Review

Gene therapy for intracranial aneurysms: systemic review

Malia McAvoy,[1] Buddy Ratner,[2] Manuel J Ferreira,[1] Michael R Levitt [3]

[1]Neurological Surgery, University of Washington, Seattle, Washington, USA
[2]Chemical Engineering, Bioengineering, Materials Science, and Engineering, University of Washington, Seattle, Washington, USA
[3]Neurological Surgery, Radiology, Mechanical Engineering, Neurology, Stroke & Applied Neuroscience Center, University of Washington, Seattle, WA, USA

Correspondence to
Dr Michael R Levitt; mlevitt@uw.edu

Received 12 August 2024
Accepted 15 September 2024

To cite: McAvoy M, Ratner B, Ferreira MJ, *et al*. *J NeuroIntervent Surg* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnis-2024-021843

ABSTRACT

Treatment of intracranial aneurysms is currently limited to invasive surgical and endovascular modalities, and some aneurysms are not treatable with these methods. Identification and targeting of specific molecular pathways involved in the pathogenesis of aneurysms may improve outcomes. Low frequency somatic variants found in cancer related genes have been linked to intracranial aneurysm development. In particular, mutations in the *PDGFRB* gene lead to constitutively activated ERK and nuclear factor κB signaling pathways, which can be targeted with tyrosine kinase inhibitors. In this review, we describe how low frequency somatic variants in oncogenic and other genes affect the pathogenesis of aneurysm development, with a focus on gene therapy applications, such as endovascular in situ delivery of chemotherapeutics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Most studies of the genetic mechanisms of intracranial aneurysm pathogenesis have focused on hereditary and common mutations, which account for only a small fraction of all intracranial aneurysms.
⇒ There is increasing evidence that rare variants could be the primary drivers of intracranial aneurysms.

WHAT THIS STUDY ADDS

⇒ This study provides a framework for the neurointerventionalist to understand the current insights provided by whole exome sequencing studies into the pathogenesis of intracranial aneurysm formation, and potential avenues for future treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Through consolidation of the knowledge gained from whole exome sequencing studies, we discuss a path forward for the field of neurointervention.
⇒ Specifically, we discuss the targetable signaling pathways involved in the pathogenesis of intracranial aneurysms, the role of endovascular biopsy for identification of somatic variants, and the potential for local delivery of genetic therapeutics using endovascular devices.

INTRODUCTION

The wide range of endovascular and surgical options for intracranial aneurysms (IAs) has enabled our field to create a personalized approach to treat each patient's IA according to individual morphology and overall patient health.[1] However, certain IAs, such as vertebrobasilar fusiform aneurysms, remain challenging to treat, with a median survival of 9 months[2] and poor surgical or endovascular outcomes. Endovascular treatment of these IAs with stent assisted coils and flow diverters may be associated with mortality rates as high as 67% due to intraprocedural or postprocedural stroke, rupture, and implant thrombosis.[2] Disease modulating treatments could provide improved outcomes for such patients.

The neurointerventional field has thus far focused primarily on endovascular interventions, addressing the structural consequences of the disease rather than its biological pathogenesis. There remains a significant need to develop new personalized therapeutics to improve outcomes. To best serve these patients, our field could adopt an oncologic approach, targeting IA pathogenesis.

Hereditary IAs account for only 10% of all IA cases and therefore attention has been drawn to detect mutations that occur in non-germline, or somatic, cells.[3] Genome wide association studies (GWAS) have identified several common risk loci associated with IAs; however, GWAS by design are unable to identify rare variants with large effect in IA formation. Low frequency somatic variants corresponding to genes known to be important in cancer development have been detected in IAs, and there are already potential chemotherapies targeting these pathways.[4] Here, our objective was to review the latest insights from whole exome sequencing of IAs, including a discussion of somatic activating variants predicted to drive the pathogenesis of IAs, as well as future opportunities for gene therapy treatment, including personalized therapies and drug delivery devices.

METHODS

The Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) guidelines were followed for the reporting of this review (figure 1). PubMed, EMBASE, Cochrane, and Web of Science were searched from June 2014 to June 2024. The following MeSH terms were used: 'gene therapy', 'intracranial aneurysms' or 'cerebral aneurysms', and 'sequencing' or 'exome sequencing'. Genetic variants of interest were those demonstrated to be somatic, found in IA tissue, and of low allele frequency. Exclusion criteria were: familial variants,

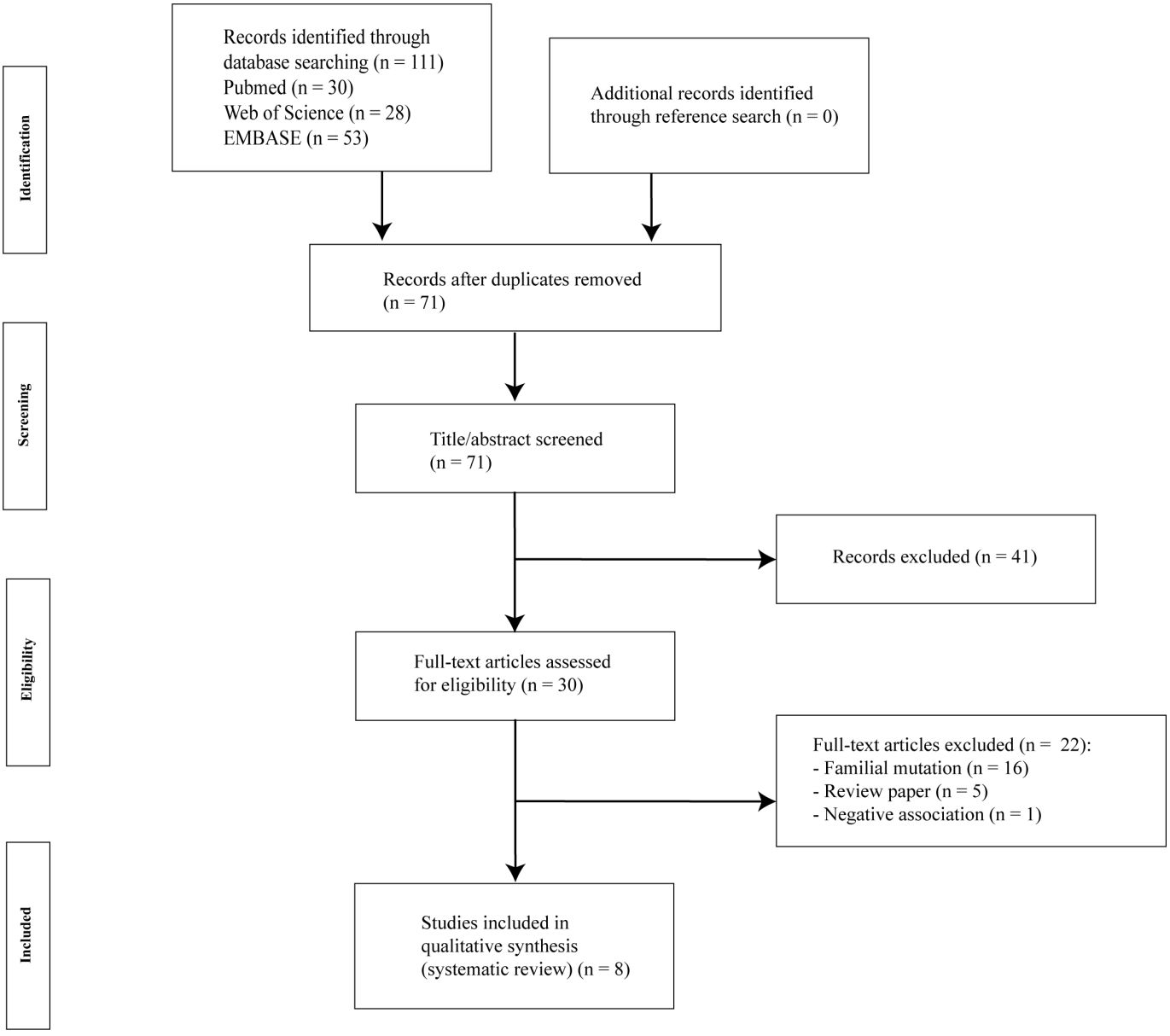

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of articles searched and excluded at each stage of the literature search after screening titles, abstracts, and full texts.

from non-aneurysmal tissue, including peripheral blood, and high frequency variants (eg, determined by GWAS). The reports were screened by one reviewer (MM) for the somatic variant of interest, number of patients, molecular pathway of the gene, and potential therapeutic targets of the somatic variant. This review was not registered. A review protocol was not prepared.

RESULTS

Eight articles describing a total of 741 patients with IA tissue were identified (table 1). The data from this literature search are openly available (10.6084/m9.figshare.26533696). Two articles studied tissue from a single patient. One article[5] described 16 total somatic variants, focusing on six variants common to both saccular and fusiform IAs. The remaining articles focused on a single gene. Four studies[5–8] described somatic variants in cancer related genes whereas the other four studies[9–12] described somatic variants in angiogenesis or vascular wall related genes.

DISCUSSION

Low frequency somatic variants in intracranial aneurysms

Until recently, genetic causes of IAs have largely focused on hereditary gene mutations, or common (high frequency) alleles identified through GWAS. We know that the risk of IAs is higher among family members with a history of IA or individuals with certain hereditary genetic disorders, such as autosomal dominant kidney disease or Ehlers–Danlos syndrome.[13] High frequency variants identified through GWAS have included *SOX17* (rs9298506 and rs10958409), *EDNRA* (rs6841581), *CDKN2B-AS1* (rs10757278), *COL1A2* (rs42524), *COL3A1* (rs1800255), *HSPG2* (rs3767137), *SERPINA3* (rs4934), and *VCAN* (rs251124 and rs173686).[13 14] Although many of these common variants have been identified, there has been little overlap with development of IAs.

Over the past decade, more evidence has suggested that low frequency variants may have a large role in common disease phenotypes.[15 16] There are currently no variants described that

Table 1 Systematic review of somatic variants in the pathogenesis of cerebral aneurysms

Study	Genes	No of patients	Aneurysm morphology	Molecular pathway	Therapeutic intervention
Hao *et al* (2024)[8]	*PDGFRB*	2	Fusiform	Promoted inflammatory related vascular smooth muscle cell phenotype and JAK-STAT pathway	Ruxolitinib, a JAK inhibitor, reversed the smooth muscle cell phenotype modulation in vitro and inhibited the vascular anomalies in zebrafish induced by *PDGFRB* mutation
Shima *et al* (2023)[5]	16 total somatic variants, 6 of which common to both ISA and IFA: *PDGFRB*, *AHNAK*i, *OBSCN*, *CACNA1E*, *OR5P3*, *RNA binding motif protein 10 (RBM10)*	65	Saccular (n=54), fusiform (n=11)	Four variants linked to the NFκB signaling pathway	Systemic administration of the TKI sunitinib blocked phenotype of fusiform-like dilatation of basilar artery in mutant *PDGFRB* mice
Lai *et al* (2022)[7]	*SVIL*	30	Saccular	Phenotypic modulation of vSMCs to the synthetic phenotype via Krüppel-like factor 4 and platelet derived growth factor and affected cell migration of vSMCs via the RhoA/ROCK pathway	ROCK inhibitors
Li *et al* (2022)[9]	*RNF213*	174	N/A	Angiogenesis, vascular wall formation	N/A
Silverstein *et al* (2022)[10]	*ANKRD17*	1	N/A	Vascular wall formation/ maintenance	N/A
Barak *et al* (2021)[11]	*PPIL4*	430	Saccular	PPIL4 potentiates Wnt signaling by binding JMJD6, a known angiogenesis regulator and Wnt activator	N/A
Sauvigny *et al* (2020)[12]	*EDIL3*	38	N/A	Edil3 promotes adhesion of endothelial and vascular smooth muscle cells	N/A
Karasozen *et al* (2019)[6]	*PDGFRB*	1	Fusiform	Overactive autophosphorylation with downstream activation of ERK, SRC, and AKT	Non-ligand-dependent autophosphorylation inhibited by TKI sunitinib in fibroblast cells from index patient

IFA, intracranial fusiform aneurysm; ISA, intracranial saccular aneurysm; N/A, not available; NFκB, nuclear factor κB; TKI, tyrosine kinase inhibitor; vSMCs, vascular smooth muscle cells.

overlap with the high frequency variants described by GWAS, although we anticipate that as more low frequency variants are discovered, there will likely be similar genes and pathways targeted because familial and sporadic aneurysms have the same pathogenesis and morphologically are indistinguishable. The few non-germline (somatic), low frequency variants known

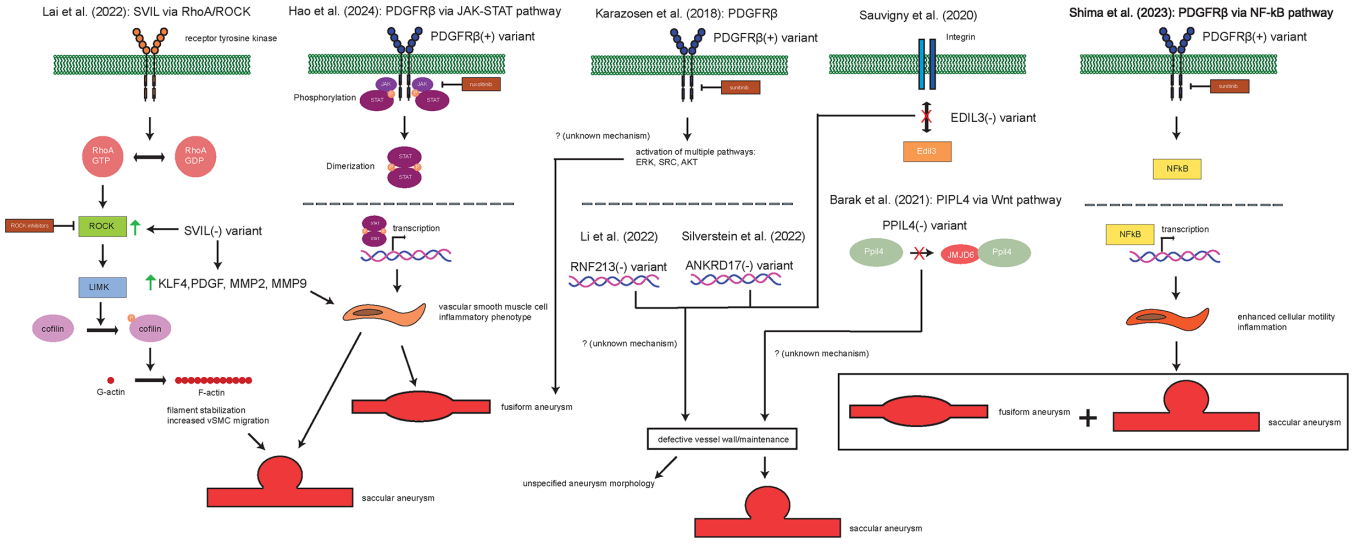

Figure 2 Somatic variants in the pathogenesis of intracranial aneurysms and their associated cellular signaling pathways.

to lead to intracranial aneurysm formation are reviewed in this study and summarized in figure 2. Somatic variants have been described in certain vascular wall associated genes such as *PPIL4*[11], *EDIL3*[12], *RNF213*,[9] and *ANKRD17*.[10] These genes are involved in angiogenesis and vascular wall formation, although the mechanism by which these variants lead to IA pathogenesis is unclear. On the other hand, certain variants in cancer related genes have been more clearly associated with the pathogenesis of IAs. Two cancer related somatic variants have been detected within vascular smooth muscle cells (vSMCs). Lai *et al*[7] found sporadic mutations in *SVIL* in 17% of saccular IAs and demonstrated the role of *SVIL* in the modulation of vSMC phenotype to the synthetic phenotype, which is characterized by increased protein synthesis, proliferation, and migration, and is thought to contribute to aneurysm pathogenesis and rupture.

Perhaps the most well described low frequency somatic variant involved in the pathogenesis of IAs is the cancer related variant in the platelet derived growth factor beta gene (*PDGFRB*). *PDGFRB* encodes a conserved transmembrane receptor tyrosine kinase that has an essential role in vascular progenitor cell signaling.[17] Loss of function mutations in *PDGFRB* have been associated with a variety of vascular diseases, such as hereditary hemorrhagic telangiectasia and chronic eosinophilic leukemia. A somatic variant in *PDGFRB*, p.(Tyr562Cyst), was first identified in an individual presenting with IFAs at the internal carotid, vertebral, radial, and coronary arteries ipsilateral to cutaneous vascular malformations.[6] Interestingly, this mutation occurs in the activation loop of *PDGFRB*, disrupting the auto-inhibitory sites of the receptor and resulting in constitutive activation. In another study by Hao *et al*,[8] four different somatic mutations in *PDGFRB* were identified in four fusiform aneurysms. All mutations also caused constitutive activation of *PDGFRB*.

While the somatic variant in *PDGFRB* in IAs has been well described, the exact pathogenesis of the *PDGFRB* mutation in aneurysm formation is just beginning to be understood. Mutant forms of both *PDGFRB* and *AHNAK* lead to constitutively activate ERK, nuclear factor κB, and JAK2 signaling, enhanced cell motility, and induced inflammation related gene expression *in vitro*.[8] One *in vivo* model of the *PDGFRB* somatic mutation inducing a fusiform aneurysm phenotype has been developed in zebrafish.[8] The model demonstrated hemorrhage and altered vascular morphogenesis. This was the first confirmation that activating *PDGFRB* variants can drive the formation of fusiform-like vessel dilation in an animal model. This study also showed that the effects of the *PDGFRB* variant could be reversed *in vitro* and in zebrafish using ruxolitinib, a JAK inhibitor. Future studies are needed to confirm these results and apply them to other *in vivo* models.

Somatic variants based on aneurysm morphology

IA morphologies, saccular and fusiform, are phenotypes that have previously been assumed to have separate genetic causes.[18] Mutations in *SVIL*[7] and *PPIL4*[11] have been described in intracranial saccular aneurysms (ISAs) only. The variants in *PDGFRB* were initially described solely in intracranial fusiform aneurysms (IFAs).[6 8] In a series of aneurysm specimens, activating variants in *PDGFRB* were found in 4/6 IFAs but in 0/38 ISAs.[6] This variant has been implicated in 14 patients in other reports,[19] including a series of 12 patients with activating *PDGFRB* mutations, 7 of which had aneurysms involving the cerebral, coronary and renal arteries.[20]

One preliminary study[21] involved whole exome sequencing of 20 ISAs of which 11 (55%) had 48 detectable somatic mutations, highly enriched in cancer related genes. A p.Tyr562Aps somatic mutation was detected in the *PDGFRB* gene and was predictably deleterious. This mutation is within the same codon as mutations detected in IFAs.

One recent study however, found somatic variants within *PDGFRB* common to both ISAs and IFAs. Shima *et al*[5] conducted whole exome sequencing on the largest series of 54 ISAs and 11 IFAs, and found multiple variants in *PDGFRB* in both tissue types. Additionally, somatic mutations in five other genes (*AHNAK*, *OBSCN*, *CACNA1E*, *OR5P3*, and *RBM10*) were also detected. These results suggest possible overlapping genetic risk factors in both ISA and IFA phenotypes. However, the frequency of somatic *PDGFRB* mutations was different among ISA and IFA tissue, at 4% and 36%, respectively. Other variants described in this review, such as mutations in EDIL3, RNF213, and ANKRD17, did not specify IA morphology. Given the results in the Shima *et al*[5] study, we advocate for future publications on somatic variants of IAs to specify the aneurysm morphology and the different frequencies of the variants described among the two different morphologies.

Mosaic effect of somatic variants

The mechanism for genetic heterogeneity within an individual leading to a unique cell lineage is called mosaicism. There are two mechanisms for genetic heterogeneity within an individual. Mosaicism occurs at any point following the first replication of the zygote with single nucleotide errors in DNA replication occurring 10^{-9} errors per cellular division.[22] This results in significant genetic variation across all tissues, increasing as we age, and this can result in beneficial changes in the development of neuronal diversity,[23] evasion of germline inherited mutations,[24] and enhancing the adaptive ability of tissues.[24] However, many of these variants are also implicated in various human diseases, including vascular diseases.[25]

Sequencing of a cohort of syndromic and non-syndromic patients with IFA and other fusiform aneurysms revealed *PDGFRB* variants, and these variants were not detected in peripheral blood.[4] This suggests a mosaic expression associated with fusiform aneurysm formation.[6] A mosaic mechanism of this variant is an important characteristic because of the therapeutic implications if this pathway is targeted with a drug. Only a subset of cells will express this variant resulting in the pathologic phenotype; therefore, systemic delivery of a drug targeting this pathway is both unnecessary and has potentially harmful off-target effects.

Personalized therapeutics: opportunities and challenges

Kinase inhibitors may theoretically alter the progression of *PDGFRB* associated disorders. Overactivity of the PDGFRB protein can be partly corrected by tyrosine kinase inhibitors (TKIs), such as sumatinib,[26] which have successfully treated patients with *PDGFRB* activating variants.[20] Patients with *PDGFRB* variants causing myofibromas have been treated with imatinib with robust responses.[27] Thus direct inhibition of activated receptor tyrosine kinases may be useful in targeting IAs, particularly IFAs. One study[5] found that virus mediated overexpression of a mutant *PDGFRB* induced a fusiform-like dilatation of the basilar artery in mice, and this phenotype was blocked by systemic administration of sunitinib, a TKI. Chenbhanich *et al*[19] reported a patient with the *PDGFRB* p(Tyr562Cys) variant with multiple progressively enlarging IFAs and coronary artery fusiform aneurysms treated with a TKI (sorafenib), one of which subsequently ruptured. It is unclear whether the rupture was related to the therapy or the natural course of the disease.

The possibility of genetic treatment for intracranial aneurysms is currently unknown. There has been no large series to date reporting TKIs to treat aneurysms associated with *PDGFRB* variants. One pitfall of this variant directed treatment is the possibility for mutation mediated resistance. Resistance may be encountered in the p.Asp850Tyr variant although kinase inhibitors targeting downstream targets (eg, AKT, ERK, and JAK2) may be an alternative, personalized strategy.[6] One example of targeting a downstream signaling pathway of *PDGFRB* was demonstrated by Hao *et al*[8] in which the JAK2-STAT pathway was successfully inhibited using the JAK specific inhibitor ruxolitinib. Inhibiting p-JAK2 effectively reversed the PDGFRB driven inflammatory phenotype in vSMCs, with implications for treatment of IFAs.

Another challenge to initiate TKI therapy for IAs is the significant systemic side effects experienced with the drug. Orally bioavailable TKIs are associated with adverse effects,[28] such as skin toxicity, edema, nausea, hypothyroidism, vomiting, and diarrhea. Most TKIs also exhibit hematological side effects, like anemia, thrombocytopenia, and neutropenia, as well as an increased risk of bleeding due to inhibition of vascular endothelial growth factor receptor.[29] In one double-blind, placebo-controlled, multicenter, randomized phase III trial studying sunitinib administration among 207 patients with gastrointestinal tumors, 83% of patients experienced an adverse event, of which 20% were considered serious.[30]

Much of the literature thus far detecting *PDGFRB* variants is based on tissue harvested from resected IAs at the time of surgery. However, many IAs (including vertebrobasilar IFAs) are often not amenable to microsurgical treatment. Since somatic variants in *PDGFRB* arise post-zygotically, testing peripheral blood is of limited efficacy. In determining whether an individual has this *PDGFRB* variant and, in turn, candidacy for personalized TKI therapy, minimally invasive endovascular biopsy techniques yielding cells amenable to such sequencing has been proposed.[31]

Endovascular biopsy is a technique for harvesting viable vascular endothelium using a deployable device, such as a coil through a microcatheter, to contact the endothelium of the aneurysm.[31] The device is then removed and isolated in a buffer, and the endothelial cells are incubated. The length of time that the devices are left in contact with the area of interest is not well reported. Several hundred endothelial cells can be collected in this way, although cell yields vary considerably across studies and devices.[32–35] Unfortunately, cell yields may be low particularly in lesions with sparse endothelial cell populations, and studies have not yet identified aneurysm specific variants of endothelial cells obtained through this technique. Despite this limitation, one study detected the *PDGFRB* variant in endovascular biopsy acquired cells obtained from a patient with cutaneous manifestations, which differed from those in the patient's iliac artery.[36] Variant to allele frequencies were 2.8% and 0.9% for the aneurysm and iliac artery, respectively. This technique paves the way for detection of other somatic variants in IFAs, yielding relevant targetable molecular information for personalized treatment.

Endovascular devices may also provide substrate to enable local drug delivery of chemotherapeutics. Local delivery would be superior for chemotherapeutic delivery to IA tissue for multiple reasons. First, the existence of the blood–brain barrier limits the ability to achieve therapeutic doses of drug to the target site.[37] Transient damage to the vascular endothelium may allow enhanced drug delivery, minimizing the blood–brain barrier limitations. Second, local drug delivery reduces systemic concentration of drug, thereby mitigating the non-target systemic exposure and organ toxicity often associated with chemotherapeutics such as TKIs.[38] Third, by delivering drugs locally, the pharmaceutical concentration at the target site can be maximized, bypassing the multiple steps of metabolic degradation that occurs when the drug is delivered systemically.[38] Finally, there is significant evidence that IAs may develop via somatic mosaic variants and the pathogenesis indicates that the lesion is localized. Therefore, delivery of the drug to all cells is both unnecessary and potentially dangerous.

The field of interventional cardiology has set a blueprint for the introduction of drug eluting stents to intracranial vessels. The same methodologies for surface modification may be applied to our field, where surface modifications of intracranial stents have been developed to reduce thromboembolic complications.[39] Surface modification of intracranial stents for local gene therapy (eg, the release of active drugs, such as TKIs) would reduce or eliminate the need for systemic drug therapy.[39]

This review serves as a guide to understand the very beginning of possible targets for gene therapy to treat IAs. Given the relatively new technology of whole exome sequencing that has enabled the detection of these low frequency variants, there are only a small number of variants reported to date.[5–9 11 12 40] Furthermore, obtaining IA tissue for sequencing is another significant limitation of this work. There are other obvious limitations to this review, including the large heterogeneity in the data reported, limited animal models and their unclear clinical relevance, as well as lack of data regarding humans treated with gene therapies such as TKIs.

CONCLUSIONS

Gene therapy for the treatment of IAs may represent a major innovation in the future of neurointervention. Somatic variants in vascular wall formation as well as more cancer related variants, such as *PDGFRB*, may be promising targets for chemotherapeutics, which must be delivered safely and effectively. Advances in both the molecular understanding of the pathogenesis of aneurysms, and the identification of drug targets and functionalization of intracranial stent surfaces, should be concurrently pursued to improve the treatment of IAs.

X Michael R Levitt @DrMichaelLevitt

Contributors MM and MRL conceptualized the study. MM carried out the analysis and wrote the first draft of the manuscript. All authors commented on draft versions of the manuscript, and read and approved it in its final form. MRL is responsible for the overall content as guarantor. The guarantor accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was supported in part by NIH/NINDS 2UE5NS079200, Neurosurgery Research and Education Foundation, Aneurysm and AVM Foundation, and Society of Neurological Surgeons.

Competing interests MRL: unrestricted educational grants from Medtronic and Stryker; consulting agreement with Medtronic, Aeaean Advisers, Metis Innovative, and Genomadix; equity interest in Proprio, Stroke Diagnostics, Apertur, Stereotaxis, Fluid Biomed, and Hyperion Surgical; editorial board of Journal of NeuroInterventional Surgery and data safety monitoring board of Arsenal Medical. BR: founder, shareholder, and board member of Healionics; founder, shareholder, and board member of Kuleana Technology.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iD
Michael R Levitt http://orcid.org/0000-0003-3612-3347

REFERENCES

1 Molyneux A, Kerr R, Stratton I, *et al*. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002;360:1267–74.
2 Nakatomi H, Kiyofuji S, Ono H, *et al*. Giant Fusiform and Dolichoectatic Aneurysms of the Basilar Trunk and Vertebrobasilar Junction-Clinicopathological and Surgical Outcome. *Neurosurgery* 2020;88:82–95.
3 Ronkainen A, Hernesniemi J, Puranen M, *et al*. Familial intracranial aneurysms. *Lancet* 1997;349:380–4.
4 Parada CA, El-Ghazali FM, Toglia D, *et al*. Somatic Mosaicism of a PDGFRB Activating Variant in Aneurysms of the Intracranial, Coronary, Aortic, and Radial Artery Vascular Beds. *J Am Heart Assoc* 2022;11:e024289.
5 Shima Y, Sasagawa S, Ota N, *et al*. Increased PDGFRB and NF-κB signaling caused by highly prevalent somatic mutations in intracranial aneurysms. *Sci Transl Med* 2023;15:eabq7721.
6 Karasozen Y, Osbun JW, Parada CA, *et al*. Somatic PDGFRB Activating Variants in Fusiform Cerebral Aneurysms. *Am J Hum Genet* 2019;104:968–76.
7 Lai PMR, Ryu J-Y, Park S-C, *et al*. Somatic Variants in SVIL in Cerebral Aneurysms. *Neurol Genet* 2022;8:e200040.
8 Hao L, Ya X, Wu J, *et al*. Somatic PDGFRB activating variants promote smooth muscle cell phenotype modulation in intracranial fusiform aneurysm. *J Biomed Sci* 2024;31:51.
9 Li Y, Liu J, Hu C, *et al*. Association of rare RNF213 variants and intracranial aneurysm risk in a Chinese population. *Ann Transl Med* 2022;10:1336.
10 Silverstein R, Kuwabara M, Appavu B. Neonatal Aneurysm Rupture in a Child with a De Novo Variant to ANKRD17. *Child Neurol Open* 2022;9:2329048X221134600.
11 Barak T, Ristori E, Ercan-Sencicek AG, *et al*. PPIL4 is essential for brain angiogenesis and implicated in intracranial aneurysms in humans. *N Med* 2021;27:2165–75.
12 Sauvigny T, Alawi M, Krause L, *et al*. Exome sequencing in 38 patients with intracranial aneurysms and subarachnoid hemorrhage. *J Neurol* 2020;267:2533–45.
13 Tromp G, Weinsheimer S, Ronkainen A, *et al*. Molecular basis and genetic predisposition to intracranial aneurysm. *Ann Med* 2014;46:597–606.
14 Alg VS, Sofat R, Houlden H, *et al*. Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116,000 individuals. *Neurol (ECronicon)* 2013;80:2154–65.
15 Lettre G. Rare and low-frequency variants in human common diseases and other complex traits. *J Med Genet* 2014;51:705–14.
16 Cirulli ET, Goldstein DB. Uncovering the roles of rare variants in common disease through whole-genome sequencing. *Nat Rev Genet* 2010;11:415–25.
17 He C, Medley SC, Hu T, *et al*. PDGFRβ signalling regulates local inflammation and synergizes with hypercholesterolaemia to promote atherosclerosis. *Nat Commun* 2015;6:7770.
18 Nakatomi H, Segawa H, Kurata A, *et al*. Clinicopathological study of intracranial fusiform and dolichoectatic aneurysms: insight on the mechanism of growth. *Stroke* 2000;31:896–900.
19 Chenbhanich J, Hu Y, Hetts S, *et al*. Segmental overgrowth and aneurysms due to mosaic PDGFRB p.(Tyr562Cys). *Am J Med Genet A* 2021;185:1430–6.
20 Wenger TL, Bly RA, Wu N, *et al*. Activating variants in PDGFRB result in a spectrum of disorders responsive to imatinib monotherapy. *Am J Med Genet A* 2020;182:1576–91.
21 Rezai Jahromi B, Valori M, Tulamo R, *et al*. E-109 cancer-type somatic mutations in saccular cerebral aneurysms. *J Neurointerv Surg* 2022;14:A136–A36.
22 Lynch M. Rate, molecular spectrum, and consequences of human mutation. *Proc Natl Acad Sci U S A* 2010;107:961–8.
23 Baillie JK, Barnett MW, Upton KR, *et al*. Somatic retrotransposition alters the genetic landscape of the human brain. *Nat New Biol* 2011;479:534–7.
24 Fernández LC, Torres M, Real FX. Somatic mosaicism: on the road to cancer. *Nat Rev Cancer* 2016;16:43–55.
25 Thorpe J, Osei-Owusu IA, Avigdor BE, *et al*. Mosaicism in Human Health and Disease. *Annu Rev Genet* 2020;54:487–510.
26 Sramek M, Neradil J, Macigova P, *et al*. Effects of Sunitinib and Other Kinase Inhibitors on Cells Harboring a *PDGFRB* Mutation Associated with Infantile Myofibromatosis. *Int J Mol Sci* 2018;19:2599.
27 Weller JM, Keil VC, Gielen GH, *et al*. PDGRFB mutation-associated myofibromatosis: Response to targeted therapy with imatinib. *Am J Med Genet A* 2019;179:1895–7.
28 Hartmann JT, Haap M, Kopp H-G, *et al*. Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects. *Curr Drug Metab* 2009;10:470–81.
29 Je Y, Schutz FAB, Choueiri TK. Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *Lancet Oncol* 2009;10:967–74.
30 Demetri GD, van Oosterom AT, Garrett CR, *et al*. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;368:1329–38.
31 Shekhtman O, Sioutas GS, Piavchenko G, *et al*. Endovascular biopsy in neurointerventional surgery: A systematic review. *Interv Neuroradiol* 2024;2024:15910199241240508.
32 Narsinh KH, Narsinh K, McCoy DB, *et al*. Endovascular Biopsy of Vertebrobasilar Aneurysm in Patient With Polyarteritis Nodosa. *Front Neurol* 2021;12:697105.
33 Cooke DL, McCoy DB, Halbach VV, *et al*. Endovascular Biopsy: In Vivo Cerebral Aneurysm Endothelial Cell Sampling and Gene Expression Analysis. *Transl Stroke Res* 2018;9:20–33.
34 Sheth SA, Verma A, Malhotra K, *et al*. Human Endothelial Cell Collection from the Middle Cerebral Artery in Acute Ischemic Stroke. *J Stroke Cerebrovasc Dis* 2018;27:669–72.
35 Alexander MD, Sun Z, Conrad MB, *et al*. Assessment of cell yield among different devices for endovascular biopsy to harvest vascular endothelial cells. *BioTechniques* 2019;66:34–6.
36 Garcia JH, Winkler EA, Müller K, *et al*. Endovascular Biopsy for Detection of Somatic Mosaicism in Human Fusiform Cerebral Aneurysms. *SVIN* 2022;2:e000354.
37 Gabathuler R. Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases. *Neurobiol Dis* 2010;37:48–57.
38 Chew SA, Danti S. Biomaterial-Based Implantable Devices for Cancer Therapy. *Adv Healthc Mater* 2017;6.
39 Zoppo CT, Mocco J, Manning NW, *et al*. Surface modification of neurovascular stents: from bench to patient. *J NeuroIntervent Surg* 2024;16:908–13.
40 Yan J, Hitomi T, Takenaka K, *et al*. Genetic study of intracranial aneurysms. *Stroke* 2015;46:620–6.