

## Clinical and Genetic Diagnosis for Inherited Cardiac Arrhythmias

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### Abstract

Molecular genetic studies in the last 2 decades have revealed a link between several inherited cardiac arrhythmias and genes encoding for ion channels or other membrane components. Two recent international expert consensus statements endorsed by 3 continental electrophysiology societies have updated the clinical and genetic diagnoses and management in patients with inherited arrhythmia syndromes, including congenital long QT syndrome (LQTS) and Brugada syndrome. Thirteen genotypes have been identified in 50% to 80% of clinically affected patients with congenital LQTS. Therefore, genotype-phenotype correlations have been investigated, especially, in the 3 major genotypes—LQT1, LQT2 and LQT3 syndromes—enabling genotype-specific management and therapy. On the other hand, less than half of patients with Brugada syndrome can be genotyped, and mainly for the sodium channel gene, *SCN5A*. However, recent advances in molecular genetic testing include genome-wide association studies using gene arrays and targeted, whole-exome and whole-genome next-generation sequencing techniques. In this article, I will review the clinical and genetic diagnoses in congenital LQTS and Brugada syndrome.

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**Key words:** genetic study, sudden death, long QT syndrome, Brugada syndrome, ion channel

Molecular genetic studies have revealed a link between several inherited cardiac arrhythmias and mutations of genes encoding for cardiac ion channels or other membrane components. These inherited arrhythmias include congenital and acquired long QT syndrome (LQTS), Brugada syndrome, progressive cardiac conduction defects, catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome, early repolarization syndrome, familial atrial fibrillation, and familial bradycardia syndrome<sup>1</sup>. Congenital LQTS is a Rosetta Stone for inherited cardiac arrhythmia syndromes<sup>1</sup>. In 1991, Keating and co-workers used linkage analyses and reported for the

first time that a Harvey ras-1 locus (*H-ras-1*) in chromosome 11 was linked to congenital LQTS<sup>2</sup>. In 1995, a potassium channel gene, *KCNH2*, was found to be responsible for type 2 congenital LQTS (LQT2)<sup>3</sup>. Then, positional cloning methods were used to identify another potassium channel gene, *KCNQ1*, as the type 1 congenital LQTS (LQT1) gene in 1996<sup>4</sup>. Since 1995, genetic studies have identified 13 genotypes of congenital LQTS. Therefore, genetic testing is now the gold standard for the diagnosis of congenital LQTS, and genotype-phenotype correlations have been rigorously investigated. Genetic diagnosis now enables risk stratification of cardiac events and better management of congenital

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LQTS<sup>1</sup>.

CPVT is another inherited cardiac arrhythmia, in which mutations of the cardiac *RyR2* gene or the *calsequestrin* gene can be identified in approximately 60% of patients with clinically diagnosed CPVT associated with ventricular tachycardia (VT) that is bidirectional or multifocal or both<sup>1</sup>. However, causative mutations have been detected in few patients with other inherited cardiac arrhythmias<sup>1</sup>. An  $\alpha$  subunit of the sodium channel gene *SCN5A* was identified in patients with Brugada syndrome in 1998<sup>5</sup>. Although *SCN5A* has been a major player as a Brugada gene, mutations were identified in only 11% to 28% of a world-wide cohort of patients with clinically diagnosed Brugada syndrome<sup>6</sup>. Therefore, the genotype-phenotype correlations in Brugada syndrome have not been extensively investigated<sup>1</sup>. The yield of disease-specific genetic testing remains unknown in other inherited cardiac arrhythmias, such as progressive cardiac conduction defect, short QT syndrome, early repolarization syndrome, familial atrial fibrillation, and familial bradycardia syndrome<sup>1,7,8</sup>. In this article, I will focus on and review the representative inherited cardiac arrhythmias: congenital LQTS and Brugada syndrome.

### Congenital LQTS

Congenital LQTS is characterized by QT interval prolongation on 12-lead electrocardiogram and a polymorphic VT known as Torsade de Pointes (TdP)<sup>9</sup>.

#### 1. Clinical Diagnosis

A tool that has long been used to diagnose congenital LQTS is the Schwartz score, which is based on the rate-corrected QT (QTc) interval at rest; cardiac events, such as syncope, aborted cardiac arrest, and sudden cardiac death; and a family history of apparent LQTS<sup>10</sup>. Of particular importance for measuring the QT interval is excluding secondary causes of QTc prolongation, which can be unmasked by the QT-prolonging drugs and cardiac conditions, such as electrolyte imbalance and bradycardia. In 2013, an international expert

consensus statement was published on the diagnosis and management of patients with inherited arrhythmia syndromes, including congenital LQTS<sup>11</sup>. This statement is the collaborative effort of 3 medical societies representing electrophysiology in North America, Europe, and the Asia-Pacific area: the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society (APHRS). Congenital LQTS can be diagnosed when the patient has a Schwartz LQTS risk score greater than 3.5 in the absence of a secondary cause for QT prolongation, an unequivocally pathogenic mutation in an LQTS gene, or a QTc of greater than 500 milliseconds in repeated 12-lead electrocardiogram in the absence of a secondary cause for QT prolongation<sup>11</sup>. Congenital LQTS can also be diagnosed in the presence of a QTc of 480 to 499 milliseconds in repeated 12-lead ECG in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation<sup>11</sup>. An episode of TdP is not required to diagnose congenital LQTS.

#### 2. Catecholamine Challenge Test

Baseline electrocardiographic (ECG) testing sometimes misses congenital LQTS, indicating the presence of latent LQTS<sup>12</sup>. An estimated 30% to 40% of genetically affected patients have a latent LQTS, especially LQT1, with a normal or borderline QTc interval at rest. Low penetrance in congenital LQTS was first genetically proved by Vincent et al<sup>13</sup>. They reported that of 82 mutation carriers from 3 families with LQT1, 5 (6%) had a normal QT interval<sup>13</sup>. Thereafter, Priori et al. reported that the percentage of genetically affected patients with a normal QTc was significantly higher in LQT1 (36%) than in the LQT2 (19%) or type 3 congenital LQTS (LQT3; 10%)<sup>14</sup>. Japanese data also show that the sensitivity (penetrance) of ECG diagnostic criteria is lower in LQT1 (68%) than in either LQT2 (83%) or LQT3 (83%)<sup>15</sup>. The identification of patients with latent LQTS is important in that it may lead to the start of potentially life-saving pharmacotherapies and lifestyle modifications. Catecholamine infusion testing with epinephrine, an  $\alpha$ + $\beta$  adrenergic agonist, has

long been used as a provocative means of unmasking latent forms of congenital LQTS<sup>15,16</sup>.

The 2 major protocols of epinephrine provocative testing are the escalating-dose protocol of Ackerman et al (Ackerman/Mayo Clinic protocol)<sup>17</sup> and the protocol of bolus injection followed by brief continuous infusion of Shimizu et al. (Shimizu protocol)<sup>15,16,18</sup>. Both protocols are useful, safe, and well tolerated and rarely induce either TdP or ventricular fibrillation. The Shimizu protocol is useful for predicting the 3 major genotypes of LQTS—LQT1, LQT2, and LQT3—and for unmasking the latent form of LQTS<sup>15,16</sup>. A pregenetic diagnosis of LQT1, LQT2, or LQT3 based on the response to epinephrine can facilitate molecular diagnosis by targeting the first gene that should be screened for.

### 3. Exercise Stress Testing

Exercise stress testing, such as treadmill exercise testing, is also useful for diagnosing congenital LQTS<sup>19-21</sup>. Takenaka et al. have performed a qualitative assessment of T-wave morphology, i.e., broad-based T waves in patients with LQT1 and notched (bifid) T waves in patients with LQT2, facilitating genotyping of subjects with LQT1 or LQT2<sup>22</sup>. The QTc prolongation with changes of posture (standing) before exercise is reportedly useful for unmasking LQT1 and LQT2 with a simple bedside screening test<sup>23,24</sup>. The new Schwartz score, revised in 2012, assigns a score of 1 point to a QTc interval of  $\geq 480$  milliseconds in 12-lead electrocardiogram 4 minutes after the stopping of exercise<sup>25</sup>.

### 4. Genotype

Thirteen autosomal dominant forms of the Romano-Ward type of congenital LQTS have been identified and found to be caused by mutations of genes of potassium, sodium, or calcium channels or the membrane adapter on chromosomes 3, 4, 7, 11, 12, 17, 20, and 21 (**Table 1**)<sup>1,26</sup>. Mutations of *KCNQ1* and *KCNE1*, the  $\alpha$  and  $\beta$  subunits of the potassium channel gene, encoding the slowly activating component of the delayed rectifier potassium current ( $I_{Ks}$ ), are responsible for LQT1 and type 5

congenital LQTS (LQT5). Mutations of *KCNH2* and *KCNE2*, the  $\alpha$  and  $\beta$  subunits of the potassium channel gene, cause defects in the rapidly activating component of the delayed rectifier potassium current ( $I_{Kr}$ ), which are responsible for LQT2 and type 6 congenital LQTS (LQT6). Mutations of *SCN5A* are responsible for LQT3 by increasing (gain of function) the late sodium current ( $I_{Na}$ ). Mutations in *KCNJ2* encoding the inward rectifier potassium current ( $I_{K1}$ ) result in QT prolongation, periodic paralysis, and dysmorphic features, underlying Andersen's syndrome (LQT7). A mutation of *Ankyrin-B*, a member of a family of versatile membrane adapters, underlies LQT4 syndrome, with intracellular calcium overload. Mutation of *CACNA1C* increases the L-type calcium current ( $I_{Ca-L}$ ), resulting in QT prolongation, dysfunction in multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism, responsible for type 8 congenital LQTS (LQT8). The genes *CAV3*, encoding caveolin-3, is responsible for type 9 congenital LQTS (LQT9), and *SCN4B*, encoding *NavB4*, an auxiliary subunit of the cardiac sodium channel, is responsible for type 10 congenital LQTS (LQT10). Mutations of both genes result in a gain of function of late  $I_{Na}$ , causing long QT intervals like those in LQT3. A mutation of *AKAP-9*, whose product, Yotiao, assembles with *KCNQ1*, is responsible for type 11 congenital LQTS (LQT11). Mutations in syntrophin- $\alpha 1$  (*SNTA1*), a cytoskeletal protein, interacts with the cardiac sodium channel, and is attributable to type 12 congenital LQTS (LQT12) with an LQT3-like phenotype. A mutation of *KCNJ5*, which encodes the  $\alpha$ -subunit of the acetylcholine-sensitive potassium current ( $I_{K-ACh}$ ) channel, is responsible for type 13 congenital LQTS (LQT13). Of the 13 genotypes, the 3 major genotypes—LQT1, LQT2 and LQT3—constitute more than 80% of genotyped patients with LQTS<sup>1</sup>. Decreases in outward potassium currents ( $I_{Ks}$ ,  $I_{Kr}$ ,  $I_{K1}$ ,  $I_{K-ACh}$ ) or increases in an inward sodium or calcium current (late  $I_{Na}$ ,  $I_{Ca-L}$ ) prolong the action potential duration and the QT interval in all 13 genotypes.

Two genotypes of autosomal recessive forms of Jervell and Lange-Nielsen syndrome, JLN1 and JLN2, are attributable to a decrease in the  $I_{Ks}$  which

Table 1 Defects of ion channels or membrane adaptors responsible for congenital long QT syndrome and Brugada syndrome

Locus	Chromosome	Gene	Ion channel or membrane adaptor
Romano-Ward syndrome			
LQT1	11 (11p15.5)	<i>KCNQ1</i>	I <sub>Ks</sub> ( $\alpha$ )
LQT2	7 (7q35-q36)	<i>KCNH2</i>	I <sub>Kr</sub> ( $\alpha$ )
LQT3	3 (3p21)	<i>SCN5A</i>	I <sub>Na</sub> ( $\alpha$ )
LQT4	4 (4q25-q27)	<i>ANK2</i>	Na-K ATPase, I <sub>Na-Ca</sub>
LQT5	21 (21q22.12)	<i>KCNE1</i>	I <sub>Ks</sub> ( $\beta$ )
LQT6	21 (21q22.12)	<i>KCNE2</i>	I <sub>Kr</sub> ( $\beta$ )
LQT7	17 (17q23.1-q24.2)	<i>KCNJ2</i>	I <sub>K1</sub>
LQT8	12 (12p13.3)	<i>CACNA1C</i>	I <sub>Ca-L</sub>
LQT9	3 (3p25)	<i>CAV3</i>	I <sub>Na</sub>
LQT10	11 (11q23.3)	<i>SCN4B</i>	I <sub>Na</sub>
LQT11	7 (7q21-q22)	<i>AKAP-9</i>	I <sub>Ks</sub>
LQT12	20 (20q11.2)	<i>SNTA1</i>	I <sub>Na</sub>
LQT13	11 (11q23.3-24.3)	<i>KCNJ5</i>	I <sub>KACH</sub>
Jervell and Lange-Nielsen syndrome			
JLN1	11 (11p15.5)	<i>KCNQ1</i> (homozygous)	I <sub>Ks</sub> ( $\alpha$ )
JLN2	21 (21q22.12)	<i>KCNE1</i> (homozygous)	I <sub>Ks</sub> ( $\beta$ )
Brugada Syndrome			
BrS1	3 (3p21)	<i>SCN5A</i>	I <sub>Na</sub>
BrS2	3 (3p24)	<i>GPD1L</i>	I <sub>Na</sub>
BrS3	12 (12p13.3)	<i>CACNA1C</i>	I <sub>Ca-L</sub>
BrS4	10 (10p12.33)	<i>CACNB2</i>	I <sub>Ca-L</sub>
BrS5	19 (19q13.1)	<i>SCN1B</i>	I <sub>Na</sub>
BrS6	11 (11q13-14)	<i>KCNE3</i>	I <sub>to</sub>
BrS7	19 (19q23.3)	<i>SCN3B</i>	I <sub>Na</sub>
BrS8	12 (12p11.23)	<i>KCNJ8</i>	I <sub>K-ATP</sub>
BrS9	7 (7q21.11)	<i>CACNA2D1</i>	I <sub>Ca-L</sub>
BrS10	1 (1p13.2)	<i>KCND3</i>	I <sub>to</sub>
BrS11	17 (17p13.1)	<i>MOG1</i>	I <sub>Na</sub>
BrS12	3 (3p21.2-p14.3)	<i>SLMAP</i>	I <sub>Na</sub>
BrS13	11 (11q23)	<i>SCN2B</i>	I <sub>Na</sub>
BrS14	3 (3p22)	<i>SCN10A</i>	I <sub>Na</sub>

is caused by homozygous or compound heterozygous mutations of *KCNQ1* and/or *KCNE1* genes (**Table 1**)<sup>1,26</sup>. They are accompanied by neurosensorial deafness and a markedly prolonged QT interval. Some mutations of the *SCN5A* gene result in multiple phenotypes, so called “overlap syndromes,” including Brugada syndrome, sick sinus syndrome, and conduction disease in addition to the LQT3 phenotype<sup>26,27</sup>.

### 5. Indications for Genetic Testing

Indications for genetic testing for inherited cardiac arrhythmias have been proposed by the 2011 HRS/

EHRA expert consensus statement<sup>7</sup>. Comprehensive or LQT1-3-targeted LQTS genetic testing is recommended as a class I indication: (1) for any patient in whom a cardiologist has established a strong clinical suspicion for LQTS based on examination of the patient’s clinical history, family history, and expressed ECG phenotype (provocative stress testing with exercise or catecholamine infusion or resting 12-lead electrocardiogram or both) or (2) for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, and

bundle branch block, i.e., otherwise idiopathic) on serial 12-lead electrocardiogram defined as QTc >480 milliseconds (prepuberty) or >500 milliseconds (adults). (3) Mutation-specific LQTS genetic testing is recommended for family members and other appropriate relatives following the identification of the LQTS-causative mutation in an index case. Comprehensive or LQT1-, LQT2-, or LQT3-targeted LQTS genetic testing may be considered a class IIb indication for any asymptomatic patient with otherwise idiopathic QTc values >460 milliseconds (prepuberty) or >480 milliseconds (adults) on serial 12-lead electrocardiogram. In contrast, genetic testing is not recommended for any asymptomatic patient with normal or borderline QTc values ≤460 milliseconds (prepuberty) or ≤480 milliseconds (adults).

### Brugada Syndrome

Brugada syndrome is characterized by specific ST-segment elevation in the right precordial ECG leads, which is known as the coved-type (type 1) Brugada ECG, and is associated with a high risk of sudden cardiac death due to ventricular fibrillation (VF) without structural heart disease<sup>1,28-31</sup>.

#### 1. Clinical Diagnosis

The first Brugada Consensus Report in 2002 proposed 3 patterns of ST-segment elevation in the right precordial leads of the electrocardiogram (**Fig. 1**)<sup>29</sup>. Type 1 ST-segment elevation is characterized by a J point elevation of ≥2 mm (0.2 mV) followed by a negative or isoelectric T-wave (**Fig. 1A**). Type 2 ST-segment elevation has a saddleback appearance with a J point elevation of ≥2 mm followed by a trough displaying ≥1-mm ST elevation with either a positive or biphasic T-wave (**Fig. 1B**). Type 3 ST-segment elevation also has a saddleback appearance with a J point elevation of <1 mm. Type 1 Brugada ECG is suggested to be associated with higher rates of VF and sudden cardiac death<sup>32</sup>. In 2005, the second Brugada Consensus Report proposed that type 1 ST-segment elevation in at least 2 right precordial leads (V1–V3) be required for the definitive diagnosis of Brugada syndrome<sup>30</sup>. The 2013

HRS/EHRA/APHS expert consensus statement on diagnosis and management has proposed that the diagnosis of Brugada syndrome be considered definitive when a type 1 ST-segment elevation is observed either spontaneously or after intravenous administration of a sodium channel blocker (ajmaline, flecainide, pilsicainide, or procainamide) in at least 1 right precordial lead (V1 or V2), wherever it is placed in a standard or higher intercostal space (up to the 2nd intercostal space) (**Fig. 1C**)<sup>11,33</sup>. Moreover, in the 2013 consensus statement, documentation of VF/VT is not required for diagnosing Brugada syndrome<sup>11</sup>.

#### 2. Genotype

Genetic studies in patients with Brugada syndrome have identified 14 genotypes on chromosomes 1, 3, 7, 10, 11, 12, 17, and 19 (**Table 1**)<sup>18,34</sup>. Following *SCN5A*, calcium-channel genes, including *CACNA1C* (Cav1.2, BrS3), *CACNB2b* (Cavβ2b, BrS4), and *CACNA2D1* (Cava2δ1, BrS9) are the second major players, and mutations in the calcium-channel genes are found in 12% to 13% of Brugada probands<sup>35</sup>. In contrast, mutations are rare in the glycerol-3-phosphate dehydrogenase 1-like enzyme gene (*GPD1L*, BrS2), *SCN1B* (β1-subunit of Na channel, BrS5), *KCNE3* (MiRP2; BrS6), *SCN3B* (β3-subunit of Na channel, BrS7), *KCNJ8* (BrS8), *KCND3* (BrS10), *MOG1* (BrS11), *SLMAP* (BrS12), and *SCN2B* (BrS13)<sup>36</sup>. Bezzina et al have recently performed a genome-wide association study using gene arrays in 312 patients having Brugada syndrome with type 1 electrocardiogram and in 1115 control subjects; 2 significant association signals with Brugada syndrome were detected at the *SCN10A* gene in chromosome 3p22 and near the *HEY2* gene in chromosome 6q22<sup>37</sup>. Hu et al have identified 17 *SCN10A* mutations, present in 25 (yield; 16.7%) of 150 patients with Brugada syndrome (BrS14)<sup>34</sup>. The *SCN10A* gene is expressed in the working myocardium and the specialized conduction system, indicating a possible role for Nav1.8 in cardiac electrical function. Overall, the yield for detection of a Brugada genotype has reached approximately 50%<sup>8</sup>. In all 14 genotypes, decreases in inward sodium or calcium currents (fast  $I_{Na}$ ,  $I_{Ca-L}$ ) or increases in outward

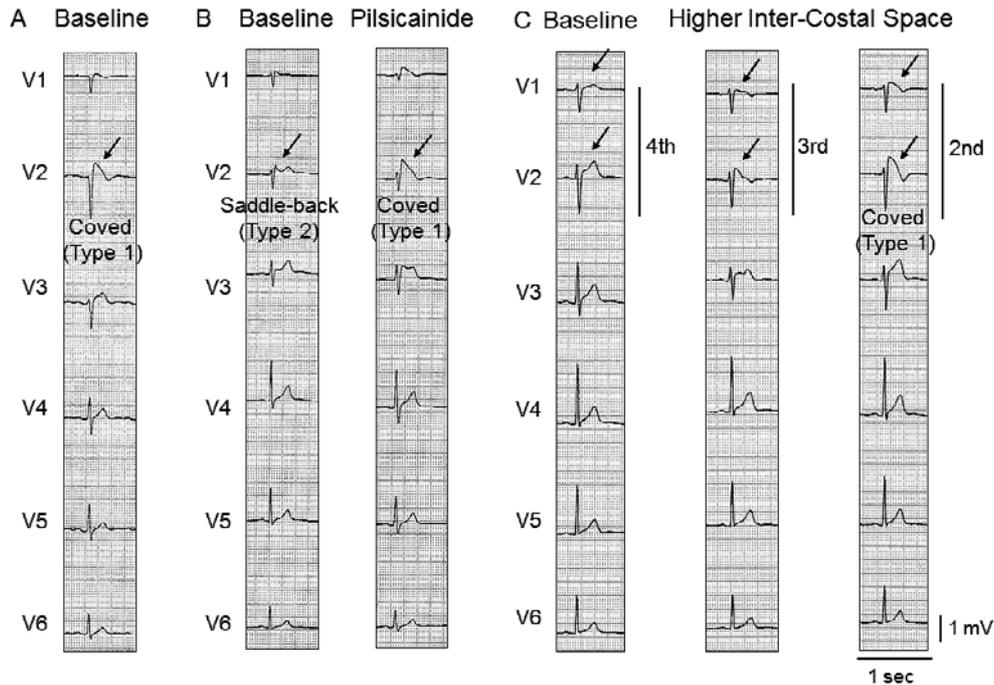


Fig. 1 **A:** Spontaneous type 1 (coved type) ST-segment elevation (**arrow**). **B:** Unmasking of ST-segment elevation by a class IC sodium-channel blocker, pilsicainide. Under baseline conditions, type 2 (saddleback type) ST-segment elevation is recorded in lead V2 (**left, arrow**). Pilsicainide injection (30 mg) unmasks type 1 ST-segment elevation in lead V2 (**right, arrow**). **C:** Unmasking of type 1 ST-segment elevation by recordings from leads V1 and V2 at the 3<sup>rd</sup> and 2<sup>nd</sup> intercostal spaces. No significant ST-segment elevation is observed in leads V1 and V2 of the standard 12-lead ECG (4<sup>th</sup> intercostal space) (**left, arrow**), whereas type 1 ST-segment elevation (**right, arrow**) is unmasked in leads V1 and V2 recorded from the 3<sup>rd</sup> and 2<sup>nd</sup> intercostal spaces, respectively.

potassium currents (transient outward potassium current [ $I_{to}$ ], adenosine-sensitive potassium current [ $I_{K-ATP}$ ]) are responsible for the Brugada phenotype<sup>8</sup>.

### 3. Indication for Genetic Testing

The HRS/EHRA expert consensus statement has proposed indications for genetic testing for Brugada syndrome<sup>7</sup>. As a class I indication, mutation-specific Brugada genetic testing is recommended for family members and appropriate relatives following the identification of the Brugada syndrome-causative mutation in an index case. As a class IIa indication, comprehensive or BrS1 (*SCN5A*)-targeted Brugada syndrome genetic testing can be useful for any patient in whom a cardiologist has a clinical suspicion of Brugada syndrome based on examination of the patient's clinical history, family history, and expressed ECG (resting 12-lead ECG or provocative drug challenge testing or both) phenotype. Genetic testing is not indicated in the

absence of a diagnostic ECG.

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