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# Novel use of trametinib for treatment of atrial arrhythmia in absence of cardiomyopathy in a patient with Costello syndrome

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**Brief Report**

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**Abbreviation:**
MEK, Mitogen-activated protein kinase kinase

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## Abstract

We describe a case of novel use of trametinib in treating arrythmia without concomitant cardiomyopathy. Our patient is a two-year-old female born with Costello syndrome due to heterozygous mutations in the HRAS gene c34 G > T p (G12C). Shortly after birth, she was diagnosed with multifocal atrial tachyarrhythmia. Her imaging studies have shown no hypertrophy or CHD. There was poor arrhythmia control despite triple antiarrhythmic therapy. Trametinib, a MEK1 and MEK2 inhibitor, was used in treating her isolated atrial arrythmia, allowing her to wean off other antiarrhythmics. Other case reports have shown trametinib to benefit certain RASopathy patients with lymphatic abnormalities, hypertrophic cardiomyopathy, and concurrent arrhythmias. This case demonstrates effective treatment of isolated arrhythmia without cardiomyopathy, broadening the potential indications for use of trametinib in certain RASopathy patients.

## Case report

Our patient is a two-year-old female born at 36 weeks gestation found to have a heterozygous HRAS mutation, consistent with Costello syndrome. This is a c34 G > T p (G12C) mutation in the H-Ras protein coding gene. Shortly after birth, our patient was diagnosed with multifocal atrial tachyarrhythmia (Figure 1). Her serial echocardiograms and cardiac MRI have shown no signs hypertrophy or CHD. She was initially started on propranolol, flecainide, and amiodarone prior to discharge from the NICU. However, she continued to have frequent atrial tachycardia episodes requiring multiple readmissions and developed mild congestive heart failure thought to be secondary to chronic arrhythmia. At 15 months old, the risks and benefits of novel treatment options were discussed with parents and she was started on 0.125 mg of trametinib as disease-modifying therapy. She was monitored for adverse effects using an unpublished protocol for trametinib that was formulated among Advanced Cardiac Therapies Improving Outcomes Network providers by consensus. Protocol available upon request. She rapidly reached rhythm control after one week, and all antiarrhythmic medications were slowly discontinued over the following six months. Her mild congestive heart failure resolved. At the time of publication, she has maintained sinus rhythm on trametinib for over a year (Figure 2), and all other cardiac medications have been discontinued for over six months. She has had no adverse drug events to date.

## Discussion

RASopathies are a family of disorders involving mutations in the Ras/mitogen activated protein kinase pathway (Ras-MAPK pathway) controlling cell-cycle arrest, apoptosis, cell survival, cell growth, cell migration, cytoskeletal remodelling, and transcription.[1] These mutations increased activation of the Ras pathway and can cause increased expression of target genes cyclin D1, cMYC, BCl2 with the end result being uncontrolled cell growth. In these syndromes, common symptoms include unusual facial features, developmental delay, cardiac anomalies, skeletal anomalies, poor feeding, and growth.[2] The most well-known RASopathies are Noonan syndrome and neurofibromatosis 1 and 2, but this family of disorders also includes Costello syndrome, Legius syndrome, and cardiofaciocutaneous syndrome (CFC).

In RASopathies, the highest mortality features are cardiac in nature, with studies showing only less than 34% of infants with hypertrophic cardiomyopathy in Noonan syndrome survive past one year.[3–4] Unfortunately, 85% of Costello patients present with cardiac disease, including hypertrophic cardiomyopathy, CHDs, and dysrhythmias.[3] While isolated non-reentrant atrial tachycardia has in the past been most associated specifically with Costello syndrome, more

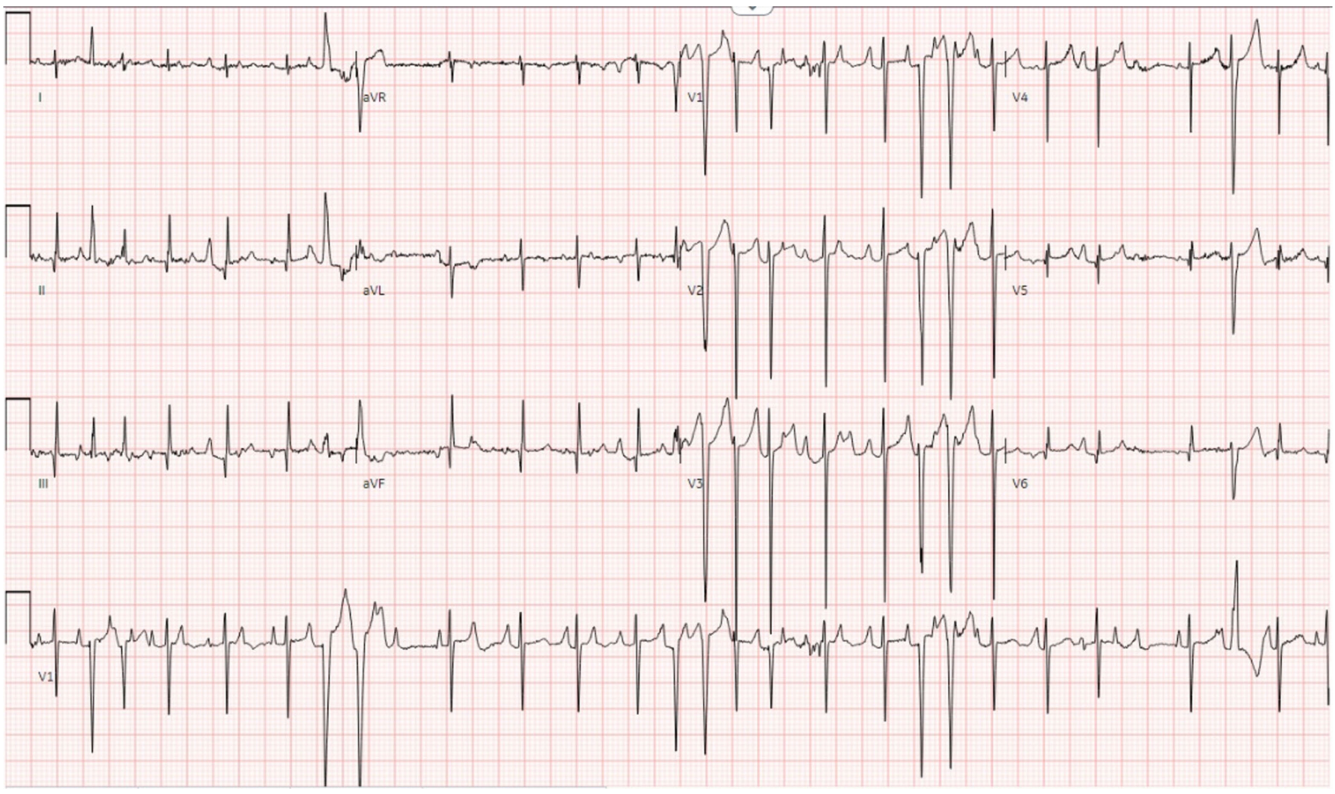


**Figure 1.** Patient's EKG prior to administration of trametinib showing frequent short salvos of atrial tachycardia and possible ventricular ectopy.

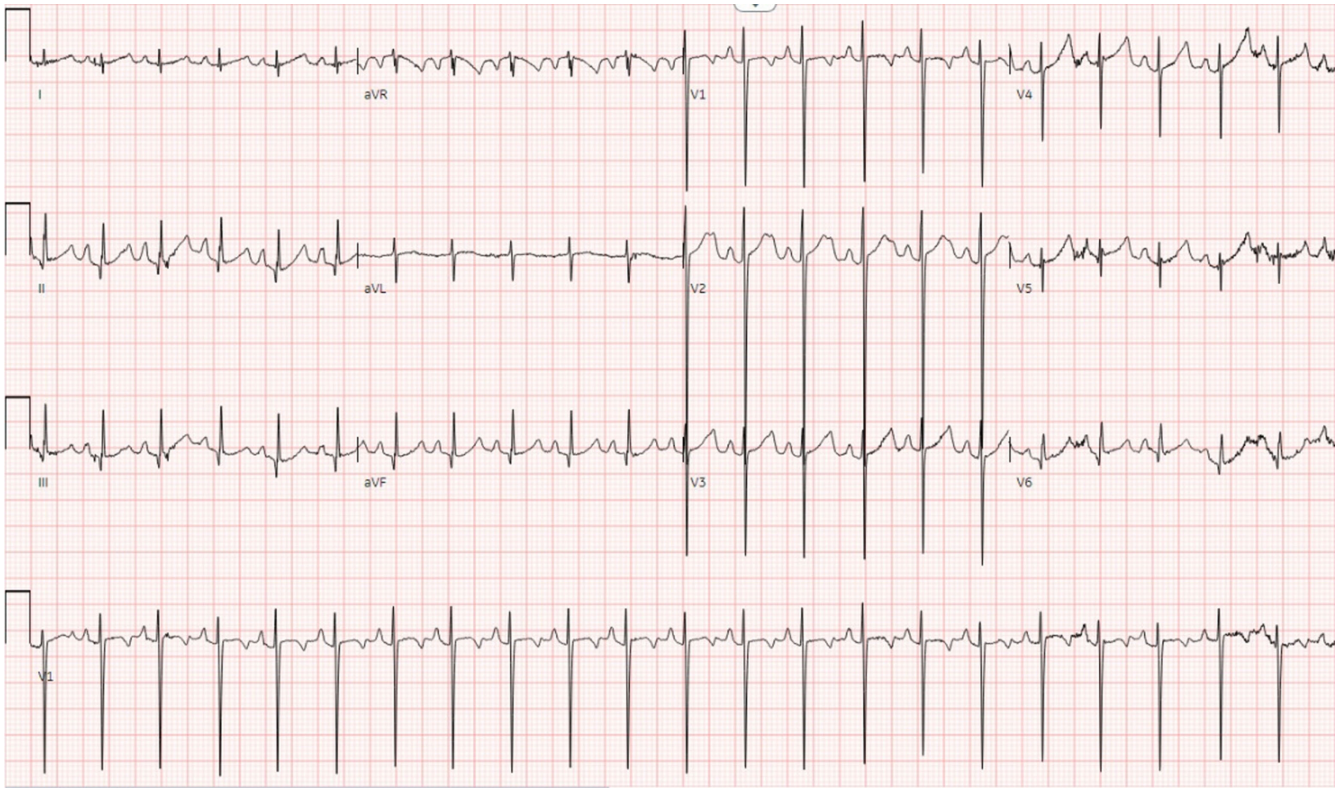


**Figure 2.** Patient's EKG at outpatient follow up visit after treatment with monotherapy trametinib showing normal sinus rhythm.

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recent case reports suggest that this is seen in a variety of RASopathies as well. Ectopic and multifocal atrial tachycardias associated with RASopathies are often refractory to standard beta blocker management and can occur independently of hypertrophic cardiomyopathy.[5–6]

Trametinib is a selective reversible allosteric inhibitor of Mitogen-activated protein kinase kinase 1 (MEK1) and Mitogen-activated protein kinase kinase 2 (MEK2 activity), approved by the United States Federal Drug Association to treat specific cancers due to mutation in the proto-onco gene serine/threonine-protein kinase B-Raf (BRAF mutations). It acts as an inhibitor of the Ras-MAPK pathway that is downstream of upregulating RASopathy mutations, including the HRAS mutation of Costello syndrome.[3]

Several case reports have shown trametinib to benefit certain RASopathy patients with hypertrophic cardiomyopathy, lymphatic abnormalities, and concurrent arrhythmias.[3–4,7] These initial models suggested that inhibition of MEK1 and MEK2 acts via reversing excess cell proliferation of the myocardium thus causing alleviation of arrythmias secondary to hypertrophy. However, some studies suggest the cardiac symptoms of RASopathies are primarily due to calcium dysregulation from the Ras-MAPK pathway's downstream impact on intracellular calcium ion channels.[5] Cases such as these provided the foundation for use of trametinib in this case. The patient's response to treatment with a disease-modifying agent supports that the arrythmia was secondary to the genetic disease process and improved via downstream effects of trametinib. Knowledge of the pathophysiology behind the mechanism of action of this arrythmia and trametinib's role in management remains limited and further study is warranted. While further study is pursued, trametinib should be considered as a disease-modifying therapy for RASopathy patients with arrhythmia who are refractory to conventional treatment.

It is worth noting that trametinib has been associated with several major side effects including dermatitis, haemorrhage, venous thrombosis, colitis, ocular toxicity, interstitial lung disease, and more. Routine monitoring for these complications is necessary. This patient was started at a low dose of 0.125 mg daily, which was not titrated due to risk of adverse events and the desired effect had been achieved. Case reports using targeted therapy for RASopathies have yet to report long-term management strategies, but due to the mechanism of action, it is likely that patients will need to continue trametinib indefinitely to maintain remission of disease.

There are additional limitations for use of trametinib in RASopathies due to the variety of possible gene mutations. If the patient also has a significant mutation in the mammalian target of rapamycin (mTOR) pathway below MEK in the signal cascade, then trametinib will likely be less effective. Likewise, the mutations causing CFC may affect the binding site of trametinib, rendering it ineffective.[7]

This case suggests that trametinib can be an effective therapeutic option for management of arrhythmias in patients with certain RASopathies, even in the absence of hypertrophic cardiomyopathy. Utilising the lowest dose necessary to achieve desired outcome may help to avoid side effects. Routine monitoring for adverse effects should be performed. Further research should include determining optimal paediatric dosing, long term treatment outcomes, and defining appropriate duration of treatment for this patient population.

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