A novel frameshift mutation, KCNH2 [p.Asp896ArgfsX79], leading to malignant ventricular arrhythmia, identified after treatment of gastro-intestinal bleed

Kim, Wan Cheol, Lemire, Edmond, Nosib, Siddarth Aryaman and Nosib, Shravankumar

Available at http://clok.uclan.ac.uk/38283/

Kim, Wan Cheol, Lemire, Edmond, Nosib, Siddarth Aryaman and Nosib, Shravankumar (2021) A novel frameshift mutation, KCNH2 [p.Asp896ArgfsX79], leading to malignant ventricular arrhythmia, identified after treatment of gastro-intestinal bleed. CJC Open . ISSN 2589-790X (In Press)

It is advisable to refer to the publisher’s version if you intend to cite from the work.
http://dx.doi.org/10.1016/j.cjco.2021.06.005

For more information about UCLan’s research in this area go to http://www.uclan.ac.uk/researchgroups/ and search for <name of research Group>.

For information about Research generally at UCLan please go to http://www.uclan.ac.uk/research/

All outputs in CLoK are protected by Intellectual Property Rights law, including Copyright law. Copyright, IPR and Moral Rights for the works on this site are retained by the individual authors and/or other copyright owners. Terms and conditions for use of this material are defined in the policies page.
A novel frameshift mutation, KCNH2 [p.Asp896ArgfsX79], leading to malignant ventricular arrhythmia, identified after treatment of gastro-intestinal bleed.

Wan Cheol Kim MD FRCPC, Edmond Lemire MD PhD FRCPC FCCMG, Siddarth Nosib BSc, Shravankumar Nosib MD FRCPC

PII: S2589-790X(21)00158-X
DOI: https://doi.org/10.1016/j.cjco.2021.06.005
Reference: CJCO 366

To appear in: CJC Open

Received date: 17 March 2021
Accepted date: 1 June 2021

Please cite this article as: Wan Cheol Kim MD FRCPC, Edmond Lemire MD PhD FRCPC FCCMG, Siddarth Nosib BSc, Shravankumar Nosib MD FRCPC, A novel frameshift mutation, KCNH2 [p.Asp896ArgfsX79], leading to malignant ventricular arrhythmia, identified after treatment of gastro-intestinal bleed., CJC Open (2021), doi: https://doi.org/10.1016/j.cjco.2021.06.005

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of Canadian Cardiovascular Society.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
A novel frameshift mutation, $KCNH2$ [p.Asp896ArgfsX79], leading to malignant ventricular arrhythmia, identified after treatment of gastro-intestinal bleed.

Short Title: Torsades de Pointes VT complicating GI bleed

Wan Cheol Kim, MD FRCPC$^1$, Edmond Lemire, MD PhD FRCPC FCCMG$^2$, Siddartha Nosib BSc$^3$, Shravankumar Nosib MD FRCPC$^4$

1. Department of Medicine, University of Dalhousie, QE11 Health Sciences Center, 1796 Summer Street, Halifax, Nova Scotia B3H 3A7, Canada

2. Division of Medical Genetics, University of Saskatchewan, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK, S7N 0W8, Canada

3. College of Medicine, University of Central Lancashire, Flyde Road Preston PR 1 2HE, United Kingdom

4. Department of Medicine, University of Saskatchewan, Royal University Hospital, 103, Hospital Drive, Saskatoon, SK, S7W 0W8, Canada

Word Count: 1617

Corresponding Author:

Dr. Shravankumar Nosib

1010 Pohorecky Bay, Saskatoon, Saskatchewan, S7W 0J4

shravan.nosib@gmail.com

1 (306) 715-9997
Summary
A novel frameshift mutation KCNH2 [ p.Asp896ArgfsX79] leading to malignant ventricular arrhythmias is identified. The proband presented with acute GI bleed, treatment of which with IKr blockers, led to TdP VT and unmasking of LQTS. The management of this patient in the setting of chronic liver disease is underlined. The significance of variants in de novo mutations is also emphasized.

Abstract
A novel frameshift mutation in the KCNH2 gene for Long QT Syndrome Type 2 (LQTS2) was identified after Torsades de Pointes ventricular tachycardia (TdP VT) in a 49-year-old patient managed with octreotide and nadolol for an acute variceal bleed. Inspite of removal of offending medications and correction of underlying electrolyte abnormalities, the patient’s QT interval remained prolonged at 521 ms, raising the suspicion of an underlying channelopathy. Genetic studies confirmed heterozygosity for a novel frameshift mutation for KCNH2 gene, D896Rfs X79. We explore the pathogenicity and clinical impact of this variant mutation.

Introduction
LQTS2 is an inherited channelopathy that results in prolongation of the QT interval that may manifest clinically as TdP VT and sudden cardiac death if untreated.

Almost two-thirds of the mutations of the KCNH2 gene are missense mutations, wherein a single change in the nucleotide sequence results in a defective amino acid causing loss
of function of ionic channel, Kv11.1. The remaining one third of the mutations of the 
*KCNH2* gene are either nonsense mutations or frameshift mutations. These mutations, by 
modifying protein synthesis, generate impaired alpha subunits of the Kv11.1 ionic 
channel.

We report a patient who presented with an acute gastrointestinal bleed, in whom therapy 
provoked TdP VT from QT prolonging drugs. Diagnostic work-up unmasked a novel 
frameshift mutation in the *KCNH2* gene causing LQTS2. This variant mutation, 
D896RfsX79, has not been reported previously in the genome databases

**Case Presentation**

A 49-year old male, recently diagnosed with liver cirrhosis, presented with a 1-week 
history of shortness of breath and fatigue secondary to a recurrent variceal bleed. His 
medications included nadolol, furosemide, spironolactone, lansoprazole, and 
levothyroxine. His medical history included a remote mitral valve repair. He denied 
history of presyncope or syncope. There was no history of sudden cardiac death in his 
family.

His vital signs were stable. Cardiorespiratory exam was normal. There was no evidence 
of chronic liver disease.

His hemoglobin was 72 g/L, with abnormal liver function tests, and he had an elevated 
serum creatinine of 124 µmol/L. His admission potassium was 4.6 mmol/L. His ECG 
showed a resting HR of 68 bpm and QTc of 520 ms (Figure 1A).
He was started on octreotide infusion (50 mcg/hr) after 50 mcg IV bolus along with nadolol therapy. He received 1 unit of packed red blood cells. Gastroscopy revealed grade II varices with active bleeding, treated with banding. Post-procedure, he developed syncope and was unresponsive. He was pulseless. Telemetry showed Torsades de Pointes VT\(^1\) (Supplementary Figure S1). He was resuscitated with one cycle of cardiopulmonary resuscitation, single defibrillation, and a 2g of IV magnesium sulfate. His serum magnesium level was 0.67 mmol/L His heart rate had dipped to 47 bpm prior to the arrest and it remained in the 50s post code (Figure 2A and 2B). Telemetry strips documented early PVCs as the initiating event of the TdP VT (Figure 1B).

He was started on isoproterenol infusion while octreotide and nadolol were discontinued. Echocardiography showed normal left ventricular systolic function and left heart catheterization showed normal coronaries. However, his QTc remained prolonged at 521 ms raising the suspicion of an underlying channelopathy (Figure 1).

A routine ECG done 5 years prior showed a corrected QT interval of 426 ms. Interestingly the patient had not been diagnosed with liver cirrhosis at the time. Genetic modulation in the setting of liver cirrhosis was thought to be unmasking QT-prolongation and possible channelopathy.

**Genetics**

Genetic analysis was carried out after discussion with patient, his wife and daughter about possible implications in case of a positive result. The following 12 genes currently known to be associated with LQTS were screened: \(KCNQ1, KCNH2, SCN5A,\)
ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9 AND SNTA1. The patient was found to be heterozygous for a frame shift mutation in the KCNH2 gene for LQTS2 syndrome with insertion of two cytosines in the genomic sequence (c.2684_2685insCC) leading to a premature stop codon at position 79 of the new reading frame (p.Asp896ArgfsX79) potentially explaining his prolonged QT interval. This mutation causes a shift in reading frame starting at codon Aspartic acid 896 and changing it to an Arginine. As a class 1 mutation, it is expected to result in either an abnormal, truncated protein product or loss of protein from this allele through nonsense-mediated RNA decay. At the molecular level the pore domain of the alpha subunit of the Ikr channel is affected, specifically transmembrane segments S5-S6 which contribute to the pore domain.

The full transcript of the mutation is: c.2684_2685insCC:p.Asp896ArgfsX79(D896RfsX79) in exon 11 of the KCNH2 gene (NM_000238.2) (Supplementary figure S2). The normal sequence with the bases that are inserted in braces is: GCAC{CC}GCAC. The mutation is not reported in major variant databases.

The patient’s only daughter declined screening and family screening could also not be performed as the patient was a first generation immigrant from India.

Management

He was offered an implantable cardioverter-defibrillator (ICD) for secondary prevention but he declined this therapy. However, he agreed to proceed with a permanent pacemaker implantation to prevent further episodes of bradycardia.
Discussion

This case highlights the unique challenges of managing acute GI bleed with beta-blockers and octreotide in the setting of undiagnosed Long QT Syndrome. Both pharmacologic agents likely caused his bradycardia, which is a known trigger for TdP VT under the setting of prolonged QT interval. In fact the patient suffered a perfect storm scenario with cirrhosis, a known QT prolonging condition, electrolyte abnormalities and acute illness.

QT prolonging agents should be discontinued. It is optimal to keep potassium levels between 4.5-5 mmol/L. Beta-blockers are recommended in Long QT Syndrome with prolonged QT or those who had cardiac events. Our patient was on nadolol, though intended for treatment of portal hypertension, had failed to prevent syncope, Torsades de Pointes, and pulseless VT during acute illness characterised by bradycardia and electrolyte abnormalities. This is not an uncommon phenomenon as one previous study had described that LQTS2 carriers despite being on beta-blocker therapy had higher rates of cardiac events compared to LQTS1 (23% vs 10% over 5 year period).

In high risk patients in whom beta-blockade is ineffective or not tolerated, ICD therapy and/or left cardiac sympathetic denervation (LCSD) is indicated as per guidelines. There is a marked reduction in the incidence of arrhythmic SCD after LCSD; however in high risk patients with LQTS, recurrent lethal electric events have been reported in up to 50% of them. LCSD is not an alternative to ICD but rather complementary to it.

Around 20 years ago, it was found that one of the long QT causing genes was mapped to chromosome 7. Later, it was determined that the KCNH2 (or HERG) gene codes for a
potassium channel that facilitates the rapid component of the delayed outward-rectifying potassium current responsible for generating a QT interval. Numerous mutations in this gene have since been reported and are thought to be responsible for prolonged QT which causes LQTS2. The mutation found in our case (c.2684_2685insCC) generates a premature termination codon at position 79 of the new reading frame (p.Asp896ArgfxX79) and is expected to result in a defective channel which clinically prolongs QT interval. Resulting haploinsufficiency would cause a milder phenotype, as only about 50% of the Kv11.1 channels would lose their function while the remaining function normally. This may explain the fact that our proband was asymptomatic prior to presentation. Other frameshift mutations in the KCNH2 gene have been reported in the HGMD(8). More recently Yoo et al. have reported a novel KCNH2 frameshift mutation (c.46delG) in a family with congenital LQTS2.(1) There was a high incidence of sudden cardiac death in this family and repeated syncopal spells in the proband, thus phenotypically very different from the proband reported in our case.

It is important to underline the fact that not all truncating variants have been labeled as pathogenic. Clinvar reports 59 nonsense variants for KCNH2 out of which 51 are pathogenic, 4 are likely benign, 6 are likely pathogenic and 1 is uncertain status. Frameshift variants, as identified in our patient, also often end up in a downstream truncation. Clinvar identifies 187 of these; 148 being pathogenic, 8 uncertain status, 1 likely benign and 5 conflicting interpretations.

Experimental evidence for truncating variants have been reported by De Zio et al in an Italian family in which the proband suffered recrurent episodes of ventricular fibrillation arrest despite a QTc interval less than 500 ms, as well as C-terminally located mutation of
the \textit{KCNH2} gene; both of which are predictive of a more benign course. However Moss et al have demonstrated in their study that patients with mutations exerting dominant-negative functional effect were more susceptible to arrhythmic events independent of clinical risk factors namely QTc duration, beta-blockade and gender.

Thus in our patient the dominant-negative effect of the variant on the Ikr channel subunits over the wild-type \textit{KCNH2} channel subunits may explain the pathogenicity of the mutation in spite of previously documented normal QTc of 426 ms and a previously benign cardiac history.

The prevalence of LQTS has been a controversial topic and it is noteworthy that Schwartz et al had suggested in 1975 that “LQTS is more unrecognized than rare.” In fact prevalence of silent mutations are high in LQT1 patients (36%), moderate in LQT2 patients (17%) and lower in LQT3 patients (10%). Thus undiagnosed LQTS may be a challenging public health hazard that needs further probing to identify new LQTS2 patients before they suffer life-threatening electric events.

\textbf{Novel Learning Points}

1. A novel frameshift mutation (cDNA: c.2684_2685insCC; Variant:p.Asp896ArgfsX79) in the \textit{KCNH2} gene, consistent with a genetic form of LQTS2 is identified.

2. Genetic Variants may modulate arrhythmic risk and may confer higher risk of life-threatening electric events beyond traditional risk factors and in spite of normal QTc intervals.
3. Cirrhosis of the liver has been associated with prolonged QT interval and this effect can be exacerbated by the use of Ikr blockers and other medications. LQTS may be unmasked in the process.

4. QT prolonging agents enhance the arrhythmic risk of SCD and must be avoided in this scenario

**Conclusion**

Our case report describes a patient presenting with QT-prolongation and Torsades de Pointes ventricular tachycardia following a variceal bleed, in whom a heterozygous frameshift mutation resulting in a premature stop codon was identified in the *KCNH2* gene. The use of Ikr blockers uncovered the LQTS2 phenotype and enhanced the risk of TdP VT in this patient.

**Acknowledgements:** None

**Funding Sources:** None

**Disclosures:** Authors declare no conflicts of interest.

**References**

1. Yoo H. S, Medina N. Von Wulffen M.A. et al.: A novel *KCNH2* frameshift mutation (c.46delG) associated with high risk of sudden death in a family with congenital LQTS type2. Int J. Arrhythm 2021, 22:1.).
2. Dessertenne F. Ventricular tachycardia with two variable opposing foci. Arch Mal Coeur Vaiss 1966; 59: 263-272.

3. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2010; 55: 934–947.

4. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. J Am Coll Cardiol 2006; 48: e247–e346.

5. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with β-blockers. JAMA 2004; 292: 1341–1344.

6. Jiang C, Atkinson D, Towbin JA, et al. Two long QT syndrome loci map to chromosomes 3 and 7 with evidence for further heterogeneity. Nat Genet 1994; 8:141-147.

7. Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995; 80: 795-803.

8. Stenson PD, Mort M, Ball EV, et al. The Human Gene Mutation Database: 2008 update. Genome Med 2009; 1: 13.
Figure 1. Electrocardiogram of a patient with congenital Long QT syndrome Type 2. (A) Patient was receiving octreotide infusion and nadolol for variceal bleed. QTc is ~520 ms. (B) Taken 60 hrs after Torsade de Pointes and monomorphic Ventricular Tachycardia. Despite correcting hypomagnesemia and bradycardia through Isoproterenol infusion, there still persists a prolonged QTc (~520 ms) indicating a raised possibility of congenital Long QT Syndrome. Evidence of macrovolt T wave alternans in precordial leads.
Figure 2. (A) Pre-code ECG showing HR of 47 bpm and a QTC of 579 ms. (B) Post-code ECG showing HR of 57 bpm and QTc of 578 ms.
**Supplementary Figure S1.** Telemetry recordings of Torsade de Pointes VT. Initiating early PVCs are seen prior to onset of TdP.

**Supplementary Figure S2.** Electropherogram showing mutated sequence (red arrow).