



# Familial Intracranial Aneurysm Requires Not Only Whole-Exome Sequencing, But Also Mitochondrial DNA Sequencing

Josef Finsterer

Neurology & Neurophysiology Center, Vienna, Austria

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I eagerly read the article by Song et al. [1] about a study on patients with familial intracranial aneurysms (FIAs) by means of whole-exome sequencing (WES), wherein three, two, and two individuals from families A, B, and C carried the variants c.1315G>A in *PLOD3*, c.968C>T in *NTM*, and c.58C>T in *CHST14*, respectively. The study is appealing, but raises concerns that require discussion.

The main limitation of the study is that the mitochondrial DNA (mtDNA) was not sequenced. Since WES does not cover the mtDNA, and as aneurysm formation can be a phenotypic feature of mitochondrial disorders (MIDs) [2], and finally, since MIDs can be caused by mutations in genes located on the mtDNA, it is crucial that patients with FIA undergo sequencing of the entire mtDNA, particularly if WES is non-informative or if there is a maternal trait of inheritance. Although aneurysm formation in MIDs has been particularly reported in the extra-cranial arteries [3], single MID patients with intra-cranial aneurysm formation have been reported [2]. Several speculations have been raised to explain aneurysm formation in MIDs [2]. First, aneurysm formation

results from a reduction of the vascular tone, which may be due to reduced nitric oxide (NO) production as a result of decreased NO-synthase (NOS), increased dimethyl-arginine, or reduced availability of the NO precursors L-arginine or L-citrulline [2]. The polymorphism c.786T>C in the *eNOS* gene has even been associated with aneurysm formation in the Asian population [4]. It is also conceivable that the vascular tone is reduced due to reduced sympathetic drive following autonomic involvement in MIDs. Second, aneurysm formation results from vessel wall inflammation due to increased pro-inflammatory cytokines, such as interleukin (IL)-6 or IL-10 [2]. Both are suspected of being vital to intracranial aneurysm formation [2]. In accordance with these findings is the association of the c.1082G>A polymorphism in the *IL-10* gene with aneurysm formation in the Chinese population [5]. A third pathophysiological mechanism explaining aneurysm formation is mitochondrial apoptosis triggered by respiratory chain dysfunction, which secondarily leads to oxidative stress and ceramide synthase-6 activation [6]. Ceramide synthase-6 activation leads to ceramide accumulation and cytochrome-c release via the outer mitochondrial membrane [6]. Cytochrome-c release activates caspase-9, which is the initial step and trigger of intrinsic apoptosis [6]. Accordingly, intrinsic, mitochondrial-dependent apoptosis of intramural cells in the aorta has been associated with aneurysm formation [7].

Other causative factors that should not be neglected in the work-up of FIAs are mutations in *PPIL4*, *RBF213*, *ANGPTL6*, *SMAD3*, *COL22A1*, *PCNT*, *ARHGEF17*, *LOXL2*, *STAT1*, *THSD1*, *ELN*, *PKD1*, *PCNT*, *COL4A1*, and *ANIB4*, angiotensin-converting enzyme gene polymorphisms [8], endoglin polymorphisms [9], apolipoprotein-E genotype, myeloperoxidase pathways [10], and the balance of the regional matrix metalloproteinase family.

Since aneurysms may not only occur in the intra-cranial arteries, but also in other vascular areas, and may be associated with cyst formation in various organs, particularly the kidneys, it is crucial for patients with intracranial aneurysms to be comprehensively investigated for multisystem involvement.

Overall, the elegant study has limitations that challenge the results and their interpretation. As mtDNA variants play major roles in aneurysm generation, FIA work-up should include sequencing of the entire mtDNA to avoid missing

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**Corresponding author:** Josef Finsterer, MD, PhD, Neurology & Neurophysiology Center, Postfach 20, 1180 Vienna, Austria.

• E-mail: [fifigs1@yahoo.de](mailto:fifigs1@yahoo.de)

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Letter to the Editor

a causative variant, particularly in cases with maternal inheritance.

### Conflicts of Interest

The author has no potential conflicts of interest to disclose.

### ORCID iD

Josef Finsterer

<https://orcid.org/0000-0003-2839-7305>

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