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Pearls & Oy-sters: Whole Genome Sequencing in Critically Ill Neurologic Patient Leads to Diagnosis with Treatment Implications

Author(s):
Jonathan Read Gaillard, MD, MHSc[1]; Zachary Whitt, MD[2]; Linda M Selwa, MD[3]; David Harris, MD[3]; Kristen N Lee, MD[2, 4]

Corresponding Author:
Kristen N Lee, lekriste@med.umich.edu

Affiliation Information for All Authors: 1. University of Michigan Department of Pediatrics, Division of Pediatric Neurology; 2. University of Michigan Department of Pediatrics, Division of Pediatric Genetics, Metabolism, and Genomic Medicine; 3. University of Michigan Department of Neurology, Division of Epilepsy; 4. University of Michigan Department of Internal Medicine, Division of Genetic Medicine

Equal Author Contribution:
Jonathan Gaillard and Zachary Whitt contributed equally to this work; Special designation of co-first authors

Contributions:
Jonathan Read Gaillard: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Zachary Whitt: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Linda M Selwa: Drafting/revision of the manuscript for content, including medical writing for content
David Harris: Drafting/revision of the manuscript for content, including medical writing for content
Kristen N Lee: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

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Pearls:

- *TANGO2*-related metabolic crisis can present at any age and can include lactic acidosis, hyperammonemia, hypoglycemia, life-threatening arrhythmias, rhabdomyolysis and/or seizures.
- Whole genome sequencing can provide new explanations for acute enigmatic presentation, altering management.

Oy-sters:

- It is important to keep genetic metabolic epilepsies in the differential for patients with undiagnosed epilepsy syndromes without identifiable structural cause.
- Repeat or re-evaluation of previous genetic testing can lead to new diagnoses with implications for management.
- Metabolic crisis can lead to life-threatening arrhythmias.

Abstract

Many adult patients with a history of seizures and global developmental delay do not have an identified etiology for their epilepsy. Rapid whole genome sequencing (rWGS) can be used to identify a genetic etiology in critically ill patients to provide actionable interventions. In this case, a 27-year-old patient with a history of epilepsy, global developmental delay, and intellectual disability presented with altered mental status and new abnormal movements. The patient acutely declined over the course of 24-48 hours of presentation, including nonconvulsive status epilepticus leading to intubation for airway protection, two episodes of ventricular tachycardia requiring synchronized cardioversion, and one episode of supraventricular tachycardia. The patient was found to be in metabolic crisis. Metabolic workup and rapid whole genome sequencing were sent. Patient was treated with 10% dextrose in normal saline and a mitochondrial cocktail. She received treatment with ammonia scavengers and hemodialysis with resolution of metabolic crisis. rWGS found a homozygous pathogenic variant in *TANGO2* and a *de novo* pathogenic variant in *KCNQ1*, ultimately leading to creation of a metabolic emergency protocol and implantable cardioverter defibrillator (ICD) placement. This case highlights the use of rWGS in an acutely ill patient leading to actionable interventions. It also highlights the utility and importance of genetic sequencing in re-evaluation of adult neurologic patients.

Case Report

A 27-year-old female with diagnosis of probable focal epilepsy previously well-controlled on levetiracetam, developmental delay (DD), intellectual disability (ID), episodic ataxia, and hypothyroidism presented to the emergency department (ED) with subacute functional decline and seizures. The day before presentation, she "slumped over" and was unable to ambulate or talk. During a neurology virtual visit, her activity, responsiveness, and mental status improved toward baseline. An increase in levetiracetam was recommended. On the day of presentation, she woke in her usual state of health but then experienced a second similar episode, prompting presentation to the ED.

Upon initial evaluation in the ED she was obtunded, but mental status improved over the next 12 hours. Workup revealed elevated transaminases [AST 78 U/L (N: <34), ALT 114 U/L (N: 10-49)], urinalysis suggestive of infection (though culture was ultimately negative), and liver lesions on ultrasound. Computed Tomography (CT) liver revealed several hypodense lesions, consistent with hemangiomas. She resumed ambulation and speech improved toward baseline. Thus, her residual altered mental status was presumed to be post-ictal. Neurology recommended 2g levetiracetam bolus and increase in maintenance dosing, with outpatient follow up. However, she became lethargic hours later and was admitted to an observation unit.

Over the next day, mental status worsened with marked lethargy. CT head, Magnetic Resonance Imaging (MRI) brain, and continuous electroencephalogram (EEG) were ordered. Neuroimaging was unrevealing (Figure 1A). EEG revealed multiple non-convulsive seizures (Figure 1B) which improved with intravenous lorazepam. Venous blood gas revealed metabolic acidosis with lactate 5.5 mmol/L (N: < 2.2). She received multiple intravenous fluid boluses, was started on empiric antibiotics at meningitic dosing, and was transferred to the intensive care unit.

She was intubated for airway protection. After induction with rocuronium and etomidate, she developed supraventricular tachycardia, treated with metoprolol (Figure 2A). On day 2, she experienced episodes of pulseless ventricular tachycardia requiring synchronized cardioversion. Long QT was noted on electrocardiogram (Figure 2B). Multiple medical specialties were consulted, including genetics who were concerned for *TANGO2*-related disease, mitochondrial disorder, or other inborn error of metabolism (IEM). Metabolic workup including plasma amino acids, urine organic acids, acylcarnitine profile, creatine kinase (CK), ammonia, and rapid trio whole genome sequencing (rWGS) was sent. Family history was non-contributory, and parents denied consanguinity.

Testing revealed hyperammonemia (208 umol/L, N: < 60) and elevated CK (1651 U/L, N: 26-180), suggesting metabolic crisis. Plasma amino acids, urine organic acids, and acylcarnitine profiles were consistent with liver dysfunction. 10% dextrose in normal saline (D10NS) and a mitochondrial cocktail were started. She received a loading dose of ammonia scavenger Ammonul and a three-hour run of hemodialysis for hyperammonemia. Ammonul infusion and D10NS were continued for 3 days, which resolved the hyperammonemia, hyperCKemia, and metabolic acidosis.

Sedation was weaned but depressed mental status persisted. Repeat MRI brain showed restricted diffusion and mild pachymeningeal enhancement involving the left parietal and occipital lobes, radiographically concerning for Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) (Figure 1C). Repeat continuous EEG on days 7-8 found two electrographic seizures at O1 (Figure 1D) treated with two separate 10 mg phenytoin equivalents/kilogram fosphenytoin loads followed by maintenance dosing.

Due to testing lab delays, rWGS resulted after 12 days, revealing a homozygous pathogenic deletion of exons 3-9 in *TANGO2* [(?_20041870)-(20074530_?)DEL 32.66kb)], one inherited from each parent, and a *de novo* pathogenic variant in *KCNQ1* (c.1766G>T, p.G589V) associated with autosomal dominant Long QT syndrome 1 (MIM# 192500). Both *TANGO2* and *KCNQ1* confer significant risk for long QT thus she underwent implantable cardioverter defibrillator (ICD) placement (Figure 2C). She received a metabolic action plan and started supplementation of B-complex vitamins. Nitrogen-scavenging medications were discontinued based on genomic results. After further improvement, she was discharged to inpatient rehabilitation and subsequently home.

Discussion

TANGO2-Related Metabolic Encephalopathy and Arrhythmias (TRMEA, MIM#: 616878) is an autosomal recessive condition first described in the literature in 2016[1]. TRMEA was originally described in 9 families with episodic rhabdomyolysis, hypoglycemia, hyperammonemia, and susceptibility to tachyarrhythmias. The phenotype has expanded to include seizures, episodic ataxia, ID, DD, and hypothyroidism. The exact pathophysiology of TRMEA is unknown. Efforts to localize the protein have shown it to be involved in transport from the endoplasmic reticulum to the Golgi apparatus as well as functioning in the mitochondria, which may explain some features that are similar to a fatty acid oxidation disorder while in other ways acting similarly to a mitochondrial disorder[2].

TRMEA typically presents in childhood, particularly with metabolic crises, but diagnosis varies from 8 months to 26 years[3]. Our patient's diagnosis at age 27 underscores the need to consider TRMEA in adulthood. While identification of IEMs has improved with technological advancements as well as augmentation of knowledge regarding later- onset phenotypes, these syndromes are likely underdiagnosed. IEMs should be considered for patients with epilepsy who are critically ill, especially if the etiology of their epilepsy is unknown. A review of known IEMs identified 600 metabolic epilepsies, 70% which could be screened with standard metabolic testing and more than 100 had significant treatment implications[4]. While the ultimate trigger of the metabolic crisis in our patient cannot be determined, decreased caloric intake, stress, and possible infection may have contributed. Of note, despite usage immediately preceding supraventricular tachycardia, neither rocuronium nor etomidate are contraindicated from a metabolic standpoint.

This case demonstrates the utility of rWGS in a critically ill adult patient. Others have documented clear clinical and financial benefit to employing this testing[5]. However, utility of genomic testing is still dependent on information provided to the interpreting lab. While TRMEA was highly suspected based on clinical presentation and could have been identified with single gene sequencing or gene panel, targeted testing would have missed the *de novo* variant in *KCNQ1*, another risk factor for arrhythmias or death. Without genetic diagnosis this patient may not have undergone ICD placement (identification of *TANGO2* variants alone does not usually prompt ICD placement, but identification of a second significant arrhythmogenic predisposition provided additional evidence of necessity) or implementation of a metabolic action plan and supplementation of B-complex vitamins. Additionally, this diagnosis has screening protocols for long term management, which altered her ongoing care.

This case highlights the importance of genetic testing and re-evaluation in adults with epilepsy. The patient previously completed chromosomal microarray (CMA) in 2010 that was reportedly negative. However, a 6-exon deletion in a gene of unknown significance at that time may not have been reported. Using today's technology, the homozygous deletion would be reportable,

but evolution in testing will continue, and repeat testing remains important. Genetic testing panels now include multiple common genes associated with epilepsy (including *TANGO2*) and can detect multiexon deletions on Next Generation Sequencing platforms. As of May 2022, *TANGO2* is included on six commonly ordered epilepsy panels as well as other types of panels including hypoglycemia and rhabdomyolysis/metabolic myopathies.

Genetic testing in adults with epilepsy leads to diagnosis in 10.9-23% of patients tested[6–8]. Diagnostic yield of genetic testing in adults increases with decreasing age of onset of epilepsy, infancy being highest (29.5-38.6%)[8–10]. ID (14-16%) or DD (36.4%) also increase diagnostic yield[6,8,10]. Diagnostic yield in pediatric studies for epilepsy starting less than 2-3 years of age is similarly elevated at 15.3-38%, with highest yield in patients with epileptic encephalopathies[9–12]. Genetic diagnoses leads to actionable changes in management in 17-30% of patients[7,11]. Our patient's dual diagnoses of TRMEA and Long QT Syndrome 1 led to ICD placement, mitochondrial cocktail prescription, and implementation of a metabolic emergency protocol plan.

Given lower cost, CMA is usually considered first in patients with dysmorphisms, multiple congenital anomalies, autism, DD, and/or ID. Patients who do not fit these criteria may benefit instead from targeted gene panels prior to more comprehensive testing[13]. Additionally, reevaluation of previously completed genetic testing is important and can lead to diagnosis for 4.8-23.4% of patients with previously non-diagnostic tests.[9,12] Subsequent genomic sequencing can lead to a genetic diagnosis in 32.1% of patients with previously negative testing[13]. Therefore, previous negative testing does not eliminate the possibility of a genetic condition and must be considered in the differential diagnosis, especially when the clinical phenotype is consistent.

Conclusion

Our case highlights the utility of rWGS in an acutely ill patient leading to diagnosis with actionable interventions including metabolic emergency protocol, mitochondrial cocktail prescription, and ICD placement. Genetic testing in adults with epilepsy can lead to diagnoses more often in patients with younger age of onset, ID, or DD. Genetic diagnosis of epilepsy should remain on the differential in the appropriate clinical context, and genetic testing should be reevaluated as ongoing discoveries can lead to diagnoses with actionable interventions.

Figures

Figure 1. **Representative MRI and EEG findings before and after arrest.**
(A) Diffusion Weighted Imaging (DWI) MRI sequence on Day 1 of hospital admission showing no diffusion restriction and (B) initial EEG showing onset (red arrow) of a slowly evolving generalized electrographic seizure (LFF: 1 Hz HFF: 70 Hz Notch: OFF Sensitivity: 10 uV/mm Timebase: 15mm/sec). (C) DWI MRI sequence on Day 6 of admission showing left posterior quadrant cortical diffusion restriction (white arrow) correlating to (D) left posterior quadrant focal seizures black bounding boxes) in T3-T5, T5-O1, and P3-O1 seen on continuous EEG monitoring the following day (LFF: 1 Hz HFF: 70 Hz Notch: OFF Sensitivity: 10 uV/mm Timebase: 15mm/sec).

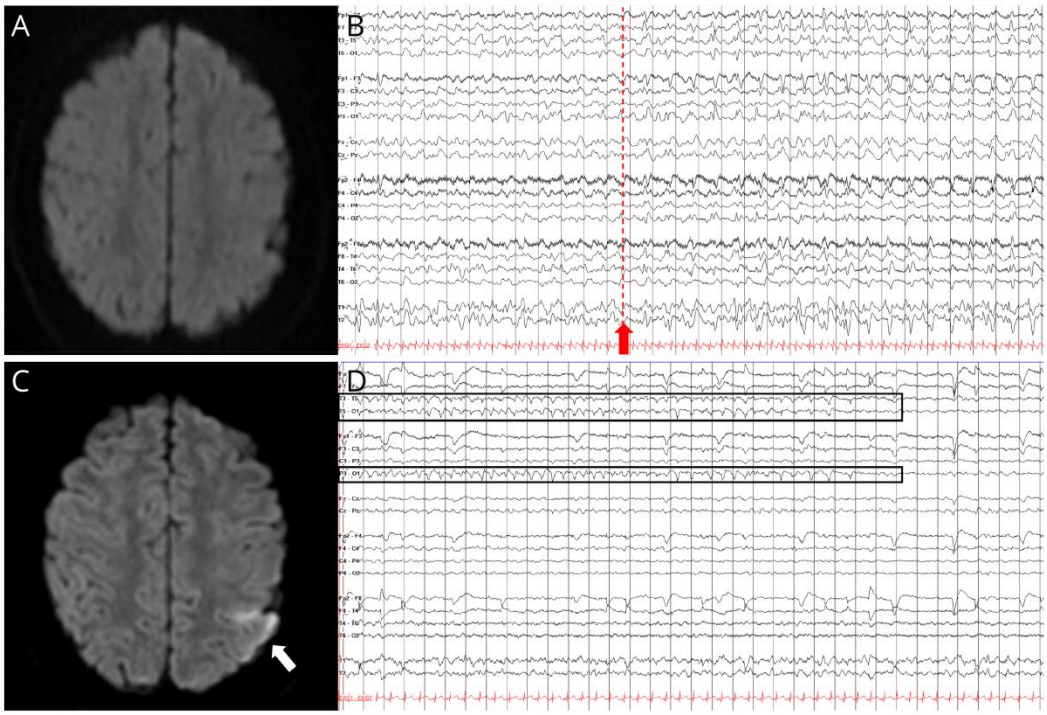
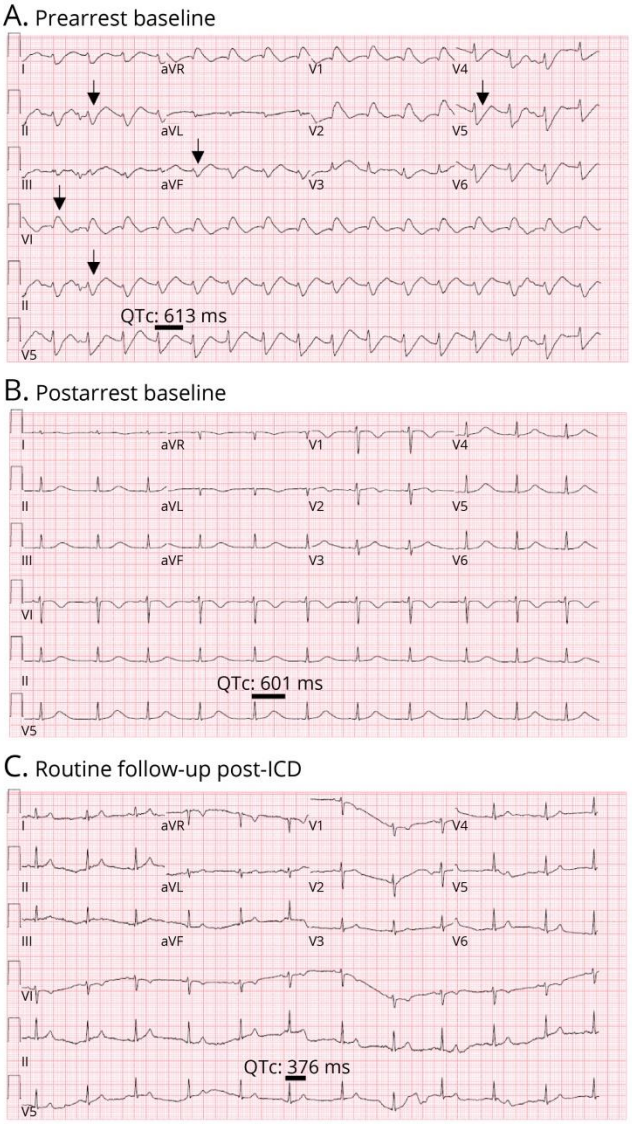


Figure 2. Electrocardiogram (EKG) findings before and after cardiac arrest.
(A) Pre-intervention EKG showing widened QRS complexes (arrows) and prolonged QT intervals with a QTc of 613ms (black bar). (B) Post-arrest and intervention EKG with continued prolonged QTc of 601ms (black bar). (C) Surveillance EKG from about one year after initial presentation and following ICD placement. QTc now at 376ms (black bar). All EKGs taken at paper speed of 25 mm/sec.



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