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REVIEW ARTICLE
Rare arrhythmias

Brugada syndrome: current diagnostics, epidemiology, genetic data and novel mechanisms (RCD code: V-1A.1)

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Abstract

Brugada syndrome (BrS) is a cardiac channelopathy associated with ventricular arrhythmias and sudden cardiac death. Diagnosis of BrS is based on type 1 BrS electrocardiogram (ECG) pattern (coved pattern) presence, observed spontaneously or after provocation test. The worldwide prevalence of BrS ECG patterns is estimated to reach 0.4% and strongly depends on the population studied. BrS results from various genetic mutations of sodium, calcium and potassium channels and/or associated proteins affecting ion currents. *SCN5A* mutations are the most prevalent in BrS. Pathogenesis of BrS is explained by the depolarization theory, the repolarization theory and the neural crest theory, which seem to be complimentary, at least partially. This review summarizes current diagnostic criteria of BrS and epidemiology of BrS ECG patterns. We also discuss the recent understanding of BrS pathophysiology and the role of genetic testing in BrS. JRCD 2017; 3 (3): 73–80

Key words: Brugada syndrome, diagnostics, epidemiology, genetic testing, mechanisms, rare disease

Introduction

Brugada syndrome (BrS) is an inherited cardiac channelopathy associated with ventricular arrhythmias and sudden cardiac death (SCD), which may be the first manifestation of the disease. In a study of natural history of BrS the mean age of patients at cardiac event was 33 ± 13 years and ranged from 2 months to 55 years [1]. BrS, which is phenotypically, genetically, and functionally the same clinical disorder as sudden unexplained nocturnal death syndrome (SUNDS), beside early repolarization syndrome (ERS), belongs to J-wave syndromes [2–5].

According to the European Society of Cardiology (ESC) clinical practice guidelines, only type 1 BrS electrocardiogram (ECG) pattern (coved pattern), either spontaneous or provoked by intravenously administered sodium channel blockers (including ajmaline, flecainide, procainamide, pilsicainide), is considered diagnostic. Type 2 BrS ECG pattern (saddleback pattern) is considered suggestive for BrS (Figure 1) [6,7]. BrS may be diagnosed when ST-segment elevation ≥2mm is present in at least 1 precordial lead (V1 and/or V2) during standard and/or higher precordial leads placement (also positioned in the second and/or third intercostal space) [6]. Importantly, other tests including ECG exercise testing may also reveal BrS ECG pattern [8,9].

Epidemiology

Estimated prevalence of BrS is 1 in 1000 to 1 in 10 000 and depends on the population studied, with higher occurrence in Southeast Asia, when compared to western countries [6,8,10]. The prevalence of BrS ECG patterns in different regions of the world (selected studies) is shown in Table 1 [11]. Interestingly, the average presence of spontaneous type 1 BrS ECG pattern among East Asian population investigated in the Healthy Aging

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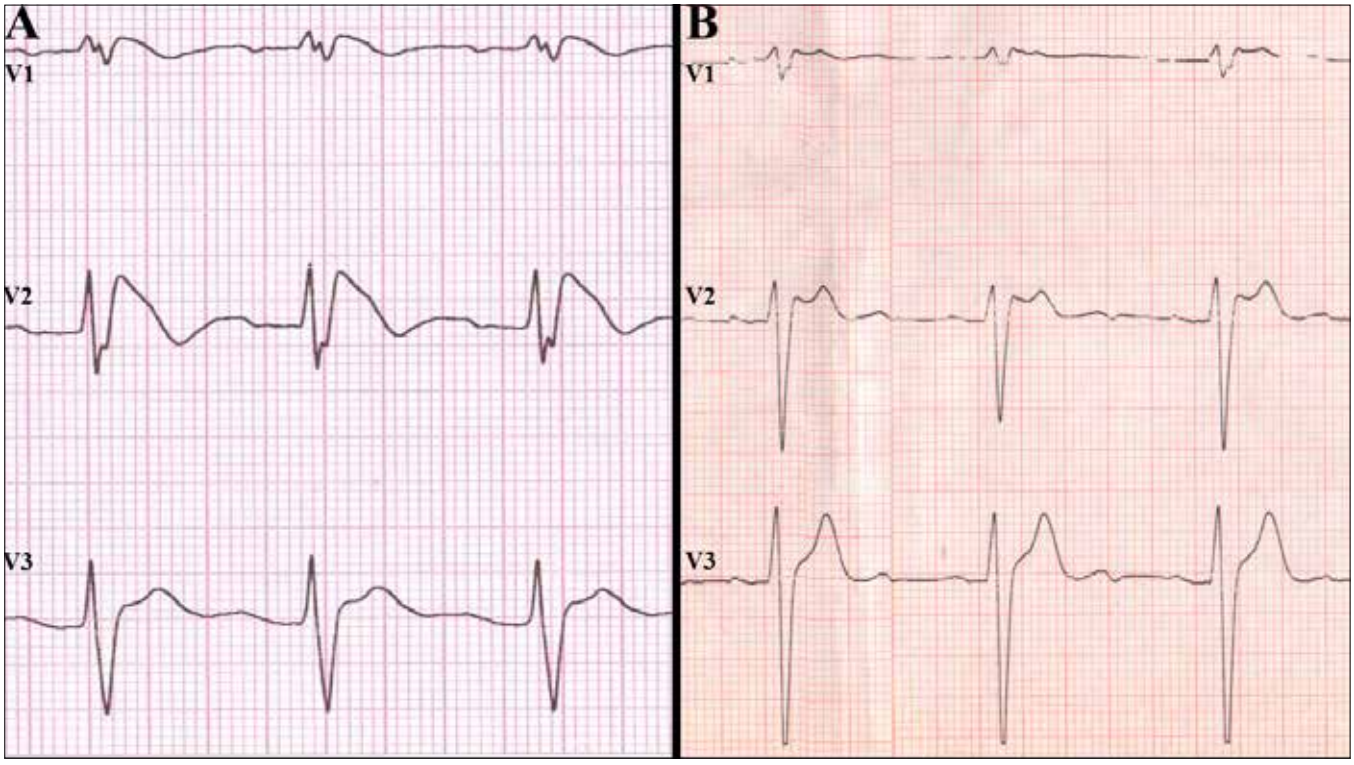

Figure 1. Electrocardiogram (ECG) recordings (25 mm/s, 10 mm/mV) in Brugada syndrome (BrS). ECG diagnostic for BrS: drug (ajmaline)-induced type 1 BrS ECG pattern (Panel A, in lead V2). ECG suspected of BrS: spontaneous type 2 BrS ECG pattern (Panel B, in lead V2)

Longitudinal Study in Taiwan (HALST) cohort was similar to world-wide prevalence (0.077 vs. 0.07%), but saddleback BrS ECG pattern (type 2 and type 3 according to previous classification) was over 10 times more frequent in this Asian population when compared to the world-wide frequency (3.24 vs. 0.28%) [12]. Recent meta-analysis, which included, in most of the studies, all BrS ECG patterns, revealed that worldwide BrS ECG patterns prevalence is 0.4% and it is 9 times higher in men than in women (0.9% vs. 0.1%) [13]. This result is consistent with other reports which indicate that the BrS occurrence may be even eight times higher in men than in women [6, 14]. The trends in incidence of spontaneous type 1 BrS ECG pattern are changing. Casado-Arroyo et al. in a prospective, dual-center registry, compared 447 patients with BrS type 1 ECG pattern diagnosed over nearly 30 years [15]. In patients diagnosed between 1986 and 2002 incidence of spontaneous type 1 ECG pattern was 52.7% (n=87), while in those diagnosed after 2002 (years range: 2003–2014) the percentage reached 26.2% (n=74) [15]. As expected, to unmask type 1 BrS ECG pattern in asymptomatic patients, sodium-channel blockers were used more frequently in the latter group (74.3% vs. 50.0%). Less frequent spontaneous type 1 ECG changes translated to a different clinical manifestation with lower rate of history of aborted SCD (4.6% vs. 12.1%), lower ventricular tachycardia (VT)/ventricular fibrillation (VF) inducibility in electrophysiological study (19.2% vs. 34.8%) and lower incidence of arrhythmic events (VF, SCD, appropriate shock) during follow-up [15].

Importantly, findings of the reported studies must be interpreted in light of different studies methodologies, including not only terms of BrS diagnosis but also changing BrS ECG patterns definitions and populations studied. We should take into account that previous type 2 and type 3 BrS ECG patterns are currently collectively termed type 2 BrS ECG pattern and detailed ECG characteristics were provided in a consensus report [7].

Variability of ECG changes

ECG changes typical for BrS are often transient, and may show dynamic changes depending on the time of the day. In BrS ECG changes usually normalize or do not change with increasing heart rate [16]. Typical BrS ECG changes and ventricular arrhythmia more often occur at rest or during sleep, what indicates the influence of high vagal activity [6]. BrS ECG may also be induced by large meals, especially if rich in carbohydrates, which are believed to shift potassium from the circulation into the cells [6, 17]. This mechanism may be also implicated in unmasking BrS ECG changes during glucose load and glucose and insulin intravenous infusion tests [8].

Importance of genes and genetic data

BrS is inherited in an autosomal-dominant pattern. Genes associated with BrS susceptibility encode sodium, potassium and calcium channels or proteins associated with them. Nowadays numerous pathogenic variants have been identified in over 20 genes [18]. Despite this huge progress, only 30–35% of clinically diagnosed cases are explained by current genetic testing. Contribution

Table 1. Prevalence of Brugada syndrome electrocardiogram patterns in different regions and populations of the world

Study	Population studied (number)	Country	Prevalence of BrS type 1 ECG pattern	Prevalence of BrS saddleback ECG pattern
EUROPE				
Holst et al., 2012, [33]	4 056 152	Danemark	0.001%	0.0005%
Schukro et al., 2010, [34]	47 606	Austria	0.25%	0.27%
Pecini et al., 2010, [35]	18 974	Danemark	0	0.07%
Sinner et al., 2009, [36]	4 149	Germany	0	0
Gallagher et al., 2008, [37]	12 012	Italy	0.02%	0.26%
Letsas et al., 2007, [38]	11 488	Greece	0.02%	0.2%
Blangy et al., 2005, [39]	35 309	France	0.03%	0.20%
Junttila et al., 2004, [40]	3 021	Finland	0	0.60%
ASIA				
Juang et al., 2015, [11]	5 214	Taiwan	0.077%	3.2%
Juang et al., 2011, [41]	20 562	Taiwan	0.005%	0.12%
Uhm et al., 2011, [42]	10 867	Korea	0	0.91%
Wajed et al., 2008, [43]	1 100	Pakistan	0.18%	0.64%
Gervacio-Domingo et al., 2008, [44]	3 907	Phillippines	0.18%	2.23%
Tsuji et al., 2008, [45]	13 904	Japan	0.27%	0.44%
Bigi et al., 2007, [46]	3 895	Iran	0.36%	2.21%
Bozkurt et al., 2006, [47]	1 238	Turkey	0.08%	0.4%
Shin et al., 2005, [48]	225	Korea	0	1.3%
Miyasaka et al., 2001, [50]	13 929	Japan	0.12%	0.58%
Furuhashi et al., 2001, [51]	8 612	Japan	0.05%	0.09%
NORTH AMERICA				
Patel et al., 2009, [52]	162 590	USA	0.005%	0.007%
Donohue et al., 2008, [53]	1 348	USA	0	0.14%
Ito et al., 2006, [54]	8 006	USA	0.15%	0.14%
Greer et al., 2003, [55]	27 328	USA	0	0.07%
AFRICA				
Ouali et al., 2011, [56]	540	Tunisia	0	1.66%

of particular genes to BrS incidence vary within wide range [19]. Genes that are associated with BrS or modulating (but not obviously resulting in) BrS are listed in Table 2.

The first and the most common gene associated with BrS, *SCN5A*, was reported in 1998. It encodes the α-subunit of the voltage-gated Nav1.5 cardiac sodium channel [20]. Patients with an *SCN5A* mutation more often have a spontaneous type 1 BrS ECG pattern compared with the remainder BrS patients [21]. Over 300 mutations in *SCN5A* gene have been described so far [20]. They cause dysfunction of the sodium channel, that is responsible for fast inward sodium current in the phase 0 of the cardiac action potential. Loss of function of this channel results in decreased conduction velocity of depolarization in the heart muscle, which is the underlying proarrhythmic mechanism in BrS. The molecular mechanism may be due to decreased expression of the Nav1.5 (sodium channel) protein, non-functional channels expression, or impaired gating properties

Table 2. Genes associated with or modulating Brugada syndrome (BrS), encoding particular ion channels or associated proteins affecting functioning of the channel

Gene	Locus	Protein	Functional effect on the ion channel	Percentage of probands	Reference
Genes associated with Brugada syndrome					
Sodium channel					
SCN5A	3p21	$Na_v1.5$	↓ I_{Na}	20–25% (Caucasian) 10–15% (Asian)	[19]
SCN1B	19q13.1	$Na_v\beta1$ / β1b	↓ I_{Na}	1.1%	[5, 57]
SCN2B	11q23	$Na_v\beta2$	↓ I_{Na}	Rare	[5, 58]
SCN3B	11q23.2	$Na_v\beta3$	↓ I_{Na}	Rare	[5, 59]
SCN10A	3p22.2	$Na_v1.8$	↓ I_{Na}	2.5%, up to 16.7%	[19, 23]
Calcium channel					
CACNA1C	12p13.3	$Ca_v1.2$	↓ I_{Ca}	6.6%	[5, 60]
CACNB2b	10p12.33	$Ca_v\beta2$	↓ I_{Ca}	4.8%	[5, 60]
CACNA2D1	7q21.11	$Ca_v\alpha2\delta$	↓ I_{Ca}	1.8%	[5]
Potassium channel					
KCND3	1p13.2	$K_v4.3$, Ito	↑ I_{to}	Rare	[61]
KCNE3	11q13-14	MiRP2	↑ I_{to}	Rare	[5, 62]
KCNJ8	12p11.23	Kir6.1	↑ $I_{K\text{-}ATP}$	2%	[5, 63]
ABCC9	12p12.1	SUR2A	↑ $I_{K\text{-}ATP}$	Rare	[5, 64]
Sodium channel-associated					
RANGRF	17p13.1	MOG1	↓ I_{Na}	Rare	[19, 65, 66]
GPD1-L	3p24	G3PD1L	↓ I_{Na}	Rare	[5, 67]
SLMAP	3p21.2-p14.3	SLMAP	↓ I_{Na}	Rare	[68]
PKP2	12p11.21	Plakophillin-2	↓ I_{Na}	2.5%	[19, 69]
TRPM4	19q13.33	NSCCa	↓ I_{Na}	~6%	[19, 24]
HEY2	6q22	$Na_v1.5$	↓ I_{Na}	Rare	[70]
Potassium channel-associated					
SEMA3A	7p12.1	Semaphorin	↑ I_{to}	Rare	[5]
Genes modulating Brugada syndrome					
KCNH2	7q35	$K_v11.1$	↑ I_{Kr}	1–2%	[19, 71, 72]
KCNE5 (KCNE1L)	Xq22.3	MiRP4, $K_v4.3$	↑ I_{to}	Rare	[19, 73]
HCN4	15q24.1	I_f	↓ I_f	Rare	[19, 74–76]

SUR2A – sulfonylurea receptor subunit 2A; G3PD1L – glycerol-3-phosphate dehydrogenase 1-like protein; SLMAP – sarcolemmal membrane-associated protein; TRPM4 – transient receptor potential melastatin protein number 4; NSCCa – calcium-activated nonselective cation channel; ↓ – decreased current; ↑ – increased current

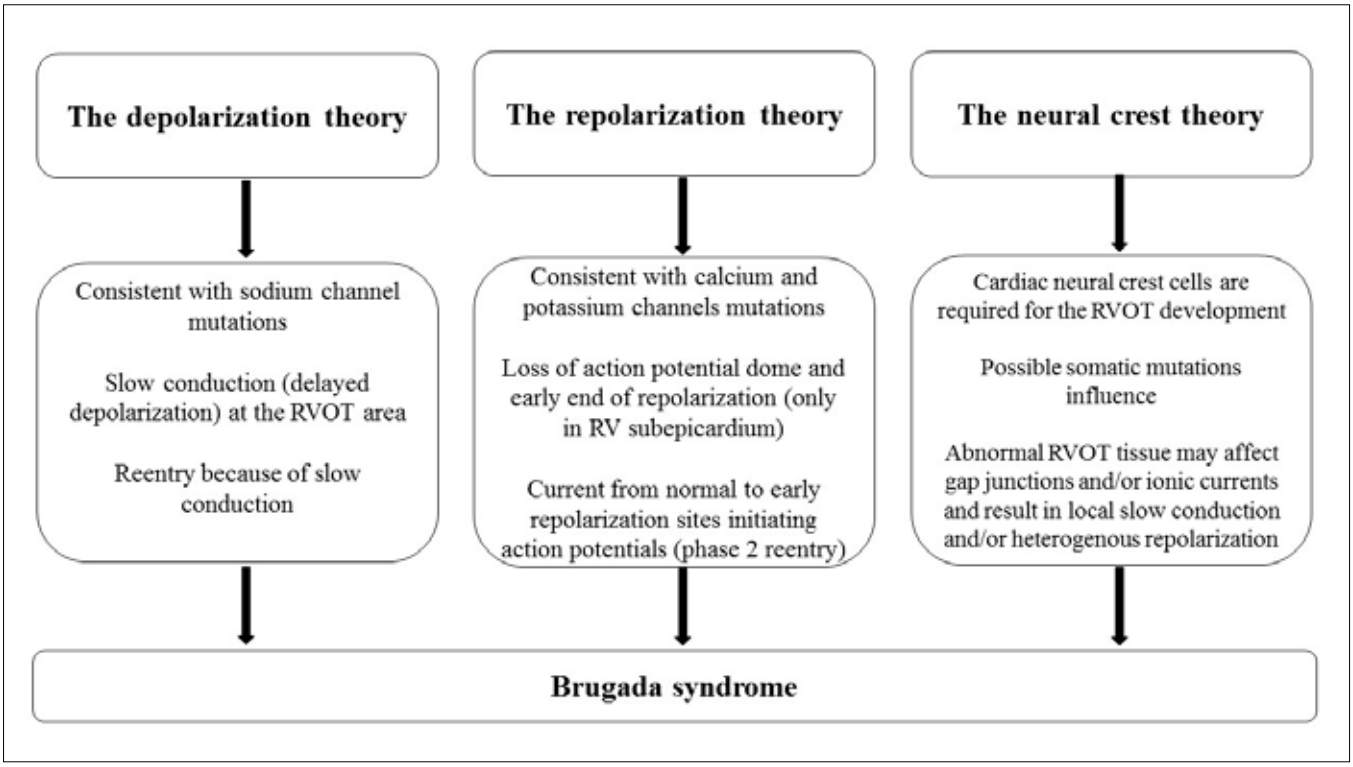

Figure 2. Theories in Brugada syndrome pathogenesis. RVOT – right ventricular outflow tract

(earlier or faster inactivation, enhanced slow inactivation, delayed activation or recovery from inactivation) [20]. On the other hand, it is estimated that overall penetrance of mutation (the proportion of persons with the mutation who exhibit phenotype) in *SCN5A* gene is about 16% (12.5–50%) [20,22].

In *SCN5A*-negative patients, mutations in several other genes have been described. Mutations affecting the L-type cardiac calcium channel seem to be the second in terms of frequency among BrS patients. Loss of function of calcium channel leads to reduction of inward calcium current and decreased conduction. The mutations in genes encoding channels that conduct outward potassium currents have also been reported in BrS patients and result in a gain of function effects.

Other genes related to BrS include genes that encode proteins interacting with above mentioned ion channels. What is worth noting is that different types of mutations in the same genes (i.e. leading to loss or gain of function of a protein) may lead to different diseases. Pathogenic variants of *SCN5A* are found not only in BrS, but also account for about 5% of the following diseases: long QT syndrome (LQTS) type 3, cardiac conduction disease (CCD), dilated cardiomyopathy with cardiac conduction disease (DCM + CCD) and sudden infant death syndrome (SIDS) [23]. Mutation in *CACNA1C* and *CACNB2b* result in a coexistence of BrS and shortened QT interval [18]. Depending on the type of mutation, genes encoding potassium channels may be involved not only in BrS, but also, as it was reported for *KCNH2*, in LQTS and short QT syndrome (SQTS) [18].

The majority of the above mentioned BrS genes have been identified in a small number of patients through candidate gene analysis [18]. Moreover, there is some discrepancy in reporting genes other than *SCN5A*, that account substantially for positively genotyped patients. Hu et al. reported *SCN10A* mutation in up to 16.7% of BrS probands [24]. However, this percentage seems to be overestimated. ESC guidelines list only *SCN5A* and *CACN1AC* as accounting for >5% of positively genotyped patients [6]. Guidelines also omit *TRPM4*, even though it was reported in 2013 that *TRPM4* mutations account for about 6% of BrS patients [25].

The assessment of genetic predisposition is important particularly for family members of the patient diagnosed with BrS. Especially in family members of patients with sudden unexplained death syndrome or sudden arrhythmic death at a young age, it is rational to look for inherited causes of SCD [6, 26]. Targeted molecular testing and genetic counselling for family members are advised if there is clinical suspicion of an inherited disease. Heart Rhythm Society/European Heart Rhythm Association Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies (from 2011) formed wide recommendation for genetic testing in BrS, including mutation-specific genetic testing of members of the family and appropriate relatives, when BrS-causative mutation was identified in an index case (class I recommendation). Moreover, this consensus statement recommended comprehensive or *SCN5A* targeted genetic testing of any patient with established clinical suspicion of BrS (class IIa recommendation), but not in patients with an isolated saddleback BrS ECG morphology (class III recommendation) [23].

According to current ESC guidelines, we do not have appropriate genetic predictors of SCD in BrS [6]. Moreover, genetic testing in BrS does not currently modify treatment strategy. Considering above mentioned facts, it is reasonable that current ESC guidelines on management of ventricular arrhythmias and sudden cardiac

death prevention, did not form a strict recommendation regarding genetic testing in BrS [6]. Heterogenous genetic background, incomplete penetrance and variable expressivity of particular pathogenic variants (the variations in a phenotype among persons with identical pathogenic variants) of genes involved in BrS make future clinical utility of genetic testing in terms of BrS patients risk prediction questioned [20].

Mechanisms in BrS pathogenesis

Since 1992, when first detailed clinical description of BrS as a new clinical entity was published, there are several theories which aim to explain BrS pathophysiology [15,27]. Heterogenous genetic BrS basis implicates heterogenous BrS pathophysiological mechanisms [28]. The hypotheses of BrS include the depolarization and repolarization theories, and the neural crest theory (Figure 2) [28]. The transmural dispersion of repolarization hypothesis explains how loss of the action potential dome and early end of repolarization at the right ventricular subepicardium may lead to BrS ECG pattern and initiate VF (Figure 2) [29]. The depolarization theory is supported by studies that were performed on a heart of a BrS patient who underwent cardiac transplantation due to intolerable numbers of implantable cardioverter-defibrillator (ICD) discharges [30]. In this patient, it was shown that conduction slowing (but not transmural repolarization changes), based on interstitial fibrosis in the right ventricular outflow tract (RVOT), caused ECG sign and was the origin of VF [30]. In BrS the conduction delay in RVOT is reflected by the fractionated (split) electrograms and the late potential activity [31]. Interestingly, the depolarization theory is also supported by a local 2:1 conduction block which was observed during VF/ventricular flutter over the right ventricle (RV) [32]. Cardiac neural crest cells are required in the development of RVOT [33]. The neural crest theory (development abnormality) underlines the complex nature of the RV [33]. Abnormal RVOT tissue may affect gap junctions and/or ionic currents, may change action potential and, under provoking factors, result in local slow conduction and/or heterogenous repolarization (Figure 2) [33]. This hypothesis is consistent with possible somatic mutations in BrS and explains cases of non-familial BrS occurrence [28]. Right-bundle branch block QRS morphology which is common in BrS patients, as well as arrhythmias originating from RV strongly suggest arrhythmogenic substrate localized in the RV. Moreover, recent successful ablations in the RVOT region in BrS support depolarization and neural crest theories [28].

Conclusions

BrS is a rare, but complex clinical condition. Its diagnosis is based on type 1 BrS ECG pattern presence, observed spontaneously or after provocation test. Numerous genetic mutations have been shown to be responsible for BrS. There are several theories which aim to explain BrS pathogenesis, but some uncertainties still persist. Further studies on BrS are needed and warranted for further understanding of BrS and implicated pathophysiological pathways.

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