Sudden Unexplained Death
Heritability and Diagnostic Yield of Cardiological and Genetic Examination in Surviving Relatives

Hanno L. Tan, MD, PhD; Nynke Hofman, BSc; Irene M. van Langen, MD; Allard C. van der Wal, MD, PhD; Arthur A.M. Wilde, MD, PhD

Background—Sudden death mostly follows from cardiac disorders that elicit lethal ventricular arrhythmias. In young individuals, it often remains unexplained because history and/or postmortem analysis are absent or provide no clue. Because such sudden unexplained deaths (SUDs) may have heritable causes, cardiological and genetic assessment of surviving relatives of SUD victims may reveal the underlying disease and unmask presymptomatic carriers. We aimed to establish the diagnostic yield of such assessments.

Methods and Results—We investigated 43 consecutive families with ≥1 SUD victim who died at ≤40 years of age. All studied relatives underwent resting/exercise ECG and Doppler echocardiography. Molecular genetic analysis was conducted to confirm the diagnosis. We identified an inherited disease and likely cause of death in 17 of 43 families (40%). Twelve families had primary electrical disease: catecholaminergic polymorphic ventricular tachycardia (5 families), long-QT syndrome (4 families), Brugada syndrome (2 families), and long-QT/Brugada syndrome (1 family). Furthermore, we found arrhythmogenic right ventricular cardiomyopathy (3 families), hypertrophic cardiomyopathy (1 family), and familial hypercholesterolemia (1 family). Molecular genetic analysis provided confirmation in 10 families. Finding the diagnosis was more likely when more relatives were examined and in families with ≥2 SUD victims ≤40 years of age. The resting/exercise ECG had a high diagnostic yield. These efforts unmasked 151 presymptomatic disease carriers (8.9 per family).

Conclusions—Examination of relatives of young SUD victims has a high diagnostic yield, with identification of the disease in 40% of families and 8.9 presymptomatic carriers per family. Simple procedures (examining many relatives) and routine tests (resting/exercise ECG) constitute excellent diagnostic strategies. Molecular genetics provide strong supportive information. (Circulation. 2005;112:207-213.)

Key Words: arrhythmia ■ death, sudden ■ genetics ■ long-QT syndrome ■ tachyarrhythmias
cardiological assessment. Importantly, these studies have raised our awareness of these disorders and have provided strong impetus to our efforts to reveal them.

The primary aim of this study was to analyze the diagnostic yield of examination of surviving relatives of SUD victims. A rigorous and extensive cardiological evaluation, one that used routine diagnostic tests (ECG at rest, exercise, or during flecainide challenge and echocardiogram), enabled us to identify the underlying disease in 17 of 43 families (40%).

The diagnosis was more likely to be made in families in which more surviving relatives were examined and in those with ≥2 SUD victims who were ≤40 years of age. The ECG has a high diagnostic yield. Our secondary aim was to analyze how many disease-carrying relatives are identified presymptomatically by these efforts. Aided by molecular genetic analysis, delineation of the familial disease in the 17 families resulted in the identification of 151 affected surviving relatives (8.9 per family).

Methods

Definitions

SUD

SUD was defined as death in a person with no family history of known heart disease that occurred suddenly (1 hour after complaints or within 12 hours of the victim being seen alive) and was unexplained because a relevant documented medical history (eg, syncope, seizures, palpitations) and antemortem cardiological tests (eg, ECG) were absent and detailed postmortem macroscopic and microscopic examinations of the heart and its vessels either were not performed or were performed but initially did not provide an explanation.

Diagnosis

A diagnosis was established when generally accepted clinical criteria for a particular disease were fulfilled (Table 1) even if molecular genetic analysis, when performed, revealed no mutations.

Proband

The proband was the first surviving relative to be studied and the person through whom the pedigree was identified.

Index SUD Victim

The SUD victim whose death prompted analysis of his/her family was considered the index SUD victim.

Study Aims

The primary aim of this study was to analyze the diagnostic yield of cardiological and genetic assessment of surviving relatives of SUD victims by establishing the proportion of families in whom the familial disease was identified. The secondary aim was to analyze how many disease-carrying relatives are identified.

Inclusion of Families and Surviving Relatives

We consecutively included all families (n=43) with ≥1 SUD victim who had died at ≤40 years of age to our hospital from 1996 to 2003. These families presented initially to our hospital (n=28) or were referred from elsewhere (n=15) to our hospital, which is a tertiary referral center. Postmortem analysis was performed in 22 families. Overall, these families contained 67 SUD cases ≤40 years of age (51 in first-degree relatives of the proband, 16 in second-degree relatives) and 29 SUD cases >40 years of age (12 in first-degree relatives of the proband, 17 in second-degree relatives). To diagnose the familial disease, we studied 183 surviving relatives among these 43 families, including first- and second-degree relatives of the proband. After the familial disease was identified in 17 families, we studied another 150 surviving relatives from these families to unmask other presymptomatic disease carriers. Before screening, all relatives received the opportunity of informed choice after extensive genetic counseling that included discussions of potential advantages and disadvantages of presymptomatic screening, as we previously reported.

Cardiological and Genetic Assessment

We assessed the circumstances (exercise/stress, rest) and age at which the lethal event and/or cardiac symptoms occurred in the index SUD cases and their surviving relatives. Cardiological examination of all surviving relatives included a 12-lead resting ECG, an exercise ECG, and Doppler echocardiography (Figure 1). When Brugada syndrome was suspected, we performed flecainide challenge. When arrhythmogenic right ventricular cardiomyopathy (ARVC) was suspected, we performed cardiac MRI. These investigations sometimes prompted reanalysis of postmortem cardiac specimens or additional tests, eg, serum lipid profile analysis. In 16 of the 17 families in which a clinical diagnosis was made, molecular genetic analysis was conducted in surviving relatives (no postmortem molecular genetic analysis). This analysis used a candidate gene approach driven by history and cardiological workup. For instance, analysis of the ECG T-wave morphology and the circumstances of symptoms may point to the subtype of long-QT syndrome (LQTS). We have previously shown the efficacy of such an approach. In ARVC, we screened the plakophilin-2 gene, given the reported high prevalence of mutations in subjects of western European descent. We screened the whole gene in each disease except for catecholaminergic polymorphic ventricular tachycardia (CPVT); for CPVT, we screened only those domains of the RyR2 (ryanodine receptor) gene that are implicated in this disease. To support that all identified gene variants were disease-causing mutations, we used generally accepted criteria. Thus, at least 200 alleles obtained from subjects with the same ethnic background were also studied to rule out that the gene variants were polymorphisms. Furthermore, the gene variants always cosegregated with the expected phenotypes.

Statistical Analysis

Data are expressed as mean±SD. Group comparisons were made with the Mann-Whitney test or the χ² test when appropriate. Statistical significance was defined as P<0.05.

Results

Diagnostic Yield and Heritability

We identified an inherited disease and likely cause of death of the SUD victim(s) in 17 of 43 families (40%) (Figure 2 and Table 2). Most diagnoses (12 families) involved primary electrical disease, ie, disruptions in cardiac excitability in the absence of structural changes. Accordingly, the resting ECG, exercise ECG, or flecainide challenge revealed the diagnosis in 12 families: CPVT (5 families), LQTS (4 families), Brugada syndrome (2 families), and a mixed phenotype of LQTS and Brugada syndrome (1 family). Furthermore, the ECG raised the suspicion of ARVC in 1 other family; this suspicion was supported by cardiac MRI and subsequently confirmed by reanalysis of the cardiac postmortem specimens by a cardiovascular pathologist who was blinded to the ECG and cardiac MRI. In 2 other ARVC families, the diagnosis was made after direct reanalysis of the cardiac postmortem specimens (these patients were referrals from elsewhere). Echocardiography raised the suspicion of hypertrophic cardiomyopathy (HCM) in 1 family; this suspicion was confirmed by molecular genetic analysis. Serum lipid profile analysis fulfilled criteria for familial hypercholesterolemia in 1 family, thereby raising the likelihood of coronary atherosclerosis as the cause of death in the SUD victim.
Molecular genetic analysis confirmed the diagnosis in 10 families by revealing mutations in the causative genes. All CPVT families had a mutation in RyR2. Of the 4 LQTS families, 1 had a mutation in KCNQ1 (slow component of delayed rectifier potassium channel), whereas 1 had compound heterozygosity in KCNQ1 and SCN5A (cardiac sodium channel). In the remaining families, ion channel encoding genes involved in LQTS were screened, but mutations therein were not identified. Of the 2 Brugada syndrome families, 1 had a mutation in SCN5A, whereas SCN5A mutations were not found in the other. The family with LQTS/Brugada syndrome had an SCN5A mutation. In the HCM family, a mutation in TNNT2 (troponin T) was found.

In addition to the 17 families in which a diagnosis was established, 4 families in which no diagnosis was found probably also had an underlying inherited disease, given that ≥2 first-degree relatives of the proband had died at ≤40 years of age.

Clinical Determinants of Likelihood of Establishing a Diagnosis
We analyzed which clinical variables may be useful for predicting the likelihood of establishing a diagnosis (Table 3). The number of investigated relatives was significantly larger in the families in which a diagnosis was established than in those without a diagnosis (6.1±3.2 versus 3.1±2.8;
relative of SUD victim who died suddenly at age ≤40 years without cardiac history, and negative or no postmortem analysis

12-lead ECG
exercise test
echocardiography
serum lipid analysis

BS suspected (non-type I ECG)

no

yes

ARVC suspected

pharmacologic challenge

negative

BS

Figure 1. Algorithm for identification of familial disease from analysis of relatives of SUD victims. BS indicates Brugada syndrome; DCM, dilated cardiomyopathy; and FH, familial hypercholesterolemia. *According to Reference 7. †When available, postmortem specimens should be analyzed by cardiac pathologist; this may also be considered in families in which the diagnosis is unclear.

Identification of Disease-Carrying Relatives

Our secondary aim was to study the number of surviving relatives who were identified as disease carriers; they had previously remained unrecognized as being affected. Identification of the underlying disease in these individuals allowed timely treatment to prevent potential sudden death. Among the 17 families in which a diagnosis was made, 102 surviving relatives were studied up to the time of establishment of the diagnosis. Forty-seven individuals were affected. This was verified by carriership of the causative mutation in 35. After the diagnosis was established, 150 more surviving relatives were screened; this screening yielded another 104 affected subjects (103 mutation carriers). Thus, overall, we unmasked 151 affected surviving relatives (138 mutation carriers) who were at risk of sudden death (8.9 per family).

Discussion

We found that cardiological and genetic examination in surviving relatives of young (≤40 years of age) SUD victims reveals an underlying inherited disease and probable cause of death in as many as 40% of families. This is particularly likely in families in which ≥2 SUD cases at age ≤40 years have occurred. The likelihood of establishing the diagnosis is also enhanced when efforts are made to examine as many first- and second-degree relatives as possible. The ECG (at rest/exercise or during flecainide challenge) has a high diagnostic yield. These efforts unmask a large number of affected surviving relatives, who were previously unrecog-
nized as disease carriers, thereby allowing timely treatment to prevent sudden death.

Heritability of SUD and Cardiological Assessment of Surviving Relatives
The high proportion of families (40%) in which a diagnosis was made approaches the estimated prevalence of heritable causes of sudden death in young individuals. It is likely that future discoveries of other diseases will increase this proportion. For instance, in 1 ARVC family, the initial postmortem analysis could not have identified ARVC because it had taken place in 1977, well before the recognition of this disease entity in the 1980s. In this instance, the family was included through the index SUD victim who died in 2001. Subsequent

### TABLE 2. Families With Diagnosis

<table>
<thead>
<tr>
<th>Family</th>
<th>Diagnosis</th>
<th>Molecular Genetics*</th>
<th>Mutation</th>
<th>Clinical Test to Establish Diagnosis†</th>
<th>Examined relatives,‡ n</th>
<th>SUDs, n</th>
<th>SUDs ≤40 y of Age, n</th>
<th>Youngest Age of SUD, y</th>
<th>Circumstance of SUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CPVT</td>
<td>RyR2+</td>
<td>E4676K</td>
<td>X-ECG</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>14</td>
<td>Stress/exercise</td>
</tr>
<tr>
<td>2</td>
<td>CPVT</td>
<td>RyR2+</td>
<td>E4187Q</td>
<td>X-ECG</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>16</td>
<td>Exercise/swimming</td>
</tr>
<tr>
<td>3</td>
<td>CPVT</td>
<td>RyR2+</td>
<td>R420W</td>
<td>X-ECG</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>24</td>
<td>Stress/emotion/anxiety</td>
</tr>
<tr>
<td>4</td>
<td>CPVT</td>
<td>RyR2+</td>
<td>A2252V</td>
<td>X-ECG</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>14</td>
<td>Stress/exercise</td>
</tr>
<tr>
<td>5</td>
<td>CPVT</td>
<td>RyR2+</td>
<td>c.14757–6C→T and c.14757–7T→A</td>
<td>X-ECG</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>17</td>
<td>Swimming</td>
</tr>
<tr>
<td>6</td>
<td>LQTS</td>
<td>−§</td>
<td>ECG, X-ECG</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>24</td>
<td>Sleep/startling</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>LQTS</td>
<td>−§</td>
<td>ECG, X-ECG</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>35</td>
<td>Alarm clock</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>LQTS 1</td>
<td>KCNQ1+</td>
<td>Y184S</td>
<td>ECG, X-ECG</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>Exercise/swimming</td>
</tr>
<tr>
<td>9</td>
<td>LQTS 1+3</td>
<td>Compound heterozygosity</td>
<td>KCNQ1+ and SCN5A+</td>
<td>ECG, X-ECG</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>14</td>
<td>Sleep</td>
</tr>
<tr>
<td>10</td>
<td>Brugada</td>
<td>SCN5A−</td>
<td>ECG, flecainide ECG</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>32</td>
<td>Rest</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Brugada</td>
<td>SCN5A+</td>
<td>1570insl</td>
<td>ECG, flecainide ECG</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>21</td>
<td>Exercise</td>
</tr>
<tr>
<td>12</td>
<td>LQTS 3/Brugada</td>
<td>SCN5A+</td>
<td>1795insD</td>
<td>ECG</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>22</td>
<td>Sleep</td>
</tr>
<tr>
<td>13</td>
<td>ARVC</td>
<td>Plakophilin-2−</td>
<td>ECG, MRI, PA</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>28</td>
<td>Rest</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>ARVC</td>
<td>Plakophilin-2−</td>
<td>PA</td>
<td>13</td>
<td>5</td>
<td>4</td>
<td>29</td>
<td>Rest/sleep</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>ARVC</td>
<td>Plakophilin-2−</td>
<td>PA</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>32</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>HCM</td>
<td>TNNT2+</td>
<td>R92W</td>
<td>TTE, molecular genetics</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>17</td>
<td>Unknown</td>
</tr>
<tr>
<td>17</td>
<td>FH</td>
<td>Not performed</td>
<td>Serum lipids</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>32</td>
<td>Exercise</td>
<td></td>
</tr>
</tbody>
</table>

X indicates exercise; ins, insertion; PA, postmortem analysis; FH, familial hypercholesterolemia; and TTE, transthoracic echocardiography.

* + Indicates mutation present; −, mutation absent.
† In family 16, the diagnosis was made by molecular genetic analysis.
‡ Until establishment of diagnosis.
§ Ion channel encoding genes involved in LQTS: KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2.

### TABLE 3. Clinical Determinants of Likelihood of Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>With Diagnosis (n=17)</th>
<th>Without Diagnosis (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relatives examined, n</td>
<td>6.1±3.2</td>
<td>3.1±2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>SUD cases per family, n</td>
<td>2.7±1.7</td>
<td>1.9±1.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Youngest age range of SUD, y</td>
<td>5–35</td>
<td>6–40</td>
<td>0.3</td>
</tr>
<tr>
<td>Families with ≥2 SUDs at ≤40 y of age, n</td>
<td>11</td>
<td>7</td>
<td>0.014</td>
</tr>
<tr>
<td>Families with ≥2 SUDs, n</td>
<td>12</td>
<td>13</td>
<td>0.2</td>
</tr>
<tr>
<td>Families with ≥3 SUDs, n</td>
<td>8</td>
<td>6</td>
<td>0.1</td>
</tr>
<tr>
<td>Families with ≥4 SUDs, n</td>
<td>4</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Families with SUD at ≤30 y of age, n</td>
<td>13</td>
<td>15</td>
<td>0.2</td>
</tr>
<tr>
<td>Families with SUD at ≤20 y of age, n</td>
<td>7</td>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>SUDs during exercise or stress,* n</td>
<td>10</td>
<td>9</td>
<td>0.2</td>
</tr>
<tr>
<td>SUDs at rest,* n</td>
<td>5</td>
<td>11</td>
<td>0.5</td>
</tr>
<tr>
<td>SUDs under unknown circumstances,* n</td>
<td>2</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Postmortem conducted, n</td>
<td>10</td>
<td>12</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Index SUD victim.
examination revealed that the postmortem analysis of the first-degree relative who sustained SUD in 1977 was the only analysis performed in this family. On reanalysis of these cardiac specimens in 2001, typical ARVC features were clearly recognized.

Our high success rate in establishing a diagnosis highlights the importance of examining surviving relatives of SUD victims to reveal the underlying familial disease. This study provides the first comprehensive report on the diagnostic yield of this strategy. It extends previous findings of a 19% (6 of 32) success rate in extracting a diagnosis from studying relatives of the subgroup of SUD victims in whom postmortem analysis had failed to identify the cause of death. We show that the diagnostic success of such an approach is not restricted to this SUD subgroup but relates to the SUD group as a whole, ie, including those in whom postmortem analysis was not performed (in the Netherlands, postmortem analysis in SUD is not mandatory). Of note, these efforts result in the identification of a large number of affected surviving relatives (8.9 per family) who were previously unrecognized as disease carriers but were also at risk of sudden death. Although the proportion of asymptomatic relatives who were identified as disease carriers is in accordance with the autosomal mode of inheritance of these diseases, it may appear surprisingly high because the fact that no clue about the diagnosis was initially present in the index SUD victims may suggest low disease penetrance. This high proportion may be explained in several ways. First, in most presymptomatic relatives, disease carriership was simply proved by mutation carriership. Second, the fact that death in the SUD victims was unexplained does not imply that disease penetrance was low but may stem from the fact that SUD victims had not sought medical attention. Indeed, although syncope before SUD was not previously documented, it was reported postmortem in 8 families (4 families with a diagnosis, 4 families without a diagnosis).

The high success rates in diagnosing families and unmasking affected surviving relatives clearly indicate that these efforts should be strongly advised. This is particularly true because most diagnoses in these families involve primary electrical disease. These disorders not only are highly amenable to treatment but also, if treated correctly, are associated with a virtually normal life expectancy, given that structural derangements are absent. Future studies must validate these expectations by providing follow-up of thus identified and appropriately treated presymptomatic disease carriers to establish how many lives were saved. This may entail analysis of the incidence of aborted sudden death from ventricular tachyarrhythmias by appropriate shocks of implantable cardioverter-defibrillators.

The high diagnostic yield of the ECG (resting, exercise, flecainide challenge) may have important practical implications. These tests, which are simple and routinely available, are ideally suited as initial screening methods.

Growing Role for Molecular Genetics

We found molecular genetic analysis highly useful. First, although it was not required as proof of a diagnosis, it did increase the diagnostic yield in cases where the phenotype was not so prominent. For instance, the relatively rare involvement of the TNNT2 gene found in our HCM family is associated with a high incidence of malignant arrhythmias and sudden death but produces only mild structural derangements that may remain undetected by imaging techniques. Thus, molecular genetic confirmation is highly supportive in this HCM type. Second, molecular genetics strongly facilitated the identification of other disease carriers in that family, particularly those who were presymptomatic.

Still, it is equally clear that efforts should be directed at further improvements in molecular genetics. Most importantly, more causative genes for particular diseases must be found. For instance, SCN5A is the only gene now known to be involved in Brugada syndrome, but mutations can be found in only 30% of patients at best. Furthermore, molecular genetic diagnosis should improve its practicability. For example, the usefulness of RyR2 screening in clinical practice is currently limited because it is very time consuming with the present methods because RyR2 is the largest known ion channel encoding gene. Clearly, further improvements in molecular genetics require the concerted efforts of clinicians, geneticists, and basic scientists. Hence, examination of surviving relatives of SUD victims not only bears direct clinical significance (timely treatment of presymptomatic disease carriers) but also may serve as a model to shape future improvements in clinical practice at large.

Study Execution and Limitations

The primary aim of our study was to assess how effectively the causes of SUD can be extracted from analysis of surviving relatives in a real-world situation, ie, using routine cardiological examination in a clinical setting designed primarily for patient care. This study design carries inherent limitations. For instance, given the mode of recruitment of the families (more than one third were referred from other hospitals), it is conceivable that our success rate in establishing a diagnosis is an underestimation of the true potential of these efforts. Because our hospital is a tertiary referral center, we possibly attracted a sizeable proportion of patients who presented a diagnostic challenge, while the remaining patients may already have been diagnosed by the referring physicians. This may be particularly true for structural diseases such as HCM that usually are readily detectable by postmortem studies and echocardiography. It is conceivable that these diseases were already diagnosed by the referring physicians and therefore not referred to us. This may explain why we identified only 1 HCM family and why primary electrical diseases were predominant among our final diagnoses. Here, it should be emphasized that investigation of surviving relatives must be hypothesis driven if it is to be successful because clinical signs may be subtle. For instance, although CPVT patients have a normal baseline ECG and echocardiogram, history taking will reveal that their symptoms occur during exercise. Accordingly, exercise testing is a logical next step in the diagnostic workup and may typically reveal polymorphic ventricular tachycardia at fast heart rates. However, even single ventricular premature beats during exercise may already be significant when the clinical suspicion is high. Thus, increased awareness and recognition of inherited causes of
sudden death may raise the diagnostic yield of examination of surviving relatives. Clearly, referring physicians and the general public must also be made aware that these efforts are worthwhile as a result of their high yield because it is conceivable that referral bias has caused an underestimation of the true potential of these efforts. For instance, we may have examined only families and individuals who were highly motivated to undergo these studies; the proportion of inherited causes of sudden death may have been even higher among those who were not (self-)referred.

Conclusions
Examination of relatives of young SUD victims has such a high diagnostic and therapeutic yield that it should be strongly advised. Although rigorous cardiological evaluation is required, simple procedures (examining as many relative as possible) and routine tests (ECG at rest/exercise or during flecainide challenge) constitute excellent initial diagnostic strategies. Molecular genetics strongly contribute to the high diagnostic yield.

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