Polymorphisms in PDLIM5 gene are associated with alcohol dependence, type 2 diabetes, and hypertension

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A B S T R A C T

The PDZ and LIM domain 5 (PDLIM5) gene may play a role in alcohol dependence (AD), bipolar disorder, and major depressive disorder; however, no study has identified shared genetic variants within PDLIM5 gene among AD, type 2 diabetes (T2D), and hypertension. This study investigated the association of 72 single nucleotide polymorphism (SNPs) with AD (1066 AD cases and 1278 controls) in the Study of Addiction - Genetics and Environment (SAGE) sample and 47 SNPs with T2D (878 cases and 2686 non-diabetic) and hypertension (825 cases and 2739 non-hypertensive) in the Marshfield sample. Multiple logistic regression models in PLINK software were used to examine the associations of genetic variants with AD, T2D, and hypertension and SNP x alcohol consumption interactions for T2D and hypertension. Twenty-five SNPs were associated with AD in the SAGE sample (p < 0.05); rs1048627 showed the strongest association with AD (p = 5.53 × 10^{-4}). Of the 25 SNPs, 5 SNPs showed associations with both AD in the SAGE sample and T2D in the Marshfield sample (top SNP rs11097432 with p = 0.00107 for T2D and p = 0.0483 for AD) while 6 SNPs showed associations with both AD in the SAGE sample and hypertension in the Marshfield sample (top SNP rs125004026 with p = 0.0119 for hypertension and p = 1.51 × 10^{-2} for AD). SNP (rs6532496) showed significant interaction with alcohol consumption for hypertension. Our results showed that several genetic variants in PDLIM5 gene influence AD, T2D and hypertension. These findings offer the potential for new insights into the pathogenesis of AD, T2D, and hypertension.

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1. Introduction

Alcohol consumption is reported to be the third leading cause of poor health globally (WHO, 2014a). In fact, about 6% (3.3 million) of all global deaths and 5.1% of the global burden of disease and injury were attributed to alcohol drinking in 2012. Alcohol dependence (AD) as a chronic disorder has been linked to excessive and compulsive drinking (Kalsi et al., 2009). Studies have implicated genetic and environmental factors and their interactions as significant contributory factors to the development of AD (Bierut et al., 2010; Goldman et al., 2005; Heath et al., 1997). The heritability of AD in twin studies has been estimated to be 0.50–0.60 (Gelernter and Kranzler, 2009). Using European samples, Treutlein et al. (2009) reported the first genome-wide association study (GWAS) of AD with single nucleotide polymorphisms (SNPs) mapped to chromosome 2q35. AD has also been associated with AUTS2 locus (Schumann et al., 2011) and SNP rs1789891, located between ADH1B and ADH1C, in persons of European ancestry (Frank et al., 2012). Recently, several GWAS and meta-analyses have been conducted and a number of candidate genes have been found to be associated with AD and alcohol consumption (e.g., Bierut et al., 2010; Edenberg et al., 2010; Schumann et al., 2011; Wang et al., 2011; Zuo et al., 2012; Gelernter et al., 2014).

Diabetes is an important global health concern. It was estimated that diabetes caused 1.5 million deaths in adults (18 + years) in 2012 (WHO, 2014a), and 9% of the global adult population were living with diabetes in 2014 (WHO, 2014b). The World Health Organization (WHO) has projected that diabetes will be the 7th leading cause of death globally by 2030 (Mathers and Loncar,
About 90% of all cases of diabetes in the world are type 2 diabetes (T2D) (WHO, 2014b). In the United States (U.S.), it was reported that over 29 million people were living with diabetes and 37% of adults aged 20 years or older were pre-diabetic in 2012 (CDC, 2014). The concordance rate of T2D among monozygotic twins is 76%, compared with 40% among dizygotic twins, providing convincing evidence that genetic factors contribute to the development of T2D (Elbers et al., 2007). The role of genetics in T2D development has been studied, and there are currently several candidate genes showing association with T2D. A variant of TCF7L2 gene on 10q25.2 was associated with T2D risk in the U.S., Iceland, and Denmark cohorts (Grant et al., 2006). PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX genes were also identified to be associated with T2D (Lyssenko et al., 2008; Scott et al., 2011; Goyen et al., 2003). Recently, more than 76 loci affecting T2D have been identified in GWAS and meta-analysis (e.g., McCarthy and Zeggini, 2009; Hara et al., 2014; Ng et al., 2014; DiAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al., 2014; Karaderi et al., 2015). Alcohol consumption is strongly linked to the risk of diabetes in several studies. Available evidence suggests that moderate drinking may confer some protection against T2D; whereas excessive alcohol consumption is associated with increased risk of T2D. This association of alcohol consumption with T2D is due to its effects on the risk of diabetes (Conigrave et al., 2001; Balinias et al., 2009; Ajani et al., 2000; Wannamethee et al., 2002; Wang and Wang, 2014). Furthermore, a closely related area of interest concerns the possible link between alcohol consumption, diabetes, and metabolic syndrome. For example, alcohol consumption may be associated with increased risk for hypertension, diabetes, and metabolic syndrome (e.g., Parekh and Klag, 2001; Bellin and Puddye, 2006). However, the results are inconsistent (Stranges et al., 2004; Bellin and Puddye, 2006). For example, alcohol consumption is associated with hypertension but not diabetes (Saremi et al., 2004); whereas heavy alcohol drinking increases the risk of hypertension, but the relationship between light-to-moderate alcohol consumption and hypertension remains inconsistent (Sesso et al., 2008). A recent meta-analysis showed that in men, heavy alcohol consumption is associated with increased risk of hypertension, whereas there is a trend toward increased risk of hypertension with low and moderate alcohol consumption; however, the relationship between alcohol consumption and hypertension is J-shaped in women (Briasoulis et al., 2012).

2. Subjects and methods

2.1. Subjects

2.1.1. The SAGE data

The SAGE samples are obtained from Study of Addiction - Genetics and Environment (SAGE), a part of Gene Environment Association Studies initiative (GENEVA). SAGE is a comprehensive GWAS including approximately 4000 unrelated subjects of European and African-American descent. There were 1944 subjects with the primary phenotype having been DSM-IV diagnosed with AD (Bierut et al., 2010). Controls consist of 1965 subjects who had used alcohol, but had never been addicted to alcohol or other illicit substances. Each SAGE sample contains about 1 million Illumina SNPs. Samples were genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR). Demographic factors included age and gender. Genotyping was performed using Illumina Human1Mv1_C BeadChips and the Illumina Infinium II assay protocol (Gunderson et al., 2006). Allele cluster definitions for each SNP were determined using Illumina BeadStudio Genotyping Module version 3.1.14 and the combined intensity data from the samples. A SNP call rate of 98% was required. Within the PDLIMS gene, 72 SNPs in the SAGE sample were available. In the present study, we used 1066 AD Caucasian cases and 1278 Caucasian control individuals.

2.1.2. The Marshfield data

The Marshfield samples are from the publicly available data from a GWA Study on Cataract and HDL in the Personalized Medicine Research Project Cohort - Study Accession: phs000170.v1.p1 (dbGaP). The details of these subjects have been described elsewhere (McCarty et al., 2005, 2008). Social and behavioral factors used in this study were age, gender, and alcohol use in the past month (yes or no). Genotyping data using the ILLUMINA Human660W-Quad_v1_A are available for 3564 individuals (878 T2D cases and 2686 non-T2D; 825 with hypertension and 2739 non-hypertensive). Samples were genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR). Within the PDLIMS gene, 47 SNPs were available in the Marshfield samples.

2.2. Statistical methods

Hardy-Weinberg equilibrium (HWE) was tested for all of the SNPs in controls by using HAPLOVIEW software (Barrett et al., 2005). Then, minor allele frequency (MAF) was determined for each of the SNPs and the linkage disequilibrium (LD) structure based on r² values was constructed using HAPLOVIEW software. For the SAGE samples, logistic regression analysis of AD as a binary trait, adjusted for age and sex, was performed; while for the Marshfield sample, logistic regression analysis of T2D and hypertension, adjusted for age, sex and alcohol consumption in past month, was conducted. The asymptotic p-values for the logistic regression models were observed while the odds ratio (OR) and its standard error were estimated using PLINK v1.07 (Purcell et al., 2007). Haplotype analyses of AD, obesity and hypertension were performed using the PLINK software. In addition, multiple logistic regression model in PLINK was used to detect SNP x alcohol consumption interactions influencing T2D and hypertension in the Marshfield sample. Descriptive statistics for age, sex, alcohol consumption in past month, in both cases and controls were conducted with SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).
3. Results

3.1. Genotype quality control and descriptive statistics

All the 72 SNPs in the SAGE sample were in HWE in the controls (p > 0.001), with MAF >3%. In the Marshfield data, 4 of the 47 SNPs with MAF<1% were removed and the remaining 43 SNPs were in HWE in the controls (p > 0.001). Participants’ characteristics for the two samples are presented in Table 1. There were more females than males in controls in both datasets. The mean ages for the two samples are presented in Table 1. There were more females and OR ¼ 0.81, 95%CIequals 0.71–0.91 with p = 6.1 × 10⁻⁴; and OR ¼ 0.81, 95%CIequals 0.71–0.91 with p = 6.14 × 10⁻⁴; The associated results of these SNPs remained significant after Bonferroni correction (α = 0.05/72 = 6.94 × 10⁻⁴). Furthermore, we conducted a permutation test in PLINK and found that all the 25 associated SNPs had empirical pointwise p < 0.05 using a permutation test (data not shown).

3.2. Association with AD in the SAGE sample

Single marker analysis showed that 25 SNPs in the SAGE data were associated with AD (p < 0.05) (Table 2). The top three SNPs showing significant associations with AD were rs1048627, rs1043853, and rs11724023 (OR = 0.8, 95%CI = 0.71–0.91 with p = 5.53 × 10⁻³; OR = 0.8, 95%CI = 0.71–0.91 with p = 6.1 × 10⁻⁴; and OR = 0.81, 95%CI = 0.71–0.91 with p = 6.14 × 10⁻⁴). The associated results of these SNPs remained significant after Bonferroni correction (α = 0.05/72 = 6.94 × 10⁻⁴). Furthermore, we conducted a permutation test in PLINK and found that all the 25 associated SNPs had empirical pointwise p < 0.05 using a permutation test (data not shown).

3.3. Association with diabetes and hypertension in the Marshfield sample

Of the 25 SNPs associated with AD in the SAGE sample, 19 SNPs were also found in the Marshfield sample (Table 2) and 5 SNPs were associated with T2D (rs1056772, rs17336353, rs2452593, rs11097432, rs6816687 with p = 0.0199, 0.0391, 0.0471, 0.0483 and 0.0499, respectively for AD in the SAGE sample and p = 0.00586, 0.00339, 0.0116, 0.00107 and 0.00348 for T2D, respectively) (Table 2). Of the 25 AD associated SNPs, 6 SNPs showed associations with both AD in the SAGE sample and hypertension in the Marshfield data (rs11724023, rs11732687, rs12500426, rs7690296, and rs1509620 with p = 6.14 × 10⁻⁴, 7.18 × 10⁻⁴, 1.51 × 10⁻³, 2.84 × 10⁻³, 4.16 × 10⁻³ and 0.0212, respectively for AD and p = 0.0352, 0.0314, 0.0191, 0.0301, 0.0424 and 0.0204, respectively for hypertension) (Table 2). In addition, SNP rs2577056 showed strong association with hypertension (OR = 0.82, 95%CI = 0.72–0.94, p = 0.00478) in the Marshfield data but no associations with AD in the SAGE sample.

3.4. Haplotype analysis

We identified 3 haplotype blocks for 23 SNPs using HAPLOVIEW software including the most significant associated SNPs in both samples. Fig. 1 shows the LD (r²) structure in the SAGE sample. The A-C haplotype from rs11732687 and rs11724023 (r² = 0.99) revealed significant association with AD in the SAGE sample (p = 5.65 × 10⁻⁴) while the T-A haplotype from rs11724023 and rs7690296 (r² = 0.95) revealed significant association with AD in the SAGE sample (p = 6.76 × 10⁻⁴ (Table 3). The C-T haplotype from rs11097432 and rs6532496 (r² = 0.96) revealed significant associations with T2D in the Marshfield sample (p = 0.00107). The C-A haplotype from rs463423 and rs12500426 (r² = 0.93) showed significant association with hypertension in the Marshfield sample (p = 0.0115) (Table 3).

3.5. SNP x alcohol interaction analysis in the Marshfield sample

Multiple logistic regression showed that rs6532496 had significant interaction effect with alcohol consumption in influencing hypertension (OR = 0.79, 95%CI = 0.63–0.99 with p = 0.046). This SNP was associated with the risk of AD (p = 1.02 × 10⁻³) and nominally associated with the risk of hypertension (p = 0.0805) (Table 2).

3.6. In silico analysis

We evaluated whether these variants are located within the regions of the gene that might have potential functional importance. The sequences containing the associated SNPs were examined for microRNA binding sites, splicing sites, regulatory gene regions, and species-conserved regions using NIH-SNP Function Prediction (http://snpinfo.niehs.nih.gov/cgi-bin/snpinfo/snpfunc.cgi). We found one rs7690296 is a nonsynonymous SNP and an exonic splicing enhancer (ESE) or exonic splicing silencer (ESS); while 5 SNPs (rs1043853, rs1048627, rs1056772, rs12642449 and rs14082) are located at microRNA-binding sites and rs11732687 is located at a species-conserved region.

4. Discussion

Here, we present novel SNPs associated with AD, T2D, and hypertension obtained from GWAS datasets. We identified 25 SNPs in the PDLIM5 gene from Caucasians in the SAGE sample associated with AD including rs11724023 reported by Gelernter et al. (2014).

Table 1 Descriptive characteristics of cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>SAGEb</th>
<th>Marshfield</th>
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<tbody>
<tr>
<td></td>
<td>AD</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td>Subjects</td>
<td>1066</td>
<td>1278</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>646 (61%)</td>
<td>376 (29%)</td>
</tr>
<tr>
<td>Females</td>
<td>420 (39%)</td>
<td>902 (71%)</td>
</tr>
<tr>
<td>Alcohol consumption (%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age, years</td>
<td>18–77</td>
<td>18–65</td>
</tr>
</tbody>
</table>

|                      |       |            |
| Mean ± SD           | 38.1 ± 9.9 | 38.6 ± 9.4 | 69.2 ± 10.6 | 65.4 ± 11.4 | 68.8 ± 11.6 | 65.6 ± 11.1 |
| Range               | 18–77 | 18–65      | 46–90        | 46–90        | 46–90        | 46–90        |

a Standard deviation.
b From Study of Addiction - Genetics and Environment.
c Alcohol dependence.
Five of these SNPs were associated with T2D and 6 SNPs associated with hypertension in Caucasians from the Marshfield sample. Haplotype analysis further confirmed our observation. Our results suggest that shared genes may also explain the relationship between excessive alcohol drinking, T2D, and hypertension.

Previous studies have shown that *PDLM5* was expressed in various regions of the brain and associated with several mental illnesses such as bipolar disorder, schizophrenia, and major depression (Maeno-Hikichi et al., 2003; Kato et al., 2005; Iwamoto and Kata, 2006; Li et al., 2008). For example, *PDLM5* is associated with both AD and T2D. Functionally, expression of ENH may play a significant role in this association. Two decades ago, Zemel et al. (1995) demonstrated that dominant consumption with T2D and hypertension. However, to date, no known study has considered shared genes among AD, T2D, and hypertension. In this study, we have identified a novel function for the *PDLM5* gene with regard to T2D and hypertension. While our results cannot explain the mechanism by which variants in *PDLM5* are associated with T2D and hypertension, previous findings suggest that Ca$^{2+}$ may play a significant role in this association.

Previous studies have shown that alcohol consumption may have a U shape relationship with T2D (Conigrave et al., 2001; Balinunas et al., 2009; Ajani et al., 2000; Wannamethee et al., 2002; Wang and Wang, 2014). Furthermore, large amount of alcohol consumption or gender (e.g., Parekh and Klag, 1993; Segal et al., 2001; Beilin and Puddey, 2006, 2006; Stranges et al., 2004; Sesso et al., 2008) may have deleterious effect on insulin resistance and vice versa (Draznin, 1993; Segal et al., 1988; Yki-Järvinen and Nikkilä, 1985) and may have deleterious effect on islet cells, inhibit secretion of insulin and lead to increased insulin resistance (Yki-Järvinen et al., 1988; Yki-Järvinen and Nikkilä, 1985; Shelmet et al., 1988). In addition, alcohol consumption may be associated with increased risk for hypertension, and other metabolic disorders; however, such associations may depend on the amount of alcohol consumption or gender (e.g., Parekh and Klag, 2001; Beilin and Puddey, 2006, 2006; Stranges et al., 2004; Sesso et al., 2008; Bramoulis et al., 2012). These findings attempt to offer biological plausibility of the observed relationship of alcohol consumption with T2D and hypertension. However, to date, no known study has considered shared genes among AD, T2D, and hypertension. In this study, we have identified a novel function for the *PDLM5* gene with regard to T2D and hypertension. While our results cannot explain the mechanism by which variants in *PDLM5* are associated with T2D and hypertension, previous findings suggest that Ca$^{2+}$ may play a significant role in this association.
et al., 1990). These findings suggest that PDLIM5 may influence T2D and hypertension through a calcium mechanism (Maeno-Hikichi et al., 2003). Recently, it has been shown that overexpression of PDLIM5 prevents hypoxia-induced pulmonary hypertension and deletion of PDLIM5 in smooth muscle cells enhances hypoxia-induced pulmonary hypertension in vivo, which suggest a role of PDLIM5 in therapeutic target of pulmonary hypertension (Chen et al., 2015; Cheng et al., 2016). Furthermore, variants within PDLIM5 have also been linked to cancer (Wang et al., 2016) such as prostate cancer (Guyon et al., 2009), gastric cancer (Li et al., 2015) and possible increased proliferation rates of other tumors (Edlund et al., 2012). Among other functions, PDZ-LIM proteins support cellular function such as signaling and cell-fate determination (Krcmery et al., 2010).

We evaluated whether these associated SNPs were located in regions of the gene that might have potential functional importance. For example, the AD and hypertension-associated SNP rs7690296 is a nonsynonymous SNP and may play a role as an exonic splicing enhancer or silencer. 5 SNPs (rs1043853, rs1048627, rs1056772, rs12642449 and rs14082) are located at microRNA-binding sites and were associated with AD, while rs1056772 was associated with T2D and rs12642449 was nominally associated with hypertension (p = 0.0628). In addition, rs11732687 is located at a species-conserved region and associated with AD and hypertension.

Evidence presented above indicates that although some variants within PDLIM5 gene may be shared among AD, T2D and hypertension, the mechanisms by which they cause these conditions are still unclear. More studies are required to confirm our findings and also explain the mechanisms by which the polymorphisms within PDLIM5 gene affect these 3 diseases. Interpretation of the study

![Fig. 1. Linkage disequilibrium structure of 23 SNPs. The numbers indicate the r² value between the corresponding two SNPs.](image)

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
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<tr>
<td>Haplotype analysis of alcohol dependence, diabetes and hypertension.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequencya</th>
<th>ORb</th>
<th>p-valuec</th>
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<tr>
<td><strong>Alcohol dependence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs17397084 rs11732687</td>
<td>0.03</td>
<td>0.89</td>
<td>0.52</td>
</tr>
<tr>
<td>T A</td>
<td>0.4</td>
<td>0.82</td>
<td>0.00141</td>
</tr>
<tr>
<td>C G</td>
<td>0.57</td>
<td>1.24</td>
<td>7.18E-04</td>
</tr>
<tr>
<td>rs11732687 rs11724023</td>
<td>0.43</td>
<td>0.8</td>
<td>5.6E-04</td>
</tr>
<tr>
<td>A C</td>
<td>0.57</td>
<td>1.24</td>
<td>7.21E-04</td>
</tr>
<tr>
<td>rs11724023 rs7690296</td>
<td>0.42</td>
<td>0.81</td>
<td>9.09E-04</td>
</tr>
<tr>
<td>A G</td>
<td>0.53</td>
<td>1.24</td>
<td>6.76E-04</td>
</tr>
<tr>
<td>rs11097432 rs6532496</td>
<td>0.42</td>
<td>0.8</td>
<td>5.02E-04</td>
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<tr>
<td>A T</td>
<td>0.41</td>
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<td>0.367</td>
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<td>C G</td>
<td>0.37</td>
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<tr>
<td>rs11732687 rs11724023</td>
<td>0.43</td>
<td>1.13</td>
<td>0.0314</td>
</tr>
<tr>
<td>A C</td>
<td>0.57</td>
<td>0.89</td>
<td>0.0352</td>
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<tr>
<td>C G</td>
<td>0.46</td>
<td>1.15</td>
<td>0.0115</td>
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<tr>
<td>T T</td>
<td>0.02</td>
<td>0.62</td>
<td>0.105</td>
</tr>
<tr>
<td>C C</td>
<td>0.52</td>
<td>0.88</td>
<td>0.0308</td>
</tr>
</tbody>
</table>

a Haplotype frequency in the sample.  
b OR refers to the Odds ratio for each haplotype using PLINK.  
c p-value for the haplotype.
findings should take into consideration the strengths and limitations of the analysis. To the best of our knowledge, our study is the first to examine associations of PDLIM5 polymorphisms with T2D and hypertension. Our samples were also relatively large and ethnically homogeneous. We were also thorough in our analysis by examining 72 SNPs in the SAGE sample and 47 SNPs in the Marshfield sample. However, focusing on only Caucasians, we cannot tell how the results may apply to other populations. The study is also limited by the use of only one sample for AD and one sample for T2D and hypertension. Lastely, despite the rigorous analysis, our study is not insulated from type I error, hence, replication of the study is required.

5. Conclusion

These findings provide first evidence of shared genetic variants in PDLIM5 gene influencing AD, T2D, and hypertension and will serve as a resource for replication in other populations. Our findings suggest that joint intervention for treatment of AD, T2D and hypertension can be helpful.

Contributors

Daniel Owusu and Ke-Sheng Wang managed the literature searches, analyses, and the design of the study. Daniel Owusu drafted the manuscript. Yue Pan and Changchun Xie offered critical guidance on the statistical analysis and contributed for statistical expertise and improvement of the manuscript. Sam Harirforoosh provided critical review of the manuscript and edited the manuscript. All authors read and approved the manuscript.

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Conclusions

These findings provide first evidence of shared genetic variants in PDLIM5 gene influencing AD, T2D, and hypertension and will serve as a resource for replication in other populations. Our findings suggest that joint intervention for treatment of AD, T2D and hypertension can be helpful.

References


