



Received: 26-04-2026
Accepted: 06-05-2026

ISSN: 2583-049X

Letter to the Editor

There is no Evidence that Fragile-X Syndrome Due to Low CGG Repeat Expansions in FMR1 Manifests Phenotypically with Cerebral Aneurysms

Josef Finsterer

Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

DOI: <https://doi.org/10.62225/2583049X.2026.6.3.6309>

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Papadopoulos *et al.* about a man in his thirties who was diagnosed with fragile syndrome (FXS) due to a CGG expansion of 280-300 repeats in the FMR1 gene, which was only 10% methylated and produced 80% of normal levels of Fragile X mental retardation-1 (FMPP) protein ^[1]. The patient phenotypically showed an anxiety disorder and a single syncope and epileptic seizure ^[1]. Examination of the syncope incidentally revealed a fusiform aneurysm, which was successfully treated with implantation of a flow-diverter stent and was completely embolized at six-month follow-up ^[1]. The study is noteworthy, but several points should be discussed.

The first point is that the causal relationship between FXS and the aneurysm has not been proven ^[1]. A cerebral artery aneurysm can generally be primary (genetic) or secondary (acquired). Beyond the index article, there are no other reports of FXS patients with cerebral aneurysms. There is only one report of an FXS patient with an aortic aneurysm, but even in this case the casual association remains unproven ^[2]. Have all secondary and primary causes of cerebral aneurysms been thoroughly excluded? Secondary causes of cerebral aneurysm include smoking, arterial hypertension, traumatic brain injury, cocaine addiction or alcohol abuse ^[3]. The primary causes of a cerebral aneurysm include polycystic kidney disease, aortic coarctation, Ehlers-Danlos syndrome or Marfan syndrome. Was the family history positive for cerebral aneurysms, especially in the mother and grandmother of the index patient, who also carried a CGG expansion in the FMR1 gene ^[1]? Another argument against a causal relationship between FXS and the aneurysm is the fact that the patient manifested only mildly and had only a small CGG expansion.

The second point is that there is no evidence that the seizure is causally related to the aneurysm ^[1]. Seizures are known to be one of the most common clinical manifestations of FXS, along with an elongated face, protruding ears, pectus excavatum, macroorchidism and joint laxity, intellectual disability, learning disability and autism spectrum disorder ^[4].

The third point is that syncope was attributed to anxiety disorder ^[1]. What then was the reason why the patient underwent cerebral angiography anyway? Were other examinations performed to clarify the cause of the syncope? Since FXS is often associated with seizures ^[5] and the patient had a previous seizure ^[1], we should know whether epilepsy was adequately ruled out as the cause of syncope.

To summarize, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the message of the study. Currently, there is no evidence that fragile X syndrome manifests phenotypically with cerebral aneurysms. In patients with FXS and a cerebral aneurysm, other causes for the formation of the aneurysm should be considered. In order to clarify whether or not FXS manifests phenotypically with intracerebral aneurysms, these patients must be systematically examined for the presence of cerebral aneurysms.

Declarations**Ethical Approval:** Not applicable.**Consent to Participation:** Not applicable.**Consent for Publication:** Not applicable.**Funding:** None received.**Availability of Data and Material:** All data are available from the corresponding author.**Completing Interests:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.**Author Contribution:** JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval. FS and CS: contributed to literature search, discussion, correction, and final approval.**Acknowledgements:** None.**Keywords:** Fragile-X Syndrome, CGG Expansion, FMR1 Gene, Cerebral Aneurysm, Coiling**References**

1. Papadopoulos E, Abrimian A, Zarzour H, Hagerman RJ, Schmidt RF. Spontaneous distal middle cerebral artery aneurysm in a young male with full mutation of the fragile X syndrome with a high-functioning phenotype: Illustrative case. *J Neurosurg Case Lessons*, Mar 10, 2025; 9(10):CASE24889. Doi: 10.3171/CASE24889
2. Berry-Kravis E, Filipink RA, Frye RE, Golla S, Morris SM, Andrews H, *et al.* FORWARD Consortium. Seizures in Fragile X Syndrome: Associations and Longitudinal Analysis of a Large Clinic-Based Cohort. *Front Pediatr*, Dec 30, 2021; 9:736255. Doi: 10.3389/fped.2021.736255
3. Fennell VS, Kalani MY, Atwal G, Martirosyan NL, Spetzler RF. Biology of Saccular Cerebral Aneurysms: A Review of Current Understanding and Future Directions. *Front Surg*, Jul 25, 2016; 3:43. Doi: 10.3389/fsurg.2016.00043
4. Lewis S, DePass A, Hagerman RJ, Lozano R. Case Reports of Aortic Aneurism in Fragile X Syndrome. *Genes (Basel)*, Aug 30, 2022; 13(9):1560. Doi: 10.3390/genes13091560
5. Incorpora G, Sorge G, Sorge A, Pavone L. Epilepsy in fragile X syndrome. *Brain Dev*, Dec 2002; 24(8):766-769. Doi: 10.1016/s0387-7604(02)00102-x