Mosaic Copy Number Variation in a Patient with Cerebral and Pulmonary Arteriovenous Malformations and Recurrent Epistaxis

Sharri S. Cyrus,[a] Michelle L. Kluge,[a] Cherisse A. Marcou,[a] Erik C. Thorland,[a] Vivek N. Iyer,[b] and Linnea M. Baudhuin [a,*]

[a]Division of Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, United States; [b]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, United States.

* Address correspondence to this author at: Division of Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. Tel 507-538-0078; e-mail Baudhuin.Linnea@mayo.edu.

CASE DESCRIPTION

A 45-year-old female presented to internal medicine for evaluation and treatment of a cerebral arteriovenous malformation (AVM) with associated partial seizures. The patient reported her first seizure in the year prior to presentation and subsequent brain imaging confirmed the presence of an inferior right temporal cerebral AVM roughly 2.5 cm in diameter. She subsequently underwent definitive treatment of the AVM in a staged manner with initial partial coil embolization and stereotactic guided Gamma Knife radiosurgery performed 1 month later.

In addition to cerebral AVM, her medical history was significant for spontaneous and recurrent nosebleeds (epistaxis) since childhood. Epistaxis occurred multiple times a day with each episode lasting approximately 5 min and not typically gushing in nature. Her epistaxis severity score was calculated at 5.25 (moderate epistaxis severity) (1) and she had previously received multiple nasal cautery treatments. Nasal examination demonstrated significant generalized erythema and anterior rhinoscopy showed bilateral nasal telangiectasias that were treated with bipolar cauterization. Additional telangiectasias were noted, one each on the tip of her tongue and her lower lip.

During the preoperative work-up for possible surgery of the cerebral AVM, a chest X-ray showed nodular densities, suggestive of pulmonary AVMs. Further pulmonary function testing showed normal spirometry values with a reduced diffusion capacity. Subsequent computed tomography (CT) pulmonary angiography showed 2 adjacent middle lobe AVMs and she underwent 2 successful embolization procedures. Notably no other AVMs were found by abdominal CT.

The presence of spontaneous and recurrent epistaxis, along with mucocutaneous telangiectasias and the AVMs noted in her brain and lung, raised the possibility of hereditary hemorrhagic telangiectasia (HHT). A detailed family history obtained was notable for the absence of epistaxis or other manifestations of HHT in her parents (both of whom were deceased at the time of her presentation) as well as her 6 siblings. A blood sample was obtained and an external HHT and a vascular malformation next-generation sequencing (NGS) gene panel was ordered interrogating the genes *ACVRL1*, *ENG*, *EPHB4*, *GDF2*, *RASA1*, and *SMAD4*, but the results were negative. A subsequent in-house gene panel was ordered: the Mayo Clinic HHT and Vascular Malformation Gene Panel, which interrogated the genes outlined previously in addition to *BMPR2*, *CCM2*, *GLMN*, *KRIT1*, *PDCD10*, and *TEK*. This was performed using the IDT xGEN Exome targeted cocapture for library preparation, and Illumina NovaSeq6000 for sequencing. Initial bioinformatics analysis of the sequencing results did not flag any causative variants, but manual inspection of the copy number data raised suspicion of an intragenic *ENG* duplication (Fig. 1).

https://doi.org/10.1093/clinchem/hvae101

QUESTIONS TO CONSIDER	
1.	What is the most common hereditary disorder that presents with spontaneous and recurrent epistaxis along with AVMs in multiple organ systems?
2.	What should be considered in a patient with an established clinical diagnosis for a hereditary disorder, but negative genetic results and no family history?
3.	Which genetic testing methods are advantageous for detecting mosaicism?

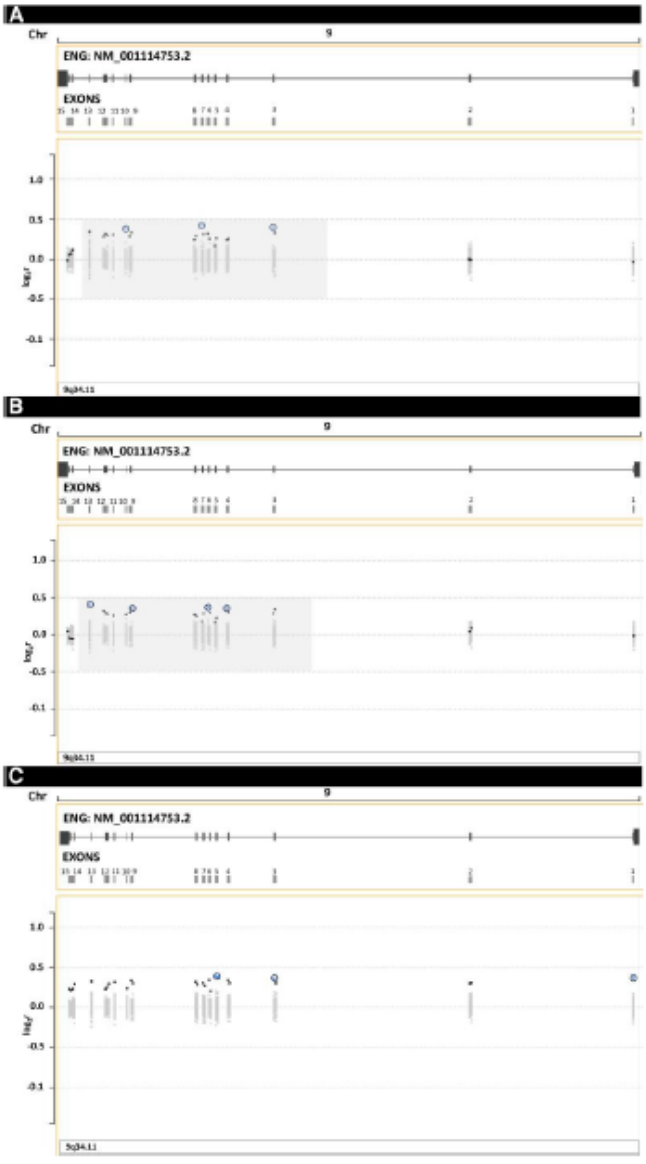

Fig. 1. *ENG* copy number plot from NGS data. (A), Original NGS run (patient sample); (B), Repeat NGS run (patient sample); (C), Repeat NGS run (mosaic full gene *ENG* duplication control sample). *ENG* mosaic duplication of exons 3–13 is shown in the shaded rectangles for (A) and (B). The squares represent the $\log_2$ ratio ($\log_2$r) values of the probes for the patient sample. The circled squares are indicative of values above the set duplication threshold for $\log_2$r and z-score. Note that for A and B, the probes in exons 3–13 have higher $\log_2$r values, with some probes indicating a duplication, compared to probes in exons 1–2, and 14–15, which hover around the 0.0. Lighter colored squares are representative of $\log_2$r values from samples (peers) on the same run. Color figure available at https://academic.oup.com/clinchem

https://doi.org/10.1093/clinchem/hvae101

REFERENCE

1. Hoag JB, Terry P, Mitchell S, Reh D, Merlo CA. An epistaxis severity score for hereditary hemorrhagic telangiectasia. Laryngoscope 2010;120:838–43..

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the November 2024 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/70/11 and follow the link to the Clinical Case Study and Commentaries.

Educational Centers

If you are associated with an educational center and would like to receive the cases and questions 1 month in advance of publication, please email clinchemed@myadlm.org.

All previous Clinical Case Studies can be accessed and downloaded online at https://www.myadlm.org/science-and-research/clinical-chemistry/clinical-case-studies.

---

https://doi.org/10.1093/clinchem/hvae101