Spine and Neurology
E-Science Information

Journal of Spine and Neurology

Volume 1, Issue 1
Editorial

The Genetic Landscape of Cerebral Small Vessel Disease

Bhagat R*

Department of Neurology, Conemaugh Memorial Medical Center, Johnstown, PA, 15905, USA.

***Corresponding author: Riwaj Bhagat,** Department of Neurology, Conemaugh Memorial Medical Center, Johnstown, PA, 15905, USA, Email: forriwaj@gmail.com; ribhagat@conemaugh.org

Received: October 05, 2023; **Accepted:** October 10, 2023; **Published:** October 17, 2023

Editorial

Cerebral small vessel disease (CSVD) encompasses spectrum of diseases resulting from small blood vessels pathology in the brain [1]. Its neuroimaging markers consist of small subcortical infarcts or lacunar infarcts or silent infarct, white matter hyper-intensities, enlarged perivascular spaces and cerebral micro bleeds [2]. They are the major contributor of stroke and vascular dementia [3]. Traditional vascular risk factors play a vital role as its causative agent. Thereby, management of vascular risk factors has been the corner stone of current medicine to reduce the disability associated with CVSD. On the other side, people can be vulnerable to CSVD secondary to underlying genetics and complex interplay of genetics and environmental factors [4]. The susceptible genes primarily function at the cellular level, within the blood vessels wall, and at the blood brain barrier, affecting the small vessels in the brain [5]. Either way led to chronic hypoperfusion of the white matter from luminal narrowing of small blood vessels, disrupted cerebral auto-regulation, focal vascular subclinical inflammation, perivascular space dysfunction [4]. To date, 35 genetic loci have been associated with sporadic forms of CSVD. (4) Powerful genetic tools like genome wide association studies, candidate gene studies, and transcriptome wide association studies has been used to pinpoint these genes [4]. Continued progress in genetic tools like epigenetic studies will undoubtedly reveal more susceptible genes and provide insights into the biochemical and molecular characteristics of gene-environment interactions [4].

The goal of these intensive genetic studies is to lessen the impact of CSVD or decrease the disability related to it. The impact has become notably apparent, especially with the CHANCE-2 trial. Identification of CYP2C19 gene's loss of function affects the metabolization of clopidogrel (P2Y12 inhibitor) has introduced ticagrelor. When combined with aspirin, ticagrelor serves as a more effective strategy for secondary stroke prevention in individuals at high-risk transient ischemic attack or minor stroke [5]. Likewise, stroke genetic score has recently been developed that can effectively predict ischemic stroke risk across various ethnic groups. The top tertile of GIGASTROKE genetic risk score has higher risk for acute ischemic stroke (adjusted Hazard ratio 1.35, 95% CI=1.16-1.58) among Europeans and East Asians [6]. Genes like PDE3A and FGA relate to drugs cilostazol and alteplase, while F11, KLKB1, F2, TFPI, and MUT relates to conditions like hereditary angioedema, thromboembolism, and drug like vitamin B12. On these regards, thromboxane A2 receptor antagonist has been proposed as an alternative antiplatelet therapy for stroke prevention and further drug of this class are under development. Similarly, F11 and F11a inhibitors (such as abelacimab)

are currently under phase 2 trial for primary or secondary stroke prevention. Further, recombinant variant of human activated protein C is under trial for treatment of acute ischemic stroke after thrombolysis and mechanical thrombectomy. Drugs that reduce blood-brain barrier disruption like anfibatide (GPIb alfa anatagonist) are being tested for myocardial infarction [6]. Other emerging strategies include angiotensin II receptor blocker like candesartan which modulates extracellular matrix accumulation and improves cerebral blood flow in CARASIL mice model. Likewise, strategies targeting NOTCH3 has shown too effective in mouse models [7]. These pharmacogenomics approach helps to tailor drug treatments based on genetic profile of an individual and allows providing "personalized medicine".

Vascular cognitive impairment and dementia and Alzheimer's dementia is other significant disability associated with CSVD. Cerebral amyloid angiopathy related diseases with susceptible genes APOE2, and APOE4 are strongly associated with both dementia and lobar hemorrhage [4]. Development of anti-amyloid immunotherapy for Alzheimer's dementia has been accelerated lately with two FDA approved drugs (aducanumab and lecanemab). However, it came with a cost of multiple individuals affected by amyloid-related imaging abnormalities (ARIA) secondary to immunotherapy, especially among APOPE4 gene carrying individuals or individual with cerebral amyloid angiopathy [8]. Thereby, anti-amyloid immunotherapy at present possesses concerns for its safety.

While genetic studies are set to provide significant leap in individualized patient care with CSVD, yet it has its several limitations. The center of CSVD still lies in its neuroimaging markers and markers beyond magnetic resonance imaging of brain is required for accurate genetic studies. Inclusion of multi-ancestry must be focused on the upcoming studies to better learn about the biological pathways and phenotypes.

Declarations

Acknowledgement: None
Conflict of Interest: None
Funding: None

References:

1. Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 9(7): 689-701.
2. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, et al. (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12(8): 822-838.
3. Debette S, Schilling S, Duperron M-G, Larsson SC, Markus HS (2019) Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. JAMA Neurol 76(1): 81-94.
4. Bhagat R, Marini S and Romero JR (2023) Genetic considerations in cerebral small vessel diseases. Front Neurol 14:1080168
5. Liu H, Jing J, Wang A, Xu Q, Meng X, et al. (2023) Genotype-guided dual antiplatelet therapy in minor Stroke or transient ischemic attack with a single small subcortical infarction. Neurology 100(16): e1643-e54.
6. Mishra A, Malik R, Hachiya T, Jürgenson T, Namba S, et al. (2022) Stroke genetics informs drug discovery and risk prediction across ancestries. Nature 611(7934): 115-123.
7. Inoue Y, Shue F, Bu G, Kanekiyo T (2023) Pathophysiology and probable etiology of cerebral small vessel disease in vascular dementia and Alzheimer's disease. Mol Neurodegener 18(1): 1-22.

8. Sveikata L, Charidimou A, Viswanathan A (2022) Vessels sing their ARIAs: The role of vascular amyloid in the age of aducanumab. Stroke. 53(1): 298-302.