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Review

Shared genetic etiology underlying Alzheimer's disease and type 2 diabetes

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ABSTRACT

Epidemiological evidence supports the observation that subjects with type 2 diabetes (T2D) are at higher risk to develop Alzheimer's disease (AD). However, whether and how these two conditions are causally linked is unknown. Possible mechanisms include shared genetic risk factors, which were investigated in this study based on recent genome wide association study (GWAS) findings. In order to achieve our goal, we retrieved single nucleotide polymorphisms (SNPs) associated with T2D and AD from large-scale GWAS meta-analysis consortia and tested for overlap among the T2D- and AD-associated SNPs at various p-value thresholds. We then explored the function of the shared T2D/AD GWAS SNPs by leveraging expressional quantitative trait loci, pathways, gene ontology data, and co-expression networks. We found 927 SNPs associated with both AD and T2D with p-value ≤0.01, an overlap significantly larger than random chance (overlapping p-value of 6.93E–28). Among these, 395 of the shared GWAS SNPs have the same risk allele for AD and T2D, suggesting common pathogenic mechanisms underlying the development of both AD and T2D. Genes influenced by shared T2D/AD SNPs with the same risk allele were first identified using a SNP annotation variation (ANNOVAR) software, followed by using Association Protein-Protein Link Evaluator (DAPPLE) software to identify additional proteins that are known to physically interact with the ANNOVAR gene annotations. We found that gene annotations from ANNOVAR and DAPPLE significantly enriched specific KEGG pathways pertaining to immune responses, cell signaling and neuronal plasticity, cellular processes in which abnormalities are known to contribute to both T2D and AD pathogenesis. Thus, our observation suggests that among T2D subjects with common genetic predispositions (*e.g.*, SNPs with consistent risk alleles for T2D and AD), dysregulation of these pathogenic pathways could contribute to the elevated risks for AD in subjects. Interestingly, we found that 532 of the shared T2D/AD GWAS SNPs had divergent risk alleles in the two diseases. For individual shared T2D/AD SNPs with divergent alleles, one of the allelic forms may contribute to one of the diseases (*e.g.*, T2D), but not necessarily to the

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other (*e.g.*, AD), or vice versa. Collectively, our GWAS studies tentatively support the epidemiological observation of disease concordance between T2D and AD. Moreover, the studies provide the much needed information for the design of future novel therapeutic approaches, for a subpopulation of T2D subjects with genetic disposition to AD, that could benefit T2D and reduce the risk for subsequent development of AD.

Contents

1. Introduction

An estimated 347 million people worldwide suffer from diabetes, with 90% of this population (312 million) suffering specifically from type 2 diabetes (T2D) (World Health Organization, 2015), exerting enormous burdens on individuals and on healthcare systems (World Health Organization, 2015), especially given that there is currently no cure for T2D. Diabetes is a risk factor for a number of disabling and even life-threatening complications over the long-term. For example, one of the major long-term complications of T2D is an increased risk for developing Alzheimer's disease (AD) (Luchsinger and Gustafson, 2009; Muller et al., 2007; Vagelatos and Eslick, 2013). AD is the most common form of age-related dementia, accounting for up to 80% of dementia cases (Alzheimer's Association, 2015); an estimated 44.4 million people worldwide suffer from AD and dementia (Alzheimer's Disease International, 2013). Similar to T2D, AD exerts an enormous burden on individual patients and healthcare systems, and there is currently no cure for AD. Extensive epidemiological, clinical, and experimental evidence strongly suggest a causative role of diabetes in the onset and progression of AD-type dementia. The National Diabetes Health Fact Sheet indicates that approximately 8.3% of Americans have diabetes, and it is estimated that approximately 30% of Americans over the age of 65 affected by AD have co-morbidity with at least one serious medical condition associated with diabetes. A recent systematic meta-analysis of 15 epidemiologic studies suggests that patients with T2D have an elevated relative risk ratio of 1.57 for developing AD (Vagelatos and Eslick, 2013). Specific mechanistic interactions connecting diabetes and AD remain unknown. There is also no information on why certain subpopulations of diabetic individuals develop AD or how to identify at-risk individuals in order to target them for early, secondary preventive interventions. Mounting evidence suggests that AD dementia can be traced back to pathological conditions, such as T2D, that are initiated several decades before clinical AD onset. Since T2D is one of the potentially modifiable risk factors for AD (Luchsinger and Gustafson, 2009; Muller et al., 2007; Vagelatos and Eslick, 2013), interventions targeting T2D phenotypes prior to the onset of AD dementia represent a potentially effective secondary preventive strategy to help reduce the prevalence of AD.

Both T2D and AD are complex diseases, each involving multiple etiologic contributing factors (Gautrin and Gauthier, 1989; Henriksen et al., 2011; Jiang et al., 2013; Morris et al., 2014; Onso-Magdalena et al., 2011; Raciti et al., 2015). Among these, genetic predisposition factors are known to play important roles in both T2D and AD (Chouraki and Seshadri, 2014; Prasad and Groop, 2015; Raciti et al., 2015; Tanzi, 2012). We hypothesize that T2D may share common underlying genetic etiologies with AD, and that the presence of these shared T2D/AD genetic etiologies in a subset of individuals may contribute to the development of T2D in these individuals, as well as the development of AD over the long-term. Recent applications of Genome-Wide Association Studies (GWAS) have led to the identification of genetic variants, particularly single nucleotide polymorphisms (SNPs), for a number of complex diseases, including schizophrenia and cardiovascular diseases (Kendler, 2015;