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Review Article

Common Genetic Variants in the HNF1B Gene Contribute to Diabetes and Multiple Cancers

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Abstract

Diabetes and cancers are major public health problems in the United States and in the world. Epidemiological studies have clearly demonstrated the associations and co morbidity between Type 2 Diabetes (T2D) and multiple cancers such as endometrial and prostate cancers. However, the mechanism of such associations has not been elucidated. Genetic variation is proposed to contribute to these diseases, and common genetic variants may explain part of the associations among these diseases. Single Nucleotide Polymorphisms (SNPs) rs4430796 and rs7501939 within the *HNF1B/TCF2* gene (Gene ID: 6928) have been observed to be associated with T2D and endometrial and prostate cancers in several studies (pleiotropic effects). Future work is needed to assess additional genetic loci sharing among these diseases. To better understand the genetic etiology of disease comorbidity it will be useful to combine the results of Genome-Wide Association Studies (GWAS), gene-gene and gene-environment interactions, with the recent rapid advances in Next Generation Sequencing (NGS) technologies.

Keywords: Diabetes; Endometrial cancer; Prostate cancer; Genome-wide association study; *HNF1B/TCF2*; Single nucleotide polymorphism; Pleiotropy

Abbreviations

BMI: Body Mass Index; GWAS: Genome-wide Association Studies; *HNF1B*: Hepatocyte Nuclear Factor-1-Beta; NGS: Next Generation Sequencing; OR: Odds Ratio; *PKHD1*: Polycystic Kidney and Hepatic Disease-1; SNP: Single Nucleotide Polymorphism; *SOCS3*: Suppressor of Cytokine Signaling 3; *SULF2*: Sulfatase 2; *TCF2*: Transcription Factor-2; T2D: Type 2 Diabetes

Introduction

Diabetes and cancers are common chronic diseases and major public health problems in the United States (US) and in the world. It's estimated that about 29.1 million people or 9.3% of the population have diabetes in the US (National Diabetes Statistics Report, 2014, http://www.cdc.gov/diabetes/pubs/statsreport14.htm). Besides, about 1.7 million of new cancer cases and 0.6 million of cancer deaths are projected to occur in the US in 2014 [1]. Epidemiological studies have shown associations between Type 2 Diabetes (T2D) and multiple cancers [2-5]. For example, several studies suggest an inverse correlation between T2D and prostate cancer [6-10], although some studies show inconsistent results [11]. Furthermore, several studies suggest possible positive correlations between T2D and certain cancers (such as colon, endometrial, stomach, liver, and pancreatic cancers) [3-5,9,12]. However, the mechanism of such associations is not clear. On the one hand, these correlations may represent casual relationships; and on the other hand, they may reflect some shared genetic background [13-15]. Recently, several Genome-Wide Association Studies (GWAS) observed some variants in the Hepatocyte nuclear factor-1-beta (*HNF1B*) gene (Gene ID: 6928) associated with endometrial and prostate cancers [9, 16-18] and T2D [16] with the effects being in the opposite direction for T2D and cancers.

HNF1B, also known as Transcription Factor-2 (*TCF2*), is located at 17q12 [16,19,20] and a member of the homeodomain-containing super family of transcription factors [20]. Kolatsi-Joannou et al [21] detected *HNF1B/TCF2* mRNA in liver, pancreas, stomach, and lung and suggested that the *HNF1B/TCF2* gene may play a role in epithelial differentiation. *HNF1B* is a transcription factor that plays a role in kidney and pancreas development [22,23]. Edghill et al [22] found early expression of *HNF1B/TCF2* in the kidney, liver, bile ducts, thymus, genital tract, pancreas, lung, and gut and suggested that the *HNF1B/TCF2* could act either as a homodimer or as a heterodimer with *HNF1A*. Ma et al [24] concluded that *HNF1B* regulates renal tubulogenesis by controlling expression of suppressor of cytokine signaling 3 (*SOCS3*) (Gene ID: 9021) as an *HNF1B* target gene in mouse kidney. Based on a mouse model, Verdeguer et al [25] hypothesized that *HNF1B* may have function as both a classic transcriptional activator and as a bookmarking factor that marks target genes for rapid transcriptional reactivation after mitosis. Mutations of *HNF1B* have been described in renal cell carcinoma [26], and epigenetic silencing of the gene has been reported in ovarian cancer, as well as gastric, pancreatic, and colorectal cell lines [27]. Furthermore, *HNF1B* over-expression has been reported to be a biomarker of clear cell carcinoma of the pancreas [28], and of clear cell carcinoma of the ovary and its probable precursor ovarian endometriosis [29-32]. Moreover, *HNF1B* encodes a home box transcription factor that controls cell proliferation and differentiation in the kidney, pancreas, liver, and genital tract tissues [33]. In addition, emerging evidence also suggests that *HNF1B* isform usage may be altered in prostate cancer tissue, with up regulated *HNF1B* isform B expression in prostate cancer tissue compared to benign tissue [34].

Susceptibility to diabetes and related diseases

Previous study has shown that mutation in HNF1B is associated

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with maturity-onset diabetes of the young [35]. Later, several studies identified some mutants in the *HNF1B/TCF2* gene in patients with renal cysts and diabetes syndrome [35-40]. Bonny castle et al [2] suggested that common variants in *HNF1B* might play a modest role in T2D susceptibility; while Winkler et al [41] identified a common Single Nucleotide Polymorphism (SNP) rs757210 in the *HNF1B* gene that was associated with T2D ($p=5\times10^{-6}$). Recently, studies showed that two SNPs (rs7501939 and rs4430796) of *HNF1B*, which were previously associated with T2D in Chinese as well as in Caucasians using GWAS reported in 2007 [16], showed the association with T2D in the Japanese population [42]. More recently, several studies in China suggested that the same *HNF1B* variants (rs7501939 and rs4430796) as the study reported in 2007 [16] may be involved in T2D risk in Chinese populations [43-45]. Particularly, a GWAS conducted among Chinese Hans confirmed rs4430796 associated with T2D ($p=1.52x10^{-11}$) [46].

However, available evidence on diabetes and genetic variations is inconsistent. For example, polymorphisms in *HNF1B* did not significantly influence insulin or glucose values nor did they predict future T2D [47]. Furthermore, no statistical association was observed between rs4430796 and 2-h glucose or impaired glucose regulation risk, but gene x physical activity interacted to influence impaired glucose regulation and 2-h glucose concentrations [33]. In addition, rs757210 just had borderline association with higher levels of fasting insulin in the Indian population (p=0.05) [48].

Susceptibility to multiple cancers

Rebouissou et al [26] found that *HNF1B* regulated the expression of polycystic kidney and hepatic disease-1 (*PKHD1*) (Gene ID: 5314) and suggested that germ line mutations of the *HNF1B* may predispose to renal tumors, and proposed that *HNF1B* may function as a tumor suppressor gene in chromophobe renal cell carcinogenesis through control of *PKHD1* expression. By screening aberrantly mentholated genes, Terasawa et al [27] suggested that *HNF1B/TCF2* is involved in the development of ovarian cancers and may represent a useful target for their detection and treatment.

Gudmundsson et al [16] performed a GWAS of 1,501 Icelandic man with prostate cancer and 11,290 controls, followed by 3 case-control replication studies in individuals from the Netherlands, Spain, and Chicago. They found the associations between prostate cancer and the A allele of rs4430796 (OR=1.22, $p=1.4 \times 10^{-11}$ for the combined studies) and C allele of rs7501939 (OR=1.19, $p = 4.7 \times 10^{-9}$ for the combined studies). Using a large GWAS of prostate cancer, Thomas et al [18] confirmed the association found by Gudmundsson et al [16] with the same SNP rs4430796 ($p=9.58 \times 10^{-10}$). In a large 2-stage GWAS of prostate cancer, Eeles et al [49] found strong associations observed for rs4430796 (random effect model $p=10^{-13}$) and rs7501939 (random effect model $p=2 \times 10^{-11}$). Sun et al [17] carried out a fine mapping study of the *HNF1B* gene and identified a second locus (rs11649743) associated with prostate cancer risk. Levin et al [50] suggested that rs4430796 and rs7501939 may play a role in early onset prostate cancer (before age 50 years). Furthermore, Waters et al [51] confirmed the association of rs4430796 with prostate cancer in a multiethnic sample of 2,768 incident prostate cancer cases and 2,359 controls from the Multiethnic Cohort (African Americans, European Americans, Latinos, Japanese Americans, and Native Hawaiians). Moreover, Berndt et al [52] performed fine-mapping of *HNF1B* in 10,272 prostate cancer cases and 9,123 controls of European ancestry from 10 case-control studies and found several SNPs (rs4430796, rs7405696, rs11649743, and rs4794758) influence prostate cancer. This study demonstrates a complex relationship between variants in the *HNF1B* region and prostate cancer risk. Recently, additional study suggested that rs757210 was associated with prostate cancer [53].

Spurdle et al [9] identified an endometrial cancer susceptibility locus rs4430796 ($p = 7.1 \times 10^{-10}$) that is also associated with risk of prostate cancer. Furthermore, Setiawan et al [54] found that rs4430796 and rs7501939 were associated with endometrial cancer risk in two large case-control studies nested in prospective cohorts: the Multiethnic Cohort Study (MEC) and the Women's Health Initiative (WHI). Di Vivo et al [55] replicated previously identified associations of endometrial cancer with genetic markers near the *HNF1B* locus. Recently, several studies found that *HNF1B* (rs4430796) is associated with lung cancer in Chinese population [56], prostate cancer in African American men [57], Chinese men [58], and Korean population [59].

Genetic links between diabetes and multiple cancers

Meta-analyses have shown that men with T2D have a reduction in their risk of prostate cancer [6,10,60], but the basis for this association is unclear. Other studies further supported an inverse association between T2D and prostate cancer [61,62]. Recently, Bansal et al [10] demonstrated strongest evidence supporting that T2D is significantly inversely associated with risk of developing prostate cancer by analyzing 8.1 million participants and 132,231 prostate cancer cases from 29 cohort and 16 case-control studies. It has been hypothesized that this inverse association is due to metabolic and hormonal changes associated with T2D as decreased testosterone or insulin, which lead to a less carcinogenic environment [6,60]. Alternative explanations for such association include unmeasured confounding, decreased Prostate-Specific Antigen (PSA) levels in diabetics, effects of T2D treatment on prostate cancer risk, and/or shared genetic factors for T2D and prostate cancer [51,63,64]. Genetic variation is proposed to contribute to both diseases, and common genetic variation may explain part of the association between T2D and prostate cancer [13,62]. Recently, GWAS provided support for a shared genetic contribution to the risk of T2D and prostate cancer. For example, in the study by Gudmundsson et al [16], the A allele of rs4430796 and C allele of rs7501939 variants in *HNF1B/TCF2* showed positive associations of risk with prostate cancer (OR>1.0), confers protection against T2D (OR<1.0). Further study confirmed the association of rs4430796 with T2D and prostate cancer and suggested that T2D has a protective effect on prostate cancer risk [62]. Stevens et al [65] found that 3 SNPs (rs11649743, rs4430796, and rs7501939) were associated with prostate cancer and were also associated, with marginal statistical significance, with T2D. Recently, Michaela et al [53] found that T allele of rs757210 in *HNF1B* gene is associated with T2D (OR=0.85) and risk of prostate cancer. In addition, a more recent study identified 17 pleiotropic gene loci between prostate cancer and low-density lipoprotein, and prostate cancer and triglycerides, respectively [66]. However, rs4810671 in Sulfates 2 (*SULF2*) gene (Gene ID: 55959) may interact with rs4430796 in *HNF1B* in influencing prostate cancer and T2D [67].

It has been reported that increased Body Mass Index (BMI) is a major risk factor for both T2D and endometrial cancer, and there is a positive correlation between T2D and endometrial cancer risk [68-70]. Recently, a GWAS has implicated that rs4430796 is associated with endometrial cancer ($p=7.1 \times 10^{-10}$) that is also associated with risk of prostate cancer and is inversely associated with risk of T2D. However, the opposite direction of the effects of rs4430796 on endometrial cancer and T2D risk may indicate that the association between rs4430796 and endometrial cancer risk is not mediated through BMI or T2D [9].

A recent meta-analysis examined the two variants (rs4430796 and rs7501939) and found them conclusively to have pleiotropic effects on both T2D and prostate cancer; however, the pleiotropy apparently does not extend to other cancer types (such as breast, lung, colorectal or pancreatic cancers or melanoma) [14]. Analysis of several lymphocyte-derived gene expression datasets reveals significant associations between rs4430796 genotype and *HNF1B* expression in individuals of European ancestry, but not for individuals of African ancestry. These observations suggest that the *HNF1B* may underlie the observed association with endometrial cancer risk, but that rs4430796 is unlikely to be the causal SNP driving the association [9].

Conclusion and Future Direction

The cause of the epidemiological associations among diabetes and multiple cancers is not known. The discovery of common risk alleles for prostate cancer and endometrial cancer and T2D may reveal part of shared etiology among these diseases. However, diabetes and cancers are complex diseases which result from the interplay of many genetic and environmental factors and potential interactions. Future work is needed to assess additional genetic loci sharing among these diseases. Examining the contributions of variants and genes across biological pathways that link diseases will be an important part of characterizing the overlap in genomic architecture across related diseases [71].

It has been suggested that future research should combine genetic susceptibility data with T2D phenotype data to determine to what degree the association between T2D genetic risk and prostate cancer is mediated by T2D or related phenotypes (such as fasting glucose, fasting insulin, or glucose tolerance) [62]. Furthermore, the elucidation of correlated pleiotropic effects on diverse phenotypes will require very large studies, given the generally subtle effects involved. Collaborative efforts between multiple teams, as in the current study, may offer a suitable approach to answer such questions [14].

In the future, it will be useful to combine the results of GWAS, gene-gene and gene-environment interactions, with the recent rapid advances in Next Generation Sequencing (NGS) technologies to better understand the genetic etiology of diabetes and multiple cancer co morbidity.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics. CA: A Cancer Journal for Clinicians. 2014; 64: 9-29.
2. Bonnycastle LL, Willer CJ, Conneely KN, Jackson AU, Burrill CP, Watanabe RM, et al. Common variants in maturity-onset diabetes of the young genes contribute to risk of type 2 diabetes in Finns. Diabetes. 2006; 55: 2534-2540.
3. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med. 2006; 166: 1871-1877.
4. Rousseau MC, Parent ME, Pollak MN, Siemiatycki J. Diabetes mellitus and cancer risk in a population-based case-control study among men from Montreal, Canada. Int J Cancer. 2006; 118: 2105-2109.
5. Stattin P, Björ O, Ferrari P, Lukanova A, Lenner P, Lindahl B, et al. Prospective study of hyperglycemia and cancer risk. Diabetes Care. 2007; 30: 561-567.
6. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006; 15: 2056-2062.
7. Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2006; 15: 1977-1983.
8. Calton BA, Chang SC, Wright ME, Kipnis V, Lawson K, Thompson FE, et al. History of diabetes mellitus and subsequent prostate cancer risk in the NIH-AARP Diet and Health Study. Cancer Causes Control. 2007; 18: 493-503.
9. Spurdle AB, Thompson DJ, Ahmed S, Ferguson K, Healey CS, O'Mara T, et al. Genome-wide association study identifies a common variant associated with risk of endometrial cancer. Nat Genet. 2011; 43: 451-454.
10. Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. Prostate Cancer Prostatic Dis. 2013; 16: 151-158.
11. Will JC, Vinicor F, Calle EE. Is diabetes mellitus associated with prostate cancer incidence and survival? Epidemiology. 1999; 10: 313-318.
12. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology. 2007; 132: 2208-2225.
13. Frayling TM, Colhoun H, Florez JC. A genetic link between type 2 diabetes and prostate cancer. Diabetologia. 2008; 51: 1757-1760.
14. Elliott KS, Zeggini E, McCarthy MI, Gudmundsson J, Sulem P, Stacey SN, et al. Evaluation of association of HNF1B variants with diverse cancers: collaborative analysis of data from 19 genome-wide association studies. PLoS One. 2010; 5: 10858.
15. Meyer TE, Boerwinkle E, Morrison AC, Volcik KA, Sanderson M, Coker AL, et al. Diabetes genes and prostate cancer in the Atherosclerosis Risk in Communities study. Cancer Epidemiol Biomarkers Prev. 2010; 19: 558-565.
16. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, 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.
17. Sun J, Zheng SL, Wiklund F, Isaacs SD, Purcell LD, Gao Z, et al. Evidence for two independent prostate cancer risk-associated loci in the HNF1B gene at 17q12. Nat Genet. 2008; 40: 1153-1155.
18. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, et al. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet. 2008; 40: 310-315.
19. Abbott C, Piaggio G, Ammendola R, Solomon E, Povey S, Gounari F, et al. Mapping of the gene TCF2 coding for the transcription factor LFB3 to human chromosome 17 by polymerase chain reaction. Genomics. 1990; 8: 165-167.
20. Bach I, Mattei MG, Cereghini S, Yaniv M. Two members of an HNF1 homeoprotein family are expressed in human liver. Nucleic Acids Res. 1991; 19: 3553-3559.
21. Kolatsi-Joannou M, Bingham C, Ellard S, Bulman MP, Allen LIS, Hattersley AT, et al. Hepatocyte nuclear factor-1-beta: a new kindred with renal cysts and diabetes and gene expression in normal human development. J Am Soc Nephrol. 2001; 12: 2175-2180.
22. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. J Med Genet. 2006; 43: 84-90.

23. Wu G, Bohn S, Ryffel GU. The HNF1Beta transcription factor has several domains involved in nephrogenesis and partially rescues Pax8/lim1-induced kidney malformations. Eur J Biochem. 2004; 271: 3715-3728.

24. Ma Z, Gong Y, Patel V, Karner CM, Fischer E, Hiesberger T, et al. Mutations of HNF-1beta inhibit epithelial morphogenesis through dysregulation of SOCS-3. Proc Natl Acad Sci USA. 2007; 104: 20386-20391.

25. Verdeguer F, Le Corre S, Fischer E, Callens C, Garbay S, Doyen A, et al. A mitotic transcriptional switch in polycystic kidney disease. Nat Med. 2010; 16: 106-110.

26. Rebouissou S, Vasiliu V, Thomas C, Bellanné-Chantelot C, Bui H, Chrétien Y, et al. Germline hepatocyte nuclear factor 1alpha and 1beta mutations in renal cell carcinomas. Hum Mol Genet. 2005; 14: 603-614.

27. Terasawa K, Toyota M, Sagae S, Ogi K, Suzuki H, Sonoda T, et al. Epigenetic inactivation of TCF2 in ovarian cancer and various cancer cell lines. Br J Cancer. 2006; 94: 914-921.

28. Kim HJ, Bae JS, Lee J, Chang IH, Kim KD, Shin HD, et al. HNF1B polymorphism associated with development of prostate cancer in Korean patients. Urology. 2011; 78: 969.

29. Tsuchiya A, Sakamoto M, Yasuda J, Chuma M, Ohta T, Ohki M, et al. Expression profiling in ovarian clear cell carcinoma: identification of hepatocyte nuclear factor-1 beta as a molecular marker and a possible molecular target for therapy of ovarian clear cell carcinoma. Am J Pathol. 2003; 163: 2503–12.

30. Mahata P. Biomarkers for epithelial ovarian cancers. Genome Inform. 2006; 17: 184-193.

31. Kato N, Motoyama T. Hepatocyte nuclear factor-1beta(HNF-1beta) in human urogenital organs: its expression and role in embryogenesis and tumorigenesis. Histol Histopathol. 2009; 24: 1479-1486.

32. Kato N, Sasou S, Motoyama T. Expression of hepatocyte nuclear factor-1beta (HNF-1beta) in clear cell tumors and endometriosis of the ovary. Mod Pathol. 2006; 19: 83-89.

33. Brito EC, Lyssenko V, Renström F, Berglund G, Nilsson PM, Groop L, et al. Previously associated type 2 diabetes variants may interact with physical activity to modify the risk of impaired glucose regulation and type 2 diabetes: a study of 16,003 Swedish adults. Diabetes. 2009; 58: 1411-1418.

34. Harries LW, Perry JR, McCullagh P, Crundwell M. Alterations in LMTK2, MSMB and HNF1B gene expression are associated with the development of prostate cancer. BMC Cancer. 2010; 10: 315.

35. Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, et al. Mutation in hepatocyte nuclear factor-1-beta gene (TCF2) associated with MODY. Nature Genet. 1997; 17: 384-385.

36. Lindner TH, Njolstad PR, Horikawa Y, Bostad L, Bell GI, Sovik O. A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1-beta. Hum Molec Genet. 1999; 8: 2001-2008.

37. Bingham C, Bulman MP, Ellard S, Allen LI, Lipkin GW, Hoff WG, et al. Mutations in the hepatocyte nuclear factor-1beta gene are associated with familial hypoplastic glomerulocystic kidney disease. Am J Hum Genet. 2001; 68: 219-224.

38. Bingham C, Ellard S, Allen L, Bulman M, Shepherd M, Frayling T, et al. Abnormal nephron development associated with a frameshift mutation in the transcription factor hepatocyte nuclear factor-1 beta. Kidney Int. 2000; 57: 898-907.

39. Bellanné-Chantelot C, Chauveau D, Gautier JF, Dubois-Laforgue D, Clauin S, Beaufils S, et al. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med. 2004; 140: 510-517.

40. Harries LW, Bingham C, Bellanne-Chantelot C, Hattersley AT, Ellard S. The position of premature termination codons in the hepatocyte nuclear factor--1 beta gene determines susceptibility to nonsense-mediated decay. Hum Genet. 2005; 118: 214-224.

41. Winckler W, Weedon MN, Graham RR, McCarroll SA, Purcell S, Almgren P, et al. Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes. Diabetes. 2007; 56: 685-693.

42. Miyake K, Yang W, Hara K, Yasuda K, Horikawa Y, Osawa H, et al. Construction of a prediction model for type 2 diabetes mellitus in the Japanese population based on 11 genes with strong evidence of the association. J Hum Genet. 2009; 54: 236-241.

43. Han X, Luo Y, Ren Q, Zhang X, Wang F, Sun X, et al. Implication of genetic variants near SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, FTO, TCF2, KCNQ1, and WFS1 in type 2 diabetes in a Chinese population. BMC Med Genet. 2010; 11: 81.

44. Wen J, Rönn T, Olsson A, Yang Z, Lu B, Du Y, et al. Investigation of type 2 diabetes risk alleles support CDKN2A/B, CDKAL1, and TCF7L2 as susceptibility genes in a Han Chinese cohort. PLoS One. 2010; 5: 9153.

45. Zhang X, Qiao H, Zhao Y, Wang X, Sun H, Liu A, et al. Association of single nucleotide polymorphisms in TCF2 with type 2 diabetes susceptibility in a Han Chinese population. PLoS One. 2012; 7: 52938.

46. Li H, Gan W, Lu L, Dong X, Han X, Hu C, et al. A genome-wide association study identifies GRK5 and RASGRP1 as type 2 diabetes loci in Chinese Hans. Diabetes. 2013; 62: 291-298.

47. Holmkvist J, Almgren P, Lyssenko V, Lindgren CM, Eriksson KF, Isomaa B, et al. Common variants in maturity-onset diabetes of the young genes and future risk of type 2 diabetes. Diabetes. 2008; 57: 1738-1744.

48. Gupta V, Vinay DG, Rafiq S, Kranthikumar MV, Janipalli CS, Giambartolomei C, et al. Association analysis of 31 common polymorphisms with type 2 diabetes and its related traits in Indian sib pairs. Diabetologia. 2012; 55: 349-357.

49. Elliott KS, Zeggini E, McCarthy MI, Gudmundsson J, Sulem P, Stacey SN, et al. Evaluation of association of HNF1B variants with diverse cancers: collaborative analysis of data from 19 genome-wide association studies. PLoS One. 2010; 5: 10858.

50. Levin AM, Machiela MJ, Zuhlke KA, Ray AM, Cooney KA, et al. Chromosome 17q12 variants contribute to risk of early-onset prostate cancer. Cancer Res. 2008; 68: 6492-6495.

51. Waters KM, Henderson BE, Stram DO, Wan P, Kolonel LN, Haiman CA. Association of diabetes with prostate cancer risk in the multiethnic cohort. Am J Epidemiol. 2009; 169: 937-945.

52. Berndt SI, Sampson J, Yeager M, Jacobs KB, Wang Z, Hutchinson A, et al. Large-scale fine mapping of the HNF1B locus and prostate cancer risk. Hum Mol Genet. 2011; 20: 3322-3329.

53. Machiela MJ, Lindström S, Allen NE, Haiman CA, Albanes D, Barricarte A, et al. Association of type 2 diabetes susceptibility variants with advanced prostate cancer risk in the Breast and Prostate Cancer Cohort Consortium. Am J Epidemiol. 2012; 176: 1121-1129.

54. Setiawan VW, Haessler J, Schumacher F, Cote ML, Deelman E, Fesinmeyer MD, et al. HNF1B and endometrial cancer risk: results from the PAGE study. PLoS One. 2012; 7: 30390.

55. De Vivo I, Prescott J, Setiawan VW, Olson SH. Wentzensen N; Australian National Endometrial Cancer Study Group, Attia J, et al. Genome-wide association study of endometrial cancer in E2C2. Hum Genet. 2014; 133: 211-224.

56. Sun JZ, Yang XX, Hu NY, Li X, Li FX, Li M. Genetic Variants in MMP9 and TCF2 Contribute to Susceptibility to Lung Cancer. Chin J Cancer Res. 2011; 23: 183-187.

57. Chornokur G, Amankwah EK, Davis SN, Phelan CM, Park JY, Pow-Sang J, et al. Variation in HNF1B and Obesity May Influence Prostate Cancer Risk in African American Men: A Pilot Study. Prostate Cancer. 2013; 2013: 384594.

58. Zhang YR, Xu Y, Yang K, Liu M, Wei D, Zhang YG, et al. Association of six susceptibility Loci with prostate cancer in northern chinese men. Asian Pac J Cancer Prev. 2012; 13: 6273-6276.

59. Kim L, Liao J, Zhang M, Talamonti M, Bentrem D, Rao S, et al. Clear cell

carcinoma of the pancreas: histopathologic features and a unique biomarker: hepatocyte nuclear factor-1beta. Mod Pathol. 2008; 21: 1075–83.

60. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia. 2004; 47: 1071-1078.

61. Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol. 2006; 164: 1094-1102.

62. Pierce BL, Ahsan H. Genetic susceptibility to type 2 diabetes is associated with reduced prostate cancer risk. Hum Hered. 2010; 69: 193-201.

63. Werny DM, Saraiya M, Gregg EW. Prostate-specific antigen values in diabetic and nondiabetic US men, 2001-2002. Am J Epidemiol. 2006; 164: 978-983.

64. Müller H, Raum E, Rothenbacher D, Stegmaier C, Brenner H. Association of diabetes and body mass index with levels of prostate-specific antigen: implications for correction of prostate-specific antigen cutoff values? Cancer Epidemiol Biomarkers Prev. 2009; 18: 1350-1356.

65. Stevens VL, Ahn J, Sun J, Jacobs EJ, Moore SC, Patel AV, et al. HNF1B and JAZF1 genes, diabetes, and prostate cancer risk. Prostate. 2010; 70: 601-607.

66. Andreassen OA, Zuber V, Thompson WK, Schork AJ, Bettella F. The PRACTICAL Consortium; and the CRUK GWAS, Djurovic S, Desikan RS . Shared common variants in prostate cancer and blood lipids. Int J Epidemiol. 2014.

67. Ciampa J, Yeager M, Jacobs K, Thun MJ, Gapstur S, Albanes D, et al. Application of a novel score test for genetic association incorporating gene-gene interaction suggests functionality for prostate cancer susceptibility regions. Hum Hered. 2011; 72: 182-193.

68. Hjartåker A, Langseth H, Weiderpass E. Obesity and diabetes epidemics: cancer repercussions. Adv Exp Med Biol. 2008; 630: 72-93.

69. Hemminki K, Li X, Sundquist J, Sundquist K. Risk of cancer following hospitalization for type 2 diabetes. Oncologist. 2010; 15: 548-555.

70. Noto H, Osame K, Sasazuki T, Noda M. Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. J Diabetes Complications. 2010; 24: 345-353.

71. Barrenas F, Chavali S, Holme P, Mobini R, Benson M. Network properties of complex human disease genes identified through genome-wide association studies. PLoS One. 2009; 4: 8090.

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