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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.

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