# Inaccurate diagnosis of Brugada syndrome in a healthy woman based on SCN5A mutation classification

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## Introduction

Brugada syndrome (BrS) is an arrhythmogenic disorder often inherited in an autosomal-dominant fashion that is suspected when an electrocardiogram (ECG) shows characteristic ST-segment elevation in the right and anterior precordial leads (type 1 Brugada ECG pattern). Patients with BrS have an increased risk of sudden cardiac death owing to episodic polymorphic ventricular tachyarrhythmias.[1] The diagnosis of BrS is based on the presence of the type 1 Brugada ECG pattern, which may occur either spontaneously or after provocation tests with sodium channel blockers.[2] *SCN5A*-mediated BrS (BrS1) represents the most common genetic subtype and loss-of-function mutations in the *SCN5A*-encoded NaV1.5 sodium channel, accounting for approximately 20% of BrS.[3] Guidelines recommend BrS genetic testing when there is a sufficient clinical index of suspicion for the disease.[4,5] However, genetic test results must be scrutinized carefully to make sure there is appropriate concordance.[6] Herein, we illustrate the potential consequences of premature and inappropriate use of BrS genetic testing and the potential danger of relying on a genetic test company's annotation and interpretation of the identified variant.

## Case report

A 45-year-old woman presented with a previous diagnosis of BrS rendered at an outside medical facility. The patient was referred to Mayo's Genetic Heart Rhythm Clinic in an effort to receive clarity about the underlying diagnosis and treatment recommendations, which relied in part on a genetic test result that was interpreted as being "positive" for the disorder. The patient requested an independent evaluation of her son as well, who also was "positive" for the identified genetic variant.

The patient was healthy previously, with no family history of BrS. She had never had a sudden, without warning, fainting episode. Starting in 2002, she experienced several episodes of rapid heart rate action, palpitations, and pressure in her throat, and a reported sense of "impending doom" or feeling like dying. In 2012, she had an echocardiogram, ECG, stress test, and tilt table test to evaluate these symptoms. Her echocardiogram was performed at an outside facility and reportedly showed mild mitral valve prolapse with trivial mitral regurgitation. Left ventricular size and function were normal. Her ECG was interpreted as suspicious for BrS although it did not evidence a type 1 Brugada ECG pattern, only incomplete right bundle branch block and T-wave inversion (Figure 1). Exercise stress test was normal. Tilt table test was performed in November 2012 and demonstrated postural orthostatic tachycardia (heart rate 76 beats/min supine to 126 beats/min after 70-degree tilt for 9 minutes) and orthostatic hypotension (blood pressure 127/75 mm Hg supine to 73/53 mm Hg). Based on the findings, the patient was diagnosed initially with mild mitral valve prolapse and vasovagal symptoms. However, this initial ECG prompted the physician to initiate BrS genetic testing rather than doing additional ECG testing, such as a Brugada high-lead ECG protocol or a provocative drug challenge with either procainamide or flecainide.

In December of 2012, the ordering physician received a "positive" genetic test result from a commercial genetic test company with the identification of a variant, p.F532C, in *SCN5A* that was classified as a "likely disease-causing" mutation. Based on this genetic test result, the physician next recommended an invasive electrophysiological (EP) study for further risk stratification and to guide the decision for a potential implantable cardioverter-defibrillator implant. The EP study was negative and the patient subsequently underwent procainamide challenge (500 mg over 20 minutes), during which no significant ST-segment changes during or after

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## KEY TEACHING POINTS

- The complexity of determining genetic causality requires that cardiac genetic results be categorized in a gradation of its pathogenic probability to allow physicians the opportunity to be wiser interpreters of genetic test results.
- A weak clinical phenotype should never compel genetic testing, as there is no consistent ruler to which a variant's potential pathogenicity is measured by genetic test companies.
- The scientific community has made considerable progress to prevent sudden cardiac death at all ages, which has allowed medical professionals a better understanding and ability to identify various cardiac channelopathies such as Brugada syndrome.

the infusion were observed (QT interval 422 ms, QTc 506 ms). Nevertheless, the diagnosis of *SCN5A*-mediated BrS secondary to F532C persisted, and mutation-specific cascade testing of her children was pursued. The test returned "positive" for her 16-year-old son.

In May 2014, the patient presented to Mayo's Genetic Heart Rhythm Clinic for a second opinion regarding her and her son's diagnosis of BrS1 secondary to F532C-SCN5A. A transthoracic echocardiogram demonstrated thickened anterior mitral valve leaflet with possible prolapse and trivial posteriorly directed mitral valve regurgitation with normal left and right ventricular size and function. The patient also had a normal Holter and normal stress test. Most importantly, considering the diagnosis in question, another ECG was performed, which demonstrated normal sinus rhythm, left atrial enlargement, incomplete right bundle branch block, and no evidence of a type 1 Brugada ECG pattern (Figure 2).

Based on this testing, as well as the patient's absent clinical phenotype, the index of suspicion for BrS was deemed extremely low. After review of her numerous ECGs from outside institutions, it was determined that none of them exhibited either the type 1 Brugada ECG pattern or any T-wave abnormalities. In fact, all ECGs were essentially normal. The patient did not show any Brugada pattern at rest, with treadmill stress testing reviewed at Mayo, with high-lead ECG protocol performed here, or with a procainamide challenge study performed at an outside institution. The patient's self-described symptoms from her 6 discrete episodes previously were not consistent with a Brugada-related presentation. Also, the patient did not have any family history that would increase the index of suspicion or the pretest probability. Therefore, it was concluded that there was insufficient clinical evidence of BrS in this patient and that the genetic test result was erroneously classified as a "likely disease-causing mutation."

After review of her son's ECGs, including high lead placement, it was determined that there was no suggestion of Brugada pattern and no further investigation necessary for him either (Supplementary Figure 1). The patient was informed that genetic testing in her younger 2 daughters was not necessary, although it was reasonable for both her daughters to receive a high-lead Brugada ECG protocol as a clinical phenotype assessment, given the past consideration of BrS in the family. Upon standard ECG screening review, both daughters were negative for a type 1 Brugada ECG pattern (Supplementary Figures 2 and 3).

## Discussion

Advances in medical genomics have led to an influx of information to the scientific community, affording physicians the ability to combine clinical data with genetic test results for use in diagnosis, risk stratification, treatment, and

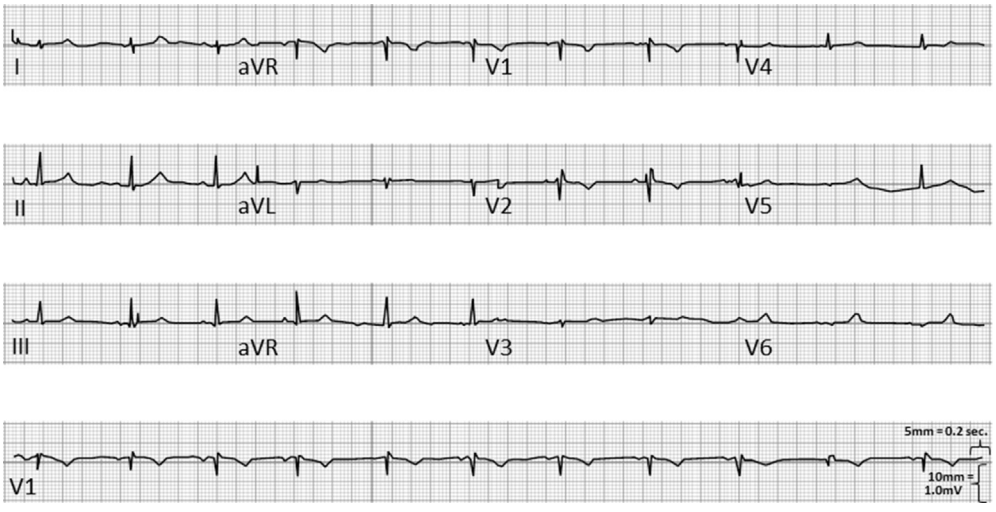


**Figure 1** First ECG obtained on October 4, 2012 showing inverted T waves in $V_{1\text{-}2}$, which compelled the incorrect suspicion of BrS, and prompted BrS genetic testing.

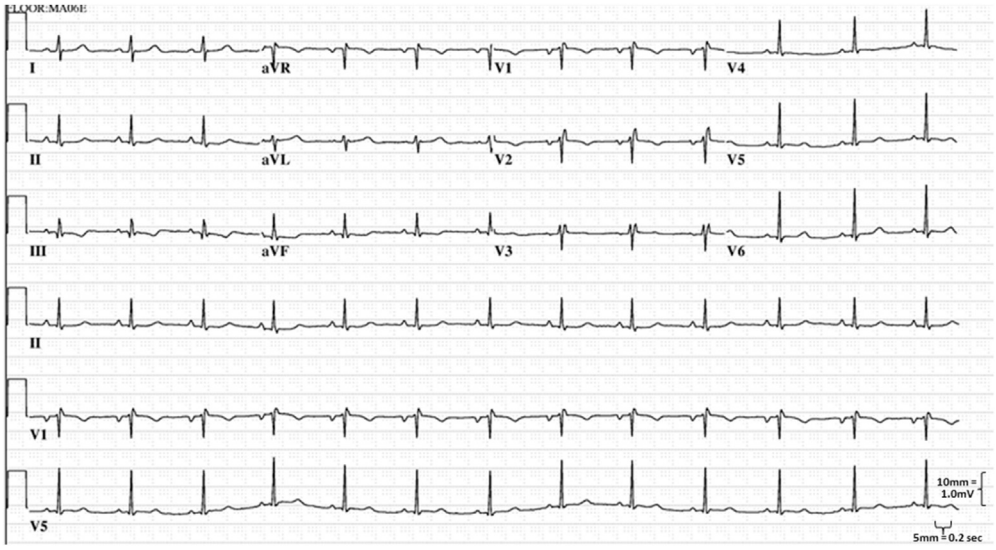


**Figure 2** Final high lead ECG obtained on May 23, 2014 showing no evidence of a Brugada pattern. V1 & V2 moved to 2nd intercostal space. V3 moved to 3rd intercostal space.

prevention.[3] Given the multifactorial nature of genetics, care must be taken in determining when it is appropriate to order a genetic test, how genetic test results should be used in an overall diagnostic evaluation, and the importance of accurate mutation classification in genetic testing. This case report demonstrates how an unwarranted genetic test pursued in the setting of a weak-to-absent clinical phenotype combined with a genetic test company's incorrect variant classification led to an inaccurate diagnosis of BrS, which almost led to an implantable cardioverter-defibrillator implantation in an otherwise healthy patient. On top of that, the patient also experienced stigma and guilt associated with the thought that she had transmitted a potentially life-threatening cardiac condition to her son.

## Patient selection for genetic testing

In any evaluation, special attention when ordering a genetic test, ideally aided by a genetic counselor, must be given, as there are negative consequences to unnecessary testing. Unnecessary genetic testing may propagate further financial burden to the patient, emotional distress, a need to address incidental findings, and the potential for misdiagnosis or mismanagement of a patient's disease.[3] It is imperative that collaboration with those who have a special interest in heritable channelopathies and cardiomyopathies take place in the care of a patient suspected of having a genetic heart disease. The HRS/EHRA Expert Consensus Statement[4] recommends that "comprehensive or BrS1 (*SCN5A*) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype." Clinical evaluation should be guided by the patient's phenotype, specific findings should be noted when genetic tests are ordered, and shotgun-based genetic testing should be avoided.[3] In the case of our patient, the symptoms and ECG findings were not sufficient for the diagnosis of BrS to support proceeding to genetic testing, which subsequently led to a cascade of negative implications and confusion for the patient.

## Interpretation of genetic testing

Even when genetic testing is appropriate, there are still gaps in understanding how to accurately interpret and apply the results to the diagnostic evaluation. The HRS/EHRA/APHRS Expert Consensus Statement[5] provides criteria for BrS diagnosis based on clinical and EP data. Specifically, the criteria for diagnosis of BrS requires ST-segment elevation with type 1 morphology occurring either spontaneously or after provocative drug testing with class I antiarrhythmic medications, or if the patient demonstrates type 2 or type 3 ST-segment elevation after provocative drug testing with class I antiarrhythmic medications inducing a type I ECG morphology. This criterion specifically states that positive genetic testing alone cannot make the diagnosis of BrS, but should be used as supporting evidence of the diagnosis, and "genetic testing is not recommended in the absence of a diagnostic ECG."[5]

In this case, the patient did not meet diagnostic criteria for BrS, thereby confusing the interpretation of a positive genetic test for our patient and her providers. Certainly, we acknowledge that the phenotype could have been masked by female gender (proband) or young age (son) in the patients presented and that we therefore cannot completely rule out the possibility of a concealed BrS phenotype. However, the absence of any evidence of BrS on provocation studies and high-lead ECGs, as well as absence of the phenotype in additional family members, makes this very unlikely. Herein, the decision to pursue genetic testing without a clear phenotype has only complicated the matter rather than being informative. Correct patient selection for testing is imperative for proper

interpretation of genetic testing. The complexities of cardiac genetic testing highlight the need for ongoing collaborative efforts to improve the ways we understand the role of genetic testing in an overall patient presentation and the pathogenicity of identified variants, as unnecessary testing or hasty considerations could have precipitous clinical diagnostic and treatment effects.

## Classification of genetic variants

The multifactorial nature of many diseases and varied outcomes of genetic testing portend the challenges when attempting to determine the pathogenicity of a variant. The complexity of determining genetic causality requires that cardiac genetic results be categorized in a gradation of its pathogenic probability.[7] The classifications given to genetic variants by gene testing companies range from likely benign to probably/definitely pathogenic, with several genetic shades of gray in between, including the dreaded and ambiguous "variant of uncertain significance." Unfortunately, most ordering cardiologists are incapable of independently vetting the genetic test company's classification of the variant, and simply read the genetic test report and act accordingly. Equally unfortunately, most genetic test companies do NOT have what the ordering cardiologist does possess, namely the phenotypic data and clinical history. Without merging of the 2 critical pieces of data (ie, the putative genotype and the ascertained phenotype), serious miscues await. In addition, this must be viewed as a dynamic process rather than a static one. Therefore, even though a variant may have been classified as benign or pathogenic, continued surveillance and constant reevaluation of classification status is required to ensure that a variant was not classified erroneously.[3]

In this case, the F532C-SCN5A variant was classified as "likely disease-causing" based on several case reports and series. This variant was cited in 1 Japanese individual with paroxysmal atrial fibrillation and atrial tachycardia, and was absent in 232 Japanese control samples.[8] Additionally, in a Japanese cohort of sudden infant death syndrome cases, F532C was positive in 1 while absent in 150 Japanese control samples.[9] However, a previously published variant does not necessarily mean that it is a pathogenic one. In fact, it has been estimated that 10% of the previously published *SCN5A*-mediated BrS-associated variants (BrS1) and long QT syndrome–associated SCN5A variants (LQT3) are wrong.[10]

For this variant, given its topological location to the domain I–domain II cytoplasmic linker loop, even if it had been derived from an individual with a compelling case of BrS, the variant would have only a 10% pretest probability of pathogenicity.[10] Given the patient's weak-to-absent phenotype, it is predictably a false-positive, as it is akin to ordering the test on a normal volunteer. In such a setting, recall that 2% of Caucasians and 4%–5% of non-Caucasians host rare variants in *SCN5A*.[11] In contrast, an estimated 1 in 20,000 individuals have BrS1. In other words, when *SCN5A* gene testing is ordered in this context, such a rare variant has 400:1 odds of being a benign variant rather than the testing having incidentally stumbled into either BrS1 or LQT3. As if this available knowledge were not enough to demote F532C's variant classification to benign, in vitro heterologous expression studies revealed normal sodium channel function for NaV1.5 channel's hosting this variant.[10]

## Conclusion

This case is a sobering reminder that serious consequences are sure to come if we fail to become wiser users of genetic testing and wiser interpreters of the genetic test results. As can be seen from this single case, there is much blame to go around. For cardiologists and heart rhythm specialists dealing with patients who may or may not have a heritable cardiac channelopathy like BrS, it is critical for them to sharpen their proverbial "phenotyper's sword" or be willing to refer to a channelopathy specialist before pursuing genetic testing. Here, the weak clinical phenotype should never have compelled use of genetic testing. For the genetic test companies, there is no consistent ruler by which a variant's potential pathogenicity is currently measured.[12] Even as societies like the American College of Medical Genetics try to provide guidance regarding variant adjudication, this case serves as a vivid reminder that the stakes are very high when it comes to variant calls and sudden death–predisposing heart conditions. Sudden cardiac death is a tragedy at any age, and the leaps that the scientific community has made to prevent this tragedy have allowed us to better understand and identify various cardiac channelopathies, such as BrS.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrcr.2017.06.003.

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