A multidisciplinary approach to understanding the influence of HDAC9 variants on STROKE, and developing therapeutics based on HDAC9 inhibition

Recently, as part of the WTCCC2 Ischaemic Stroke Study, we identified the first novel genetic association for common ischaemic stroke. This variant (RS2017595) is in the HDAC9 gene and is associated with an increased risk of large artery stroke, which occurs secondary to cerebral atherosclerosis, but not other types of stroke.(1) Further large analyses have confirmed this association.(2) We have shown this gene is up regulated in pathological tissue from patients.(3) The mechanisms by which variation in HDAC9 increases atherosclerosis and stroke are uncertain but HDAC9 is a deacetylase and possible mechanisms could include alterations in chromatin packing and epigenetic influences. Intriguingly a large epidemiological study suggests the non-specific HDAC9 inhibitor sodium valproate reduces stroke risk.(4) This offers the exciting possibly that HDAC9 inhibition may provide a novel treatment for stroke prevention. Here, we proposed to study the human HDAC9 in stroke using a multidisciplinary approach. The 3D structures of human wild-type HDAC9 and the RS2017595 variant will be predicted by homology modelling method based on X-ray structures of homologous proteins such as human HDAC7 and HDAC4 (5). The possible effects that the genetic variant may exert on the structure and dynamics of HDAC9 will be investigated by structural analysis and molecular dynamics simulations of both the wild-type and the variant (6). To further understand the mechanism through which the HDAC9 variant increases stroke risk, we will focus on ligand recognition by HDAC9 and its consequence in stroke phenotype (7, 8). Predicted ligands will be validated in cell-based assays. We will establish systematic structure-activity relationships for HDAC9-based stroke response, by introducing residue mutations and ligand analogues in computation followed by experimental tests. Collectively, we will elucidate the mechanism how HDAC9 variant alters structure and function, and use this information to develop novel therapeutic agents for stroke prevention.

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Contact Information:

Dr Hao Fan, Principal Investigator, BII, A*STAR (fanh@bii.a-star.edu.sg)
For Hao Fan's webpage at BII, A*STAR:
http://www.bii.a-star.edu.sg/research/bmad/sldd.php

Prof Hugh Markus, Department of Clinical Neurosciences, University of Cambridge (hsm32@medschl.cam.ac.uk)
For Hugh Markus's Cambridge Neuroscience webpage:
http://www.neuroscience.cam.ac.uk/directory/profile.php?hsm32