GENETIC SUSCEPTIBILITY TO VASCULAR DEMENTIA: A PATHOPHYSIOLOGICAL VIEW

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Genetic studies on vascular dementia (VaD) are scarce. Beyond the monogenic disorders, there is a growing interest in identifying genetic variants associated with sporadic VaD. In 2006, the NINDS-CNS recommended that candidate genes of VaD may include both genes implicated in vascular disease conditions in relation to stroke and cognitive impairment and genes that affect the response of the brain to vascular disease (eg, genes impacting ischemic tolerance, neuronal plasticity, etc.). This presentation will focus on association studies of the second class.

The genes involved in lipid metabolism, especially the apolipoprotein E (APOE) gene (19q13.2), have been the main research object. Several meta-analysis, including one by Sun et al (2015) which consists of 44 studies (2481 cases, 7490 controls), found a significant association between ε4 allele carriers and increased risk of VaD (ε3/ε4+ε4/ε4 versus ε3/ε3: OR=1.82, ε4/ε4 versus ε3/ε3+ε3/ε4: OR=3.12, ε4 versus ε3: OR=1.73, p=0.0001), irrespective of ethnicity. However, no difference of risk for VaD between ε2 and ε3 allele carriers was shown. Two polymorphisms (Q192R and L55M) of another gene, paraoxonase1 (PON1) (7q21.3), were associated with a higher risk of VaD in Indian and French populations, but these findings for Q192R were not confirmed in other three Caucasian studies. The significant associations published between VaD and the polymorphisms C311S of the paraoxonase2 (PON2) (7q21.3), G34995T of the sterol regulatory element binding transcription factor 2 (SREBF2) (22q13) and (CGG)5 of the very low-density lipoprotein receptor (VLDLR) (9p24) genes rely on isolated studies performed in Hungarian, Korean and French populations, respectively.

On the other hand, genes implicated in vascular reactivity have been examined. A 287 bp Alu insertion/deletion polymorphism in the intron 16 of angiotensin I-converting enzyme (ACE) (17q23.3) was proposed as a candidate genetic factor, but two meta-analysis failed to demonstrate association between this polymorphism and both Caucasians (6 studies: 349 cases, 738 controls) and Asians (4 studies: 497 cases, 478 controls). Only one report in Indians (80 cases, 170 controls) observed an increased risk of VaD in D allele carriers (OR=1.52, p<0.05). Furthermore, the variant T235M of angiotensinogen (AGT) (1q42-43) and the haplotype GTC at G-1154A, G-7A, and C13553T of vascular endothelial growth factor (VEGF) (6p12) were associated with VaD in Koreans (207 cases, 207 controls).

Several genes related to inflammation have also been analyzed. The polymorphisms C-889T and C4845T of interleukin (IL)-1α gene (2q14), which are in linkage disequilibrium, increased the risk for VaD in subjects older than 70 years in one of two Taiwanese studies, but this result was not replicated in Japanese-Americans. In contrast, C-511T of IL-1β (2q14) increased the risk for VaD in Japanese-Americans, but not in the Taiwanese. There was heterogeneity between two reports studying the polymorphism G-174C of interleukin-6 gene (IL-6) (7p21). Individuals with G allele were more susceptible to VaD in Italians, whereas those with C allele were more
susceptible to VaD in Indians. A few genetic studies with the tumor necrosis factor-α (TNF-α) (6p21.3) evidenced an association with VaD of two polymorphisms, C-857T in Caucasians and T-1031C in Asians. In addition, an association between VaD and transforming growth factor-β1 (TGF-β1) (19q13.1) was showed in its polymorphism C+29T in two Asian reports, with greater significance in women.

Two Italian studies pointed out a role for genes that participate in extracellular matrix adhesion in VaD. Three promoter loci in the matrix metalloproteinase (MMP) family, G-1607GG of MMP-1 (11q22-q23), -1171 5A/6A of MMP-3 (11q23) and C-1562T of MMP-9 (20q11.2-q13.1) were associated with VaD -and combined genotypes enhanced this association- in one report. The variant K469E of the intracellular adhesion molecule (ICAM) 1 (19p13.3-13.2) was a risk factor for VaD in the other.

Regarding the oxidative stress mechanism, the polymorphisms A140D of glutathione S-transferase ω-1 (GSTO-1) (10q25.1) and A-110C of heat shock protein 70-1 (HSP 70-1) (6p21.3) were found to be associated with VaD in a German and a Taiwanese study, respectively. Moreover, A-15T of α-1-antichymotrypsin (ACT) (14q32.1) was associated with susceptibility to poststroke dementia in one of three small studies in Caucasians.

Finally, genetic associations with other genes not mentioned above are referred to. The variant C677T of methylenetetrahydrofolate reductase (MTHFR) (1p36.3), which influences the level of homocysteine, proved to be associated with VaD in Asians (2 studies: 178 cases, 250 controls), but not in Caucasians (6 studies: 333 cases, 424 controls) or Indians (2 studies: 130 cases, 290 controls) in a recent meta-analysis. Another meta-analysis (4 studies: 278 cases, 456 controls) failed to show association between A-16C of presenilin-1 (PSEN-1) (14q24.3) and VaD. Carriers of an A allele in one of these polymorphisms, G1043A of the insulin-like growth factor-1 receptor (IGF-1R) (15q26.3) or rs4986938 of the estrogen receptor β (ER-β) (14q23.2), increased the risk for VaD in Swedish and Israelis women, respectively.

Relatively few studies focused on the interaction between genes, so-called epistasis. Some examples are the combined polymorphisms HSP 70-1 (A-110C) and TNF-α (T-1031C), TGF-β1 (C+29T) and AGT (T235M), and FAM134B (rs10041159) and TNFRSF19 (rs9317882).

To date, two genomewide association studies (GWAS) for VaD have been carried out. One of them, a retrospective study with Koreans (84 patients, 200 controls), did not detected any genetic association. The other, a prospective study of the Rotterdam cohort in the Netherlands, identified an association with the variant rs12007229 near the androgen receptor gene on the X chromosome (67 patients, 5700 controls) (p=1.3x10^-8). This last association was replicated in a German population (221 cases, 213 controls) (p=2.4x10^-8).

Limitations in association studies on genetic risk factors for VaD are the same mentioned in the NINDS-CNS VCI Harmonizations Standards and include: definition of VaD phenotypes, selection of appropriate controls, selection of candidate genes, and replication on independent samples.
In conclusion, the genetics on sporadic VaD are largely unknown because the effects of multiple genes under various environmental exposures make difficult to discover genetic determinants; and the amount of data on associations between genetic polymorphisms, except for APOE, and VaD is too small to generate convincing results. Further studies with large sample sizes are needed for a better knowledge about genetic risk factors for VaD.

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