Case report. Cervical artery dissection is an important cause of stroke, especially in younger individuals. Most cases appear to be sporadic, but rare monogenic conditions can cause dissection, such as vascular Ehlers-Danlos syndrome.1 The wider use of sequencing techniques in clinical diagnosis of genetic disorders has made it more realistic to test for multiple genes in potential monogenic stroke conditions. Here, we report the case of a cervical artery dissection in a SMAD-4 mutation carrier.

This patient is a 48-year-old man with a history of hypertension, aortic root dilation that led to surgical replacement at age 41, and a subsequent right common iliac artery aneurysm. He had experienced several episodes of mild epistaxis, but none had needed specific treatment. There was no personal history of gastrointestinal symptoms or bleeding.

His family history was suggestive of juvenile polyposis syndrome (JPS). Several colon polyps were diagnosed in his mother; his brother had experienced several episodes of serious digestive bleeding related to multiple colon polyps. The patient has 2 sons and 2 daughters. At age 4, his eldest daughter has had an episode of rectal bleeding that led to the diagnosis of colon polyps; his youngest son has experienced an episode of epistaxis. His youngest daughter and eldest son are doing well.

Physical examination showed slightly translucent chest skin and a possible small telangiectasia in his right cheek. There were no other skin abnormalities; joint examination was unremarkable; heart and neck auscultation was normal.

Because of the aortic and iliac arteriopathy, cerebral CT angiogram was performed to screen for cerebral artery abnormalities. The angiogram revealed 3 findings (figure): firstly, abnormal increased tortuosity of both internal carotids; secondly, mild arterial diameter irregularities; and thirdly, a short but distinct dissection flap in the V2 segment of the right vertebral artery, at the level of C5. The patient had no history of stroke, neck pain, or trauma; therefore, it was not possible to date the dissection. No intracranial abnormality, aneurysm, or arteriovenous malformation was found.

Owing to his multifocal arteriopathy, genetic screening was performed using an arteriopathy gene panel. A heterozygous, loss-of-function, nonsense mutation was found in exon 10 of the SMAD-4 gene (c.1336C>T; protein change p.Gln446Ter). This Class 4, likely pathogenic mutation, is predicted to create a premature termination codon, resulting in a truncated protein. This mutation has not been identified within in-house databases or in individuals from the Exome Aggregation Consortium project, although a similar c.1333C>T mutation (p.Arg445Ter) has been reported in a patient with JPS, aortic root dilation, and mitral valvulopathy.2 Segregation studies have been advised to confirm pathogenicity via the Clinical Genetics department.

Discussion. This case illustrates that cervical artery abnormal tortuosity and dissection can occur as part of a systemic arteriopathy due to SMAD-4 mutation.

SMAD-4 protein is involved in the transforming growth factor beta signaling pathway. The chromosomal location of the SMAD-4 gene is 18q21.1. Several SMAD-4 loss-of-function mutations have been described among patients with JPS and hereditary hemorrhagic telangiectasia (HHT), 2 genetically heterogeneous autosomal dominant disorders.

JPS, occurring in approximately 1/100,000 individuals, is characterized by early-onset colorectal and gastric polyph formation, with a subsequent risk of digestive bleeding, anemia, and malignancy. SMAD-4 and BMPRIA mutations are the most frequently found. The largest JPS series to date has found SMAD-4 mutations in 21% of cases.3

HHT, affecting approximately 1/5,000–10,000 individuals, is a multifocal vascular dysplasia, with skin and mucosal telangiectases and visceral arteriovenous malformations (lung, brain, and liver). Recurrent epistaxis is the most frequent manifestation. The most frequently involved genes are ACVRL1, ENG, and SMAD-4. Patient series suggest that SMAD-4 mutations account for 2% of cases.4 JPS and HHT can be associated in the same individual, usually in case of a SMAD-4 mutation.

Cardiovascular abnormalities have been described in SMAD-4 mutation carriers. Thoracic aortopathy
(aortic root dilation) has been reported in 9%–37% of patients5–7; heart valve regurgitation in 6%,5 and intracranial aneurysm in 3%.5 However, involvement of the cervical and iliac arteries does not seem to be a typical feature of this condition.

This report extends the number of monogenic causes of cervical artery dissection and highlights that SMAD-4 mutations can cause systemic multifocal arteriopathy, involving not only the aortic root but also the cervical and iliac arteries. Vascular imaging of the arterial tree is advised in at-risk individuals.

From the Department of Stroke Medicine (E.W., P.M., H.S.M.) and Department of Genetics (S.M.), Addenbrooke’s Hospital, Cambridge, United Kingdom.

Author contributions: Dr. Martin collected clinical data during clinical consultations with the patient. Dr. Wiener reviewed the literature and wrote the case. Pr. Markus reviewed the article. Dr. Mehta conducted the genetic analysis of the patient.

Study funding: No targeted funding reported.

Disclosure: E. Wiener and P. Martin report no disclosures. S. Mehta receives publishing royalties from Hodder Arnold. H.S. Markus has served on the editorial boards of the International Journal of Stroke, Clinical Neurology and Neurosurgery, BMC Medicine, and Frontiers in Neurology; receives publishing royalties from Oxford University Press; has been a consultant for Astra Zeneca; has received reimbursement from Astra Zeneca for teaching session to employees; and has received research support from Medical Research Council Experimental Medicine Grant, National Institute for Health Research, Stroke Association, EU, Wellcome Trust, The British Heart Foundation, and Alzheimer Research UK. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Received June 26, 2017. Accepted in final form July 25, 2017.

Correspondence to Dr. Wiener: ew498@medschl.cam.ac.uk

Cervical artery dissection and iliac artery aneurysm in an SMAD-4 mutation carrier
Emmanuel Wiener, Peter Martin, Sarju Mehta, et al.
Neurol Genet 2017;3;
DOI 10.1212/NXG.0000000000000191

This information is current as of September 25, 2017

Updated Information & Services
including high resolution figures, can be found at:
http://ng.neurology.org/content/3/5/e191.full.html

References
This article cites 7 articles, 1 of which you can access for free at:
http://ng.neurology.org/content/3/5/e191.full.html#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Genetics
http://ng.neurology.org/cgi/collection/all_genetics
Carotid artery dissection
http://ng.neurology.org/cgi/collection/carotid_artery_dissection
Stroke in young adults
http://ng.neurology.org/cgi/collection/stroke_in_young_adults

Permissions & Licensing
Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at:
http://ng.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://ng.neurology.org/misc/addir.xhtml#reprintsus