Identification and functional analysis of novel human-specific small vessel disease proteins

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Research Abstract
ABSTRACT Cerebral small vessel disease (SVD) is a common but untreatable condition identified over a half century ago. Affecting over half of the elderly in the United States, SVD leads to stroke and dementia and remains a significant public health concern. We study a genetic cause of SVD: CADASIL. CADASIL is the most common monogenic form of SVD and results from cysteine-altering mutations in the vascular smooth muscle protein NOTCH3. To understand mechanisms of SVD, mouse models of CADASIL have been generated with modest success. Though CADASIL models demonstrate accumulation of NOTCH3, they lack critical signs and pathological features of the disorder. For example, mutant NOTCH3 mice do not

develop stroke or cognitive dysfunction, nor do they develop vascular smooth muscle loss and arterial thickening. The overall objective of this work is to gain insight regarding human CADASIL pathology that can be used to improve CADASIL mouse models. We hypothesize that a set of vascular proteins accumulate in CADASIL patients that are not expressed in mouse blood vessels. If true, then transgenic expression of these proteins has the potential to improve mouse models. Our experimental strategy includes: 1) screening the Human Protein Atlas for new brain vascular markers; 2) identifying human specific markers by comparative immunohistochemistry; 3) identification of new human specific markers that colocalize with conformationally altered NOTCH3 in human tissue; 4) experimental analysis of human-specific CADASIL proteins in cell culture for functions relevant to CADASIL. In preliminary work aimed to prove feasibility, we downloaded and analyzed over 150,000 images from the Human Protein Atlas in search of novel vascular markers. We then used immunohistochemistry to define two new human specific vascular proteins that co-localize with mutant NOTCH3 protein in CADASIL. Ultimately, this project will identify new proteins important in the genesis of CADASIL; it is likely that absence of these proteins in mice may explain the limited phenotypes of current preclinical SVD models.

Further information available at:

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