Letter by Moccia et al Regarding Article, “Archetypal Arg169Cys Mutation in NOTCH3 Does Not Drive the Pathogenesis in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leucoencephalopathy via a Loss-of-Function Mechanism”

To the Editor:

We read with extreme interest the study by Cognat et al1 investigating the in vivo functionality of the Arg169Cys archetypal mutation in NOTCH3. In particular, they broaden our knowledge on cerebral autosomal-dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) mechanism showing that white matter pathology was only found in mice with the CADASIL mutation, despite normal NOTCH3 signaling and, thus, argued against a loss of function as a general driving mechanism for white matter lesions in CADASIL. In addition, they stressed the fact that the loss of NOTCH3 function does not cause CADASIL phenotypic manifestations. As an additional piece of evidence, they quoted the recent report by Rutten et al2 describing a NOTCH3 nonsense mutation in exon 3 (c.307C>T, p.R103X) in 2 siblings. One of them presented a clinical picture suggestive of CADASIL, the other one was symptom free, with magnetic resonance and skin biopsy findings not typical of CADASIL. Therefore, it was suggested that hypomorphic NOTCH3 mutations do not cause CADASIL. However, significant efforts have been made to clarify whether hypomorphic NOTCH3 mutations are neutral polymorphisms or causative for a distinct cerebrovascular entity, and large consecutive series have strongly been encouraged. In this view, we described the same nonsense mutation in 1 patient with parkinsonism, cognitive impairment, and typical CADASIL neuroimaging features.4 Moreover, the family history was positive for cerebral ischemic events in at least 2 different generations and the mutation clearly segregates with the disease. Considering that the molecular mechanisms leading to the development of NOTCH3-related diseases remains elusive, it is possible to hypothesize the presence of different mutations underlying phenotype heterogeneity. Therefore, the p.Arg103X nonsense mutation could be responsible of a CADASIL-like syndrome with reduced penetrance and increased clinical heterogeneity and might play a greater role in ischemic stroke than previously thought, with a spectrum of CADASIL-like disorders because of NOTCH3 variants.

In conclusion, it is important to remember that CADASIL is defined by several specific symptoms and traits and must affect the brain and demonstrate autosomal dominant inheritance. In addition, the finding of hypomorphic NOTCH3 alleles in patients with a clinical picture suggestive of CADASIL should stimulate the debate on different possible pathways in NOTCH-related diseases.

Disclosures

None.

Marcello Moccia, MD
Department of Neuroscience, Reproductive Science and Odontostomatologia
Federico II University
Naples, Italy

Silvana Penco, MSc, PhD
Department of Laboratory Medicine, Medical Genetics
Niguarda Ca’ Granda Hospital
Milan, Italy

Paolo Barone, MD, PhD
Center for Neurodegenerative Diseases (CEMAND), Neuroscience Section, Department of Medicine
University of Salerno
Salerno, Italy.


(Stroke. 2014;45:e128.)
© 2014 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org
DOI: 10.1161/STROKEAHA.114.005593
Letter by Moccia et al Regarding Article, "Archetypal Arg169Cys Mutation in NOTCH3 Does Not Drive the Pathogenesis in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leucoencephalopathy via a Loss-of-Function Mechanism"

Marcello Moccia, Silvana Penco and Paolo Barone

Stroke. 2014;45:e128; originally published online May 27, 2014; doi: 10.1161/STROKEAHA.114.005593

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/7/e128

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/