UPDATE ON THE GENETICS OF CEREBRAL SMALL VESSEL DISEASE AND STROKE

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Cerebral small-vessel disease (SVD) is a well-known risk cause of stroke, dementia and death. Although traditional risk factors such as hypertension or diabetes mellitus are well known to contribute to the development of cerebral SVD, the exact pathogenesis is still uncertain. Several lines of evidence from family and twin studies support the hypothesis that genetic factors may contribute to SVD pathogenesis. The identification of genetic susceptibility factors for SVD may improve our knowledge of SVD pathogenesis and help to identify new therapeutic targets to reduce the burden of SVD-related cognitive decline and stroke disability.

A number of single gene conditions causing SVD have been described, often characterised by overlapping clinical phenotypes. Other than the well known cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), several other inherited forms of SVD are increasingly described including cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Fabry disease, retinal vasculopathy with cerebral leukodystrophy (RVCL), collagen type IV α1 and α2 gene-related arteriopathy (COL4A1 e COL4A2) and FOXC1 deletion related arteriopathy. Although rare these single-gene disorders are expected to play a crucial role in our understanding of cerebral SVD pathogenesis. However, SVD is in most cases sporadic, underling more complex heritable traits. By candidate gene studies and more recently GWAS technique, several robust associations between genes and occurrence of various features of sporadic cerebral SVD, such as lacunar infarction, intracerebral hemorrhage, or white matter hyperintensities, have been found. However, further studies and improved animal models, that can express the full spectrum of human cerebral SVD, have to be implemented to determine the exact contribute of the genes and functional variants identified in the pathophysiology of vascular damage.