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Short Communication

Complex genetic susceptibility to vascular dementia and an evidence for its underlying genetic factors associated with memory and associative learning

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ABSTRACT

Genetic basis for vascular dementia (VD) as a typical complex disease has been limitedly reported from association studies conducted with candidate genes. Even recent genomewide association studies (GWAS) could hardly identify additional genetic factors for VD. Although a considerable complexity for its genetic architecture was suspected, there were some challenges to identify false negative associations that resulted from the GWAS. Challenges to identifying genetic factors and their functions after the trials of GWAS revealed that splicing of primary transcript was inhibited (SYK) or delayed (PHLDB2) by a nucleotide substitution of the corresponding gene. The studies gave us the lesson that integrated investigations with statistical genomics as well as functional genomics are needed to identify false negatives from the GWAS. Such endeavors would provide key insights into aspects of underlying nucleotide architectures of VD and incorporate the genetic factors into clinical practice. The recent genetic association studies for susceptibility to VD were briefly overviewed in this article. We also showed a challenge to understanding genetic dissection of VD by a genomic region enrichment analysis with distal *cis*-regulatory sequences. The analysis with a variant set of potential false negatives from the GWAS revealed that the variants were significantly enriched near genes involved in critical biological processes to VD.

1. Introduction

Vascular dementia is induced by cerebrovascular lesions with progressive deterioration in memory, thinking, behavior, motor, and/or cognitive functions (Lee, 2009). Not only patients with stroke but also people with silent stroke presenting no external symptoms are predisposed to vascular dementia. Stroke has been known as one of the most common causes of mortality (Feigin et al., 2009), and even silent strokes are thought to be five times more prevalent than symptomatic stroke (Vermeer et al., 2003). Thus, vascular dementia has been a great concern to the elderly and their families. Nevertheless, its genetic basis has been scarcely known. The most common heritable cause of vascular dementia is cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), an autosomal dominant disease caused by various mutations in *NOTCH3* gene (Fig. 1, Joutel et al., 1996). The mutations were located in tandem epidermal growth factor-like repeat region of receptor and produce an odd number of cysteine residues by either a gain or a loss of cysteine residue. The odd number affects functions and survival of vascular smooth muscle cells and causes a defect in vessel homeostasis that leads to apoptosis of these cells.

Another heritable cause of vascular dementia was familial cerebral amyloid angiopathy (FCAA) that accumulated amyloid in the wall of vessels and resulted in stroke and vascular dementia (Fig. 1, Herzig et al., 2009). An FCAA was the hereditary cerebral hemorrhage with cystatin C amyloid angiopathy caused by an amino acid substitution (Gln58Leu) in the amyloid molecule (Jensson et al., 1987). Another FCAA was the hereditary cerebral hemorrhage with Dutch type amyloidosis caused by vascular deposition of Glu22Gln-mutant β-amyloid (Herzig et al., 2009). A meningovascular amyloidosis causing a FCAA resulted from Tyr69His in transthyretin gene (Blevins et al., 2003). The FCAA was also caused by mutated gelsolin in Finnish type amyloidosis, disease-associated prion protein (PrP^{Sc}) in a variant of the Gerstmann–Sträussler–Scheinker syndrome, and ABri (ADan) amyloid

Abbreviations: ACE, angiotensin I converting enzyme; AGT, angiotensinogen; APOE, apolipoprotein E; APP, amyloid beta (A4) precursor protein; AR, androgen receptor; CADASIL, cerebral arteriopathy, autosomal dominant, with subcortical infarcts and leukoencephalopathy; CST3, cystatin C; FAM134B, family with sequence similarity 134 member B; FCAA, familial cerebral amyloid angiopathies; FDA, false discovery rate; GSN, gelsolin; GSTO1, glutathione S-transferase omega 1; GWAS, genomewide association study; HSPA1A, heat shock 70 kDa protein 1A; ICAM1, intercellular adhesion molecule 1; IGF1R, insulin-like growth factor 1 receptor; IL1A, interleukin 1 alpha; IL1B, interleukin 1 beta; IL6, interleukin 6; ITM2B, integral membrane protein 2B; MMP1, matrix metallopeptidase 1; MMP3, matrix metallopeptidase 3; MMP9, matrix metallopeptidase 9; MTHFR, methylenetetrahydrofolate reductase; NOTCH3, neurogenic locus notch homolog protein 3; PHLDB2, pleckstrin homology-like domain family B member 2; PON1, paraoxonase 1; PON2, paraoxonase 2; SREBF2, sterol regulatory element binding transcription factor 2; SYK, spleen tyrosine kinase; TGFB1, transforming growth factor beta 1; TNF, tumor necrosis factor; TNFRSF19, tumor necrosis factor receptor superfamily member 19; TNFSF14, tumor necrosis factor superfamily 14; TTR, transthyretin; VEGF, vascular endothelial growth factor; VLDLR, very low density lipoprotein receptor.

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proteins released by furin of the mutated ITM2B (also called BRI2) precursor proteins in familial British (Danish) dementia (Revesz et al., 2009).

Most patients with vascular dementia have sporadic forms as a typical complex disease caused by multiple genes under various environmental exposures. Typical approaches for identifying genetic factors are linkage analyses and association studies. Association studies for such complex diseases have been more successful in discovering genetic determinants than linkage analyses. Nevertheless, association studies with candidate genes have been hardly successful in identifying genetic variants associated with vascular dementia (Kim and Lee, 2006). The complexity of vascular dementia renders it difficult for geneticists to uncover genetic determinants, and the incomplete penetrance of vascular dementia makes such discovery even harder. The discipline has been revolutionized by genomewide association study (GWAS) which dramatically enhances identification of genetic variants for such complex disease. Recently, a few GWAS were conducted to identify nucleotide variants that influence susceptibility to vascular dementia. Here we provide a brief overview of the current status of the genetics of vascular dementia discovered from genetic association studies and discuss challenges of its genetic dissection. As an attempt to understand a broad outline of genetic architecture for vascular dementia, we performed a genomic region enrichment analysis with distal *cis*-regulatory sequences using a variant set of potential false negatives from the GWAS.

2. Genetic association with vascular dementia

2.1. Candidate gene association study

A variety of candidate genes for vascular dementia were examined for their genetic associations, and associations were reported with some genes involved in lipid metabolism, angiotensin, and inflammation (Fig. 1). For details on the genes and their risk alleles, see Kim et al. (2011). A limited number of genes with susceptible sequence polymorphisms were, however, identified to date. Furthermore, most associations with the candidate genes have not been replicated. The inconsistency might be caused by their marginally significant associations ($0.01<P<0.05$).

Recently, association studies with multiple genes revealed several genetic factors. The studies aimed not only to identify multiple factors for a larger genetic variability of vascular dementia but also to explain their epistasis. A study evaluated multiple genes as common factors for susceptibility to Alzheimer's disease and vascular dementia (Kim et al., 2012b), and the underlying premise was that vascular risk factors act to decrease cognitive abilities both in the diseases. Contrary to the expectation, common genetic factors were not found when examining associations of vascular dementia with 13 previously discovered genetic variants for association with Alzheimer's disease. Especially, the ε4 allele of *APOE* gene, the most famous locus for susceptibility to Alzheimer's disease, was not associated with susceptibility to vascular dementia ($P=0.55$). It was suggested that the underlying genetic factors were quite heterogeneous for the two major forms of dementia. The lack of association between vascular dementia and *APOE* ε4 in the current study called for a cautious inference because the result did not concur with studies that showed marginal associations in Americans ($P=0.04$, Chuang et al., 2010) and Asians ($P=0.01$, Yin et al., 2012).

A batch of studies with multiple genes examined their simultaneous actions. The epistasis was quite limitedly investigated since most studies have aimed to identify genetic associations with a parsimonious analytical model (Lee and Kim, 2008). The combined genotype with TC/CC of *TNFα* T-1031C and CC of *HSP70-1* A-110C turned out to be a better risk factor for susceptibility to vascular dementia ($OR=10.09$, $P<0.05$, Fung et al., 2005) than their individual genotypes (*HSP70-1* A-110C, $OR=3.22$ and *TNFα* T-1031C, $OR=2.32$). Another interactive association was found by analyzing combined genotypes of 12 genes (Kim et al., 2009). The optimal genetic factors were first identified for each of 1-, 2-, 3-, and 4-locus models using multifactor dimensionality reduction, and then the directions and sizes of their epistatic effects were estimated using entropy decomposition. As a result, a synergistic epistasis between 2 missense sequence variants of Pro10Leu in *TGF-β1* gene and Thr235Met of *AGT* gene was proposed to predict predispositions to vascular dementia. Recently, a stronger synergistic epistasis between *FAM134B* (rs10041159) and *TNFRSF19* (rs9317882) was identified by examining 121 sequence variants of 71 candidate genes that were expressed in the human brain (Kong et al., 2011). The entropy decomposition analysis suggested that 33% of the uncertainty in case–control status was eliminated by disclosing their interaction.

2.2. Genomewide Association Study (GWAS)

More recently, two GWAS were attempted to provide a comprehensive understanding of genetic architecture for vascular dementia. One GWAS was a case–control retrospective study with Koreans (84 patients and 200 controls, Kim et al., 2012a). Unfortunately, any genetic association was not detected from this GWAS. The other GWAS was a prospective study of the Rotterdam cohort in the Netherlands (67 patients and 5700 controls, Schrijvers et al., 2012). One variant near *AR* gene on the X chromosome (rs12007229, $P=1.3\times10^{-8}$) was identified in the cohort. The association was replicated in a German population ($P=2.4\times10^{-2}$, Schrijvers et al., 2012).

We compared the results from the two GWAS, but no common nucleotide variants were identified between the two GWAS, even with an arbitrary significance threshold of $P<10^{-5}$. The rs12007229 identified in the Dutch was unavailable after quality control in Koreans. Use of the arbitrary significance threshold resulted in associations with additional 31 SNPs showing an association signal together with the variant rs12007229 on the X chromosome (Schrijvers et al., 2012). Nevertheless, we could not find any associations with them in Koreans even with a marginal threshold ($P>0.05$, data are not shown). Furthermore, the other variants which showed associations in the Dutch population ($P<10^{-5}$) were not associated in the Korean population, and vice versa. More replication studies are needed to confirm the association signal of vascular dementia with the variant rs12007229. GWAS would be more efficient not only to learn which of such potential variants are associated with vascular dementia but also to identify novel associations. More importantly, the GWAS would considerably reduce publication bias.

3. Functional study for nucleotide sequence variants

False negative associations were suspected in the GWAS for susceptibility to vascular dementia because of their conservative statistical tests and small sample sizes. The former might systematically produce such errors at the expense of reducing spurious associations, and the latter was unlikely to achieve a certain degree of statistical power (<0.8). Although the use of small sample size was not a totally inevitable decision, it was considerably reduced when the two GWAS excluded the patients with mixed dementia displaying both vascular and Alzheimer's features in order to avoid their confounding effects.

Research efforts were made on identifying false negative association from the Korean GWAS for susceptibility to vascular dementia. They were to identify causal genetic variants underlying the weak association signals by functional studies. Before the GWAS, only one functional study with nucleotide sequence variants has been reported for vascular dementia (Kong et al., 2008). Limited findings in genetic association studies restricted such a functional study with nucleotide sequence variants. A bigger reason might be that the causal genetic variants underlying the associations were difficult to detect because the variants associated with vascular dementia were most likely