tybjaerg-Hansen A, Smith GD: **C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization.** *Int J Obes (Lond)* 2010, **35**:300-308.
29. Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW: **C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue?** *Arterioscler Thromb Vasc Biol* 1999, **19**:972-978.
30. Calabro P, Chang DW, Willerson JT, Yeh ETH: **Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation.** *J Am Coll Cardiol* 2005, **46**:1112.
31. Aronson D, Bartha P, Zinder O, Kerner A, Markiewicz W, Avizohar O, Brook GJ, Levy Y: **Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome.** *Int J Obes Relat Metab Disord* 2004, **28**:674-679.
32. Rosner W, Hryb DJ, Khan MS, Nakhla AM, Romas NA: **Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane.** *J Steroid Biochem Mol Biol* 1999, **69**:481-485.
33. Porto CS, Lazari MF, Abreu LC, Bardin CW, Gonsalves GL: **Receptors for androgen-binding proteins: internalization and intracellular signalling.** *J Steroid Biochem Mol Biol* 1995, **53**:561-565.
34. Ding EL, Song Y, Malik VS, Liu S: **Sex differences of endogenous sex hormones and risk of type 2 diabetes.** *JAMA* 2006, **295**:1288.
35. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM, Liu S: **Sex hormone-binding globulin and risk of type 2 diabetes in women and men.** *N Engl J Med* 2009, **361**:1152-1163.
36. Perry JR, Weedon MN, Langenberg C, Jackson AU, Lyssenko V, Sparsø T, Thorleifsson G, Grallert H, Ferrucci L, Maggio M, Paolisso G, Walker M, Palmer CN, Payne F, Young E, Herder C, Narisu N, Morken MA, Bonnycastle LL, Owen KR, Shields B, Knight B, Bennett A, Groves CJ, Ruokonen A, Jarvelin MR, Pearson E, Pascoe L, Ferrannini E, Bornstein SR, *et al.*: **Genetic evidence that raised sex hormone binding globulin (SHBG) levels reduce the risk of type 2 diabetes.** *Hum Mol Genet* 2010, **19**:535-544.
37. Barker DJ: **Intrauterine programming of adult disease.** *Mol Med Today* 1995, **1**:418-423.
38. Hales CN: **The pathogenesis of NIDDM.** *Diabetologia* 1994, **37**(Suppl 2):S162-168.
39. Hattersley AT, Tooke JE: **The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease.** *Lancet* 1999, **353**:1789-1792.
40. Horikoshi M, Yaghootkar H, Mook-Kanamori DO, Sovio U, Taal HR, Hennig BJ, Bradfield JP, St Pourcain B, Evans DM, Charoen P, Kaakinen M, Cousminer DL, Lehtimäki T, Kreiner-Møller E, Warrington NM, Bustamante M, Feenstra B, Berry DJ, Thiering E, Pfab T, Barton SJ, Shields BM, Kerkhof M, van Leeuwen EM, Fulford AJ, Kutalik Z, Zhao JH, den Hoed M, Mahajan A, Lindi V, *et al.*: **New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism.** *Nat Genet* 2012,

- 45:76-82.
41. Freathy RM, Mook-Kanamori DO, Sovio U, Prokopenko I, Timpson NJ, Berry DJ, Warrington NM, Widen E, Hottenga JJ, Kaakinen M, Lange LA, Bradfield JP, Kerkhof M, Marsh JA, Mägi R, Chen CM, Lyon HN, Kirin M, Adair LS, Aulchenko YS, Bennett AJ, Borja JB, Bouatia-Naji N, Charoen P, Coin LJ, Cousminer DL, de Geus EJ, Deloukas P, Elliott P, Evans DM, *et al.*: **Variants in ADCY5 and near CCNL1 are associated with fetal growth and birth weight.** *Nat Genet* 2010, **42**:430-435.
 42. Andersson EA, Pilgaard K, Pisinger C, Harder MN, Grarup N, Faerch K, Poulsen P, Witte DR, Jørgensen T, Vaag A, Hansen T, Pedersen O: **Type 2 diabetes risk alleles near ADCY5, CDKAL1 and HHEX-IDE are associated with reduced birthweight.** *Diabetologia* 2010, **53**:1908-1916.
 43. Freathy RM, Bennett AJ, Ring SM, Shields B, Groves CJ, Timpson NJ, Weedon MN, Zeggini E, Lindgren CM, Lango H, Perry JR, Pouta A, Ruokonen A, Hyppönen E, Power C, Elliott P, Strachan DP, Jarvelin MR, Smith GD, McCarthy MI, Frayling TM, Hattersley AT: **Type 2 diabetes risk alleles are associated with reduced size at birth.** *Diabetes* 2009, **58**:1428.
 44. Timpson NJ, Lawlor DA, Harbord RM, Gaunt TR, Day IN, Palmer LJ, Hattersley AT, Ebrahim S, Lowe GD, Rumley A, Davey Smith G: **C-reactive protein and its role in metabolic syndrome: mendelian randomisation study.** *Lancet* 2005, **366**:1954-1959.
 45. Dunaif A: **Hyperandrogenic anovulation (PCOS): a unique disorder of insulin action associated with an increased risk of non-insulin-dependent diabetes mellitus.** *Am J Med* 1995, **98**:S33-S39.
 46. Simon D, Charles MA, Lahlou N, Nahoul K, Oppert JM, Gouault-Heilmann M, Lemort N, Thibault N, Joubert E, Balkau B, Eschwege E: **Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone.** *Diabetes Care* 2001, **24**:2149.
 47. Lin HY, Xu Q, Yeh S, Wang RS, Sparks JD, Chang C: **Insulin and leptin resistance with hyperleptinemia in mice lacking androgen receptor.** *Diabetes* 2005, **54**:1717.
 48. Rincon J, Holmäng A, Wahlström EO, Lönnroth P, Björntorp P, Zierath JR, Wallberg-Henriksson H: **Mechanisms behind insulin resistance in rat skeletal muscle after oophorectomy and additional testosterone treatment.** *Diabetes* 1996, **45**:615-621.
 49. Plymate SR, Matej LA, Jones RE, Friedl KE: **Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin.** *J Clin Endocrinol Metab* 1988, **67**:460-464.
 50. Selva DM, Hogeveen KN, Innis SM, Hammond GL: **Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone-binding globulin gene.** *J Clin Invest* 2007, **117**:3979-3987.
 51. Pasquali R, Casimirri F, De lasio R, Mesini P, Boschi S, Chierici R, Flaminia R, Biscotti M, Vicennati V: **Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men.** *J Clin Endocrinol Metab* 1995, **80**:654-658.
 52. Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, Fiorini S, Cognigni GE, Filicori M, Morselli-Labate AM: **Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome.** *J Clin Endocrinol Metab* 2000, **85**:2767.
 53. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, Clore JN, Blackard WG: **A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome.** *J Clin Endocrinol Metab* 1991, **72**:83-89.

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