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## Genotype-Guided Successful Treatment of an Arteriovenous Malformation in a Child

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### Abstract

**Importance:** Genetic testing results can provide guidance in developing personalized treatment plans for patients with vascular anomalies.

**Objective:** To explore the efficacy of trametinib in the treatment of an extracranial arteriovenous malformation with a somatic *MAP2K1* mutation.

**Design:** Case report of a child with an arteriovenous malformation that was successfully treated with trametinib after identification of a specific somatic mutation within the malformation.

**Setting:** Outpatient Vascular Anomalies Clinic, Stanford University, Stanford, CA.

**Participant:** An 11-year-old girl with an arteriovenous malformation on the back who had failed treatment with systemic sirolimus.

**Intervention:** Paired exome sequencing using tumor and saliva DNA was performed and identified a somatic mutation within the *MAP2K1* gene. The patient was then transitioned to trametinib at a starting dose of 0.5 mg once daily then increased to 0.5 mg twice daily after one month.

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**Author Contributions:** *Lekwuttikarn and Teng* had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Teng.

Acquisition, analysis, and interpretation of data: *Lekwuttikarn, Lim, Admani, Choate, Teng*

Drafting of the manuscript: *Lekwuttikarn, Teng*

Critical revision of the manuscript for important intellectual content: *Lekwuttikarn, Lim, Admani, Choate, Teng*

Statistical analysis: *Lekwuttikarn, Teng*

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Study supervision: *Teng*

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**Main Outcome:** Trametinib was effective in reducing the size of and blood flow to the arteriovenous malformation.

**Results:** After one month on trametinib, the patient and parents noticed the malformation reduced in size and became lighter in color. After six months of treatment, quantitative analyses were performed using magnetic resonance imaging and showed significant interval decrease in the volume of the malformation and the caliber of the vasculature compared to prior examinations. To date, she has tolerated the treatment well with development of a mild acneiform eruption responding well to over the counter adapalene and benzoyl peroxide.

**Conclusion and Relevance:** Management of arteriovenous malformations is very challenging due to almost inevitable disease progression and high recurrence rates after surgical resection. The discovery of a somatic mutation associated with this arteriovenous malformation provided guidance for targeted therapy. Trametinib may be a promising targeted therapeutic option for sporadic extracranial arteriovenous malformations harboring *MAP2K1* mutations.

## Introduction

Arteriovenous malformations (AVMs) are rare, congenital vascular malformations composed of abnormal connections between arteries and veins and missing the normal capillary beds that typically lie in between. Comprising up to 4.7% of all vascular anomalies<sup>1</sup>, AVMs are the most difficult type of vascular malformations to manage. Currently, there are no FDA-approved treatments for AVMs. Here, we report a child with an AVM that successfully responded to trametinib using genotyping as guidance.

## Case report

An 11-year-old girl presented with an enlarging congenital vascular mass on her back, which had grown notably in size and darkened in color since 3 years of age. She denied restriction of shoulder movement. Physical examination revealed a 17 × 12 cm, compressible, warm, vascular mass overlying the left scapular region and extending to the mid upper back (Fig. 1A). Radioimaging and clinical evaluation were most consistent with an AVM (Fig. 1D). Due to rapid disease progression, the patient was started on systemic sirolimus with target trough levels of 10–15 ng/dl. She remained at a therapeutic dose and tolerated the treatment for nearly 8 months, with the exception of intermittent oral ulcers. There was no improvement noted in the size of the AVM either on clinical exam or with MRI (Fig. 1b and 1e). Genomic DNA was extracted from a saliva sample and tumor biopsy, and paired exome sequencing was performed, identifying a somatic *MAP2K1 c.169\_183del* (p.Lys57\_Gly61del) in-frame deletion. Deletions in this region were previously reported to activate MAPK signaling via increasing levels of pERK.<sup>2</sup> In light of this finding, in addition to the lack of clinical improvement on her current regimen, the risk of cardiac comorbidity from disease progression, and concerns regarding sirolimus side effects, the decision was made to stop sirolimus treatment. The patient was then transitioned to trametinib, a MEK inhibitor, at a starting dose of 0.5 mg once daily which was then increased to 0.5 mg twice daily after one month. At the one month follow up, the patient and her parents noted the lesion had reduced in size, lightened in color, and had decreased warmth to touch. MRI evaluation and volumetric analysis were performed following 6 months of treatment, which

confirmed significant interval decrease in the extent of the malformation and the caliber of the vasculature compared to prior examinations (Fig. 1c, 1f and Fig. 2). To date, she has tolerated treatment well with only mild acne, which has responded well to over the counter benzoyl peroxide wash and adapalene 0.1% gel.

## Discussion

All AVMs progress throughout life, with up to 80 percent of lesions beginning this progression during childhood and adolescence.<sup>3</sup> Without treatment, arteriovenous shunting can cause tissue ischemia leading to tissue destruction, bleeding, functional deficits, deformity and rarely cardiac overload. Embolization and surgical debulking have transient benefits due to often rapid recurrence.<sup>3</sup> With limited therapeutic options, there is a significant unmet medical need.

Genetic sequencing has recently been employed in diagnosing many vascular malformations and malformation syndromes. This diagnostic tool has enabled identification of pathogenic mutations associated with specific lesions which likely drive their growth. Prior studies have found somatic mutations in patients with sporadic extracranial AVMs, the most common of which are in *MAP2K1*.<sup>4</sup> Additional mutations within *KRAS* and *BRAF* have also been reported.<sup>5</sup> *MAP2K1* encodes mitogen-activated protein kinase 1 (MEK1), which plays a key role in RAS/RAF/MAPK signaling and angiogenesis. *MAP2K1* mutant endothelial cells demonstrate disrupted vascular channel formation, leading to abnormal capillary networks between developing arteries and veins.<sup>4,5</sup> In-frame deletions at *c.159\_173del*, *c.170\_184del*, and *c.172\_186del*, which encompass the deletion in our patient, have been shown to activate ERK phosphorylation in vitro for downstream MAPK signaling.<sup>2</sup> Trametinib is a MEK inhibitor used for the treatment of many oncologic disorders, as well as neurofibromatosis in children.<sup>6</sup> Given its relatively high safety profile, we initiated this treatment based on her genetic testing results and to specifically target the over-activated MAPK pathway. The patient clearly demonstrated superior clinical response to trametinib in comparison to sirolimus, which is a known anti-angiogenic agent targeting the mTOR pathway. Mild acne was the only noted side effect; repeated electrocardiogram, ocular exam and laboratory studies were all within normal. Our findings suggest that MEK inhibitors may be an effective treatment for extra-cranial AVMs, especially for patients carrying somatic *MAP2K1* mutations. Further well-controlled, large-scale studies are needed to investigate the optimal dosing, duration, long-term safety and efficacy of this treatment.

## Conclusion

Trametinib may be a promising new, targeted therapeutic option for sporadic extracranial AVMs harboring *MAP2K1* mutations. This case report highlights the value of employing genetic testing in developing personalized treatments for patients with these challenging lesions.

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	Funding/Sponsor was involved?	
Design and conduct of the study	Yes	<input type="radio"/>
Collection, management, analysis and interpretation of data	Yes	<input type="radio"/>
Preparation, review, or approval of the manuscript	Yes	<input type="radio"/>
Decision to submit the manuscript for publication	Yes	<input type="radio"/>

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### Key Points

**Question:**

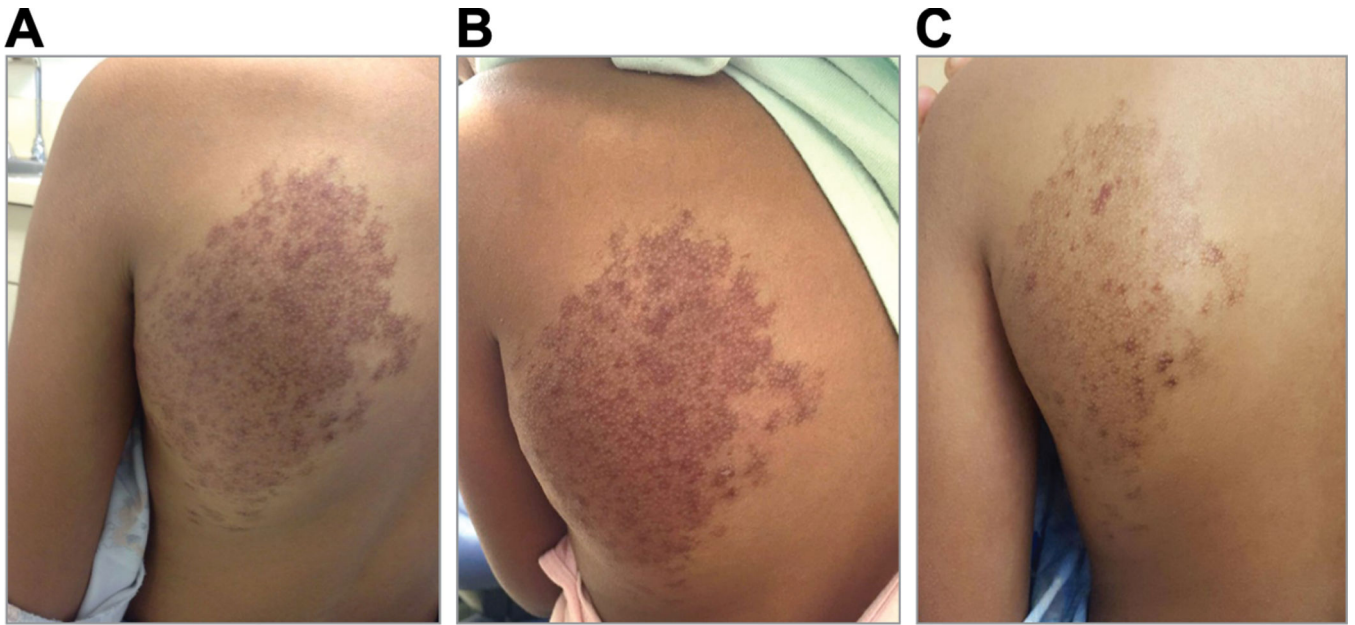
Can tramitinib be an effective treatment for extracranial arteriovenous malformation?

**Findings:**

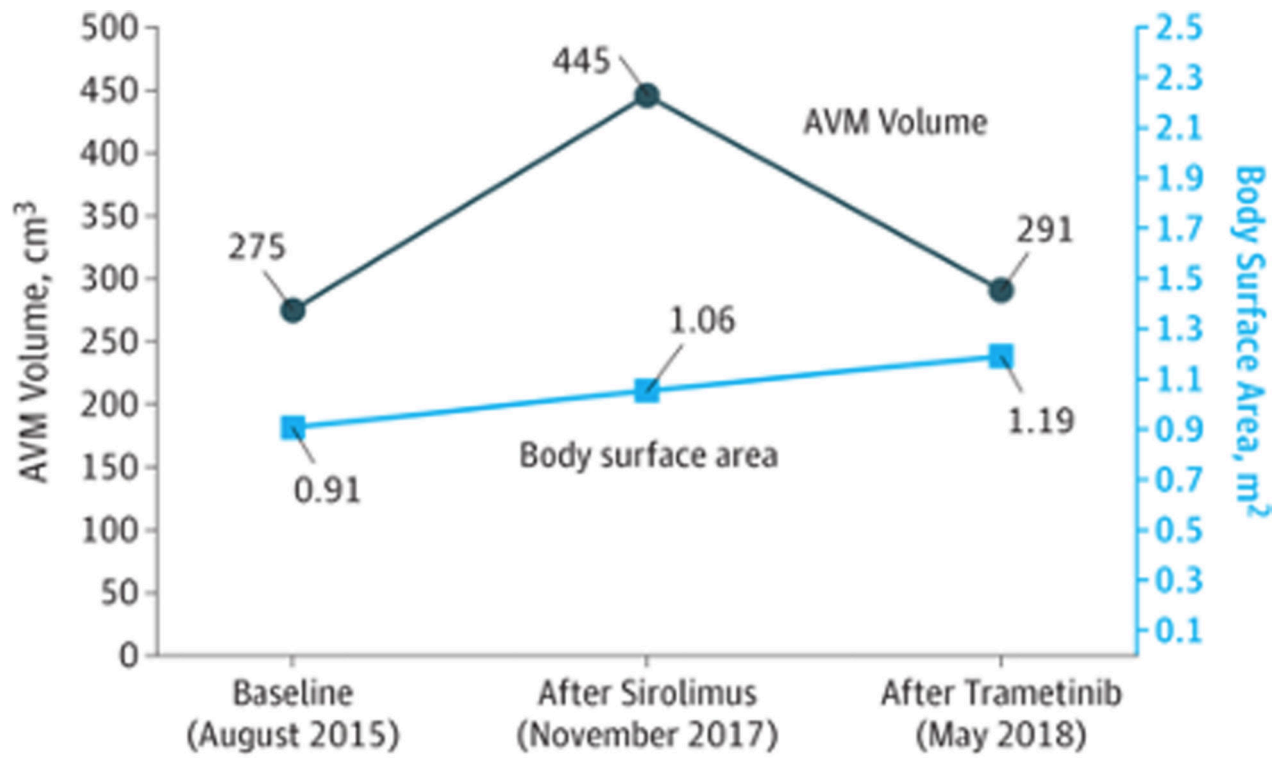
Tramitinib can be an effective and well-tolerated treatment for a child with an extracranial arteriovenous malformation due to a *MAP2K1* mutation.

**Meaning:**

MEK inhibitor may offer a new, targeted therapeutic option for sporadic extracranial arteriovenous malformations that carry *MAP2K1* mutations.



**Figure 1:** Clinical presentation and imaging studies of an arteriovenous malformation on the left scapular region of an 11 year-old girl. Clinical photos at (A) baseline; (B) after 8 months of sirolimus treatment; and (C) after 6 months trametinib treatment are shown. In addition, correlating magnetic resonance imaging (D-F).



#### Characteristics

Weight, kg	23.9	29.1	34.6
Height, cm	125.1	139.4	146.5
BSA, m <sup>2</sup>	0.91	1.06	1.19

**Figure 2:** Volumetric analysis of arteriovenous malformation response to sirolimus and trametinib treatment.

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	Funding/Sponsor was involved?	
Design and conduct of the study	Yes	<input checked="" type="radio"/>
Collection, management, analysis and interpretation of data	Yes	<input checked="" type="radio"/>
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Decision to submit the manuscript for publication	Yes	<input checked="" type="radio"/>

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