Understanding cardiac electrical phenotypes in the genomic era
Milano, A.

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Chapter

Sudden cardiac arrest and rare genetic variants in the community

Annalisa Milano†, Marieke T. Blom†, Elisabeth M. Lodder, Daniel A. van Hoeijen, Julien Barc, Tamara T. Koopmann, Leander Beekman, Ellen van der Schoot, Peter Lichtner, Connie R. Bezzina, Hanno L. Tan

† These authors contributed equally to this work.
Abstract

Sudden cardiac arrest (SCA) ranks among the most common causes of death worldwide. Because SCA mostly occurs in individuals without previously known cardiac disease, the identification of patients at risk for SCA could save many lives. Emerging evidence implies genetic factors in SCA risk. In unselected SCA victims from the community, common genetic variants (which are not disease-causing per se, but may increase susceptibility to VF) have recently been associated with increased SCA risk. However, whether rare genetic variants which may carry larger effects, contribute to SCA risk in the community is largely unexplored.

We here investigated the involvement of rare genetic variants in SCA risk at the population level, by studying the prevalence of six Dutch founder genetic variants that were previously linked to familial cardiomyopathy or cardiac electrical disease (PLN-p.Arg14del, MYBPC3-p.Trp792fsX17, MYBPC3-p.Arg943X and MYBPC3-p.Pro955fsX95, PKP2-p.Arg79X and the Chr7q36 IVF risk-haplotype) in a cohort of 1440 unselected Dutch SCA victims included in the AmsteRdam REsuscitation STudy (ARREST). The six founder mutations studied were found to be more prevalent in the cohort of SCA victims compared to a reference cohort of individuals of Dutch descent (n=1379) from the same geographical region (1.1% SCA cases carried one of the founder mutations versus 0.4% of controls, p<0.05). This finding provides proof-of-concept for the notion that rare genetic variants contribute to SCA risk in the community.
Introduction

Sudden cardiac arrest (SCA) ranks among the most common causes of death worldwide. The yearly SCA incidence in the community varies between 0.6 and >1.4 per 1,000 individuals\(^1,2\). Because SCA mostly occurs in individuals without previously known cardiac disease, the identification of patients at risk for SCA could save many lives\(^3,4\).

SCA most often results from ventricular fibrillation (VF)\(^2,5\). The causes of VF are highly complex. VF may result from genetic and acquired causes, and their interactions. Acquired causes for SCA (e.g., cardiovascular disease, concomitant co-morbidities, medication use) are well-established\(^5\). Their prevalence rises with advancing age; accordingly, SCA most commonly afflicts older persons. Emerging evidence also implies genetic factors in SCA risk. In young SCA victims, rare genetic variants that cause cardiomyopathies or primary electrical disease contribute importantly to SCA risk. This insight was gained from highly selected cohorts of young SCA victims seen at specialized Cardiogenetics departments\(^6-8\). In unselected SCA victims from the community, common genetic variants (which, due to their small contribution to risk, are not disease-causing \textit{per se}, but may increase susceptibility to VF) have recently also been associated with increased SCA risk\(^9,10\). However, whether rare genetic variants which may carry large effects on SCA risk contribute to SCA in the community is largely unexplored\(^11\).

Here, we investigated the contribution of rare genetic variants to SCA risk at the population level by studying the prevalence of six Dutch founder genetic variants previously linked to cardiomyopathy or primary electrical disease in a cohort of unselected Dutch SCA victims from the community.
METHODS

In this case-control study, we compared the prevalence of six selected founder mutations between an SCA case cohort (ARREST) a non-SCA control cohort (controls obtained from blood donors from the same region) and prevalence information available in the literature (Go-NL\textsuperscript{12} and PREVEND\textsuperscript{13}). This study was conducted at the Academic Medical Center, a university hospital in Amsterdam, the Netherlands, with a Cardiogenetics department (in the Netherlands, Cardiogenetics departments are only present in the eight university hospitals).

SCA cases (ARREST)

The ARREST SCA case cohort consisted of 1440 SCA patients included in the AmsteRdam REsuscitation STudy (ARREST) in the period June 2007 until December 2011\textsuperscript{10}. ARREST is an ongoing, prospective, community-based SCA registry, coordinated from the Academic Medical Center and designed to establish the genetic\textsuperscript{9,10} and clinical\textsuperscript{14} determinants of SCA, and outcome of resuscitation attempts\textsuperscript{15} in the general population. The ARREST study protocol is described in detail elsewhere\textsuperscript{16}. In short, the ARREST research group prospectively collects data of all cardiopulmonary resuscitation efforts in collaboration with all Emergency Medical Services in the North Holland province of the Netherlands; this study region contains the Amsterdam area and covers 2404 km\textsuperscript{2} (urban and rural communities) with a population of 2.4 million people. ARREST catches >95% of all people with out-of-hospital SCA\textsuperscript{17}. ECG recordings from the ambulance monitor/defibrillator or automated external defibrillator (AED) are used to determine whether VF had occurred. SCA cases are defined as people who had a cardiac arrest in an out-of-hospital setting with VF. Patients with an obvious non-cardiac cause of VF (e.g., trauma, intoxication, drowning, suicide) are excluded. Patients in whom only asystole (but no VT/VF) was recorded were excluded, because we could not ensure that cardiac arrest stemmed from cardiac causes, as asystole is the end stage of any cardiac arrest, and may be due to non-cardiac causes (e.g., respiratory failure)\textsuperscript{18}. Medical histories are obtained from the general practitioner (GP) and the diagnosis of the cause of the SCA is obtained from hospital records. Genomic DNA is extracted from peripheral blood samples drawn during routine patient care, according to standard procedures. Written informed consent is obtained from all surviving patients.

Non-SCA controls

**Blood donor controls**: These control samples were obtained at Sanquin Blood Supply (Amsterdam) from 1379 healthy volunteer blood donors of Dutch European descent from the same geographic region as ARREST (Amsterdam area). We genotyped the
six founder mutations with the same assays used in ARREST. Informed consent was obtained from all participants.

**Founder mutations: selection and genotyping**

The following six founder mutations were selected for study because of their recurrence (indicative of a founder effect) in DNA diagnostic testing of patients with inherited cardiac disorders at Cardiogenetics departments in the Netherlands. These mutations were: three mutations associated with hypertrophic cardiomyopathy (HCM, mutations MYBPC3-p.Trp792fsX17, MYBPC3-p.Arg943X, MYBPC3-p.Pro955fsX95); one mutation associated with arrhythmogenic right ventricular cardiomyopathy (ARVC, PKP2-p.Arg79X); one mutation associated with an overlap phenotype of dilated cardiomyopathy (DCM) and ARVC (PLN-p.Arg14del), and a founder haplotype linked to idiopathic VF (IVF, the Chr7q36 IVF risk-haplotype), which was detected by either the chr7:154002240 c.-340C>T, or the chr7:g.154056404.TA/- variant, both of which are unique to the risk haplotype.

Genotyping for the six founder mutations in ARREST and in the sample of non-SCA controls was performed on the MassARRAY system using MALDI-TOF mass spectrometry with the iPLEX Gold chemistry (Sequenom Inc, San Diego, CA, USA). Primers were designed using Assay Designer 4.0.0.2 with iPLEX Gold default parameters. The probe sequences are listed in Supplementary Table 1. Automated genotype calling was done with Typer Analyzer 4.0.22.67. We included DNA from a known carrier for each mutation as a positive control. Genotype clustering was visually checked by an experienced evaluator. The average call rate of all samples in the study cohort was 98%. Once carriership of a founder mutation was identified, this was subsequently validated by PCR-Sanger sequencing.

**Statistical analysis**

To evaluate if the observed distribution of founder mutation carriers diverged from the expected distribution in the general population, we used the \( \chi^2 \)-test. Error bars denote the standard error (SEM) of the proportion (based on group size). Confidence intervals are given \( \pm 2 \times \text{SEM} \).
RESULTS

Prevalence of founder mutations in the ARREST SCA case cohort

The total ARREST cohort consisted of 1440 cases (mean age 64 years, 78% men). All six founder mutations were successfully genotyped with an average call rate of 98%. The six positive controls for each founder mutation were successfully genotyped and properly called. The place of residence of the successfully genotyped ARREST individuals is shown in Figure 1.

No case carried the MYBPC3-p.Pro955fsX95 mutation or the Chr7q36 IVF risk-haplotype. Sixteen cases were heterozygous carriers of one of the four remaining founder mutations: eight carried the PLN-p.Arg14del mutation, six carried MYBPC3-p.Trp792fsX17, one carried MYBPC3-p.Arg943X, and one PKP2-p.Arg79X (Figure 2 and Table 1). No case carried any of the founder mutations homozygously or compound

Figure 1. Distribution of the genotyped SCA cases (ARREST) individuals according to their place of residence. The number of individuals per region is indicated by the shade of red (in parenthesis: the number of postal code regions, 90 in total). On average each region contains 180,000 inhabitants. Bold numbers refer to the location of the presumed origin of the respective founder mutations: PLN-p.Arg14del (1), MYBPC3-p.Trp792fsX17 (2), PKP2-p.Arg79X (3), Chr7q36 IVF risk-haplotype (4) MYBPC3-p.Arg943X (5) and MYBPC3-p.Pro955fsX95 (6). The city of Amsterdam is located in the darkest red region (underneath the 3).
heterozygously. When considered in aggregate, the prevalence of the studied founder mutations in ARREST was 1.1% (16 of 1440 cases).

**Prevalence of founder mutations in the non-SCA control cohorts**

Six blood donor controls (6 of 1379, 0.4%) were found to carry one of the mutations, PLN-p.Arg14del (n=3), MYBPC3-p.Trp792fsX17 (n=2) or MYBPC3-p.Arg943X (n=1). No control carried the MYBPC3-p.Pro955fsX95 mutation or the Chr7q36 IVF risk-haplotype. When the founder mutations were considered in aggregate, we found an enrichment of founder mutation carriership in ARREST cases versus blood donor controls (1.1% versus 0.4%, p<0.05). When considered separately, there was no difference in the abundance of the MYBPC3-p.Trp792fsX17, PLN-p.Arg14del or
MYBPC3-p.Arg943X mutations between the SCA and blood donor control cohorts (p>0.05, Table 1).

We additionally looked up the frequency of the six founder mutations in 500 unrelated subjects from the Genome of the Netherlands (GoNL) database which contains individuals from eleven of the twelve Dutch provinces of the Netherlands without selection on the basis of phenotype or disease.12,25 No control from GoNL

Table 1 Prevalence of founder mutations in SCA cases and non-SCA controls

<table>
<thead>
<tr>
<th>Founder Mutation</th>
<th>SCA cases (ARREST)</th>
<th>Blood donor controls (Sanquin)</th>
<th>GoNL controls</th>
<th>PREVEND controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLN-p.Arg14del</td>
<td>8/1426</td>
<td>3/1348</td>
<td>0/500</td>
<td>6/8261</td>
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<tr>
<td>Prevalence</td>
<td>0.56%</td>
<td>0.44%</td>
<td>0%</td>
<td>0.07%</td>
</tr>
<tr>
<td>C.I.</td>
<td>0.17-0.96%</td>
<td>0.08-0.79%</td>
<td>n.a.</td>
<td>0.01-0.13%</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.16</td>
<td>p=0.09</td>
<td>p=7.4*10^-6</td>
<td></td>
</tr>
<tr>
<td>MYBPC3-p.Trp792fsX17</td>
<td>1/1420</td>
<td>2/1354</td>
<td>0/500</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.42%</td>
<td>0.15%</td>
<td>0%</td>
<td>n.a.</td>
</tr>
<tr>
<td>C.I.</td>
<td>0.08-0.77%</td>
<td>-0.06-0.36%</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.18</td>
<td>p=0.55</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>MYBPC3-p.Arg943X</td>
<td>1/1417</td>
<td>1/1354</td>
<td>0/500</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.07%</td>
<td>0.07%</td>
<td>0%</td>
<td>n.a.</td>
</tr>
<tr>
<td>C.I.</td>
<td>-0.07-0.21%</td>
<td>-0.07-0.22%</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.97</td>
<td>p=0.55</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>PKP2-p.Arg79X</td>
<td>1/1419</td>
<td>0/1331</td>
<td>0/500</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.07%</td>
<td>0%</td>
<td>0%</td>
<td>n.a.</td>
</tr>
<tr>
<td>C.I.</td>
<td>-0.07% - 0.21%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.96</td>
<td>p=0.55</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>MYBPC3 p.Pro955fsX95</td>
<td>0/1440</td>
<td>0/1350</td>
<td>0/500</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>n.a.</td>
</tr>
<tr>
<td>C.I.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Chr7q36 IVF risk- haplotype</td>
<td>0/1440</td>
<td>0/1379</td>
<td>0/500</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>n.a.</td>
</tr>
<tr>
<td>C.I.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Total Yield</td>
<td>16/1440</td>
<td>6/1379</td>
<td>0/500</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>1.1%</td>
<td>0.44%</td>
<td>0%</td>
<td>n.a.</td>
</tr>
<tr>
<td>C.I.</td>
<td>0.56-1.66%</td>
<td>0.08-0.79%</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>p-value*</td>
<td>p&lt;0.05</td>
<td>p&lt;0.02</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

C.I., confidence interval (±2*SEM); GoNL, Genome of the Netherlands; IVF, Iodiopathic Ventricular Fibrillation; n.a., not applicable; n.d. not determined; the p-value reflects the likelihood that the observed difference in prevalence between the SCA cases and the respective controls is based on chance (χ2-test).
carried any of the founder mutations. Since the PLN-p.Arg14del mutation is thought to originate in the northern region of the Netherlands\textsuperscript{26}, we additionally compared the prevalence of this founder mutation between the SCA cohort and PREVEND, a sample consisting of 8267 individuals of the general Dutch population from the north of the Netherlands\textsuperscript{13}. The PLN-p.Arg14del occurred significantly more often in the SCA cases compared to PREVEND (0.56\% versus 0.07\%, p<0.00001, Table 1).

**Clinical characteristics of cases**

In aggregate, the mean age of the 16 cases was 57 years, 75\% were men. Six cases (38\%) were young (age <50 years, range 22-46). While mutation carriersonship was not known before the SCA episode in any of the cases, all young cases, but no older case (age ≥50 years, range 57-86), were referred to a Cardiogenetics department for DNA analysis after the SCA episode.

**Young cases**

Four young cases were already treated for DCM before their SCA episode, including three with heart failure; DNA analysis at the Cardiogenetics department revealed that they all carried the PLN-p.Arg14del mutation. In the two remaining young cases, we found the MYBPC3-p.Trp792fsX17 mutation. In both, carriersonship was unknown prior to the present study. In one of them, the diagnosis after the clinical workup post-SCA was ARVC; accordingly, ARVC-related genes were screened at the Cardiogenetics department (PLN, PKP2, DSP, DSG2, DSC2, JUP, TMEM43), but no pathogenic mutation was found. In the other case, no putative cause for SCA was found at the post-SCA clinical workup, yielding the diagnosis IVF; no DNA analysis was conducted at the Cardiogenetics department.

**Older cases**

In five of ten older cases (50\%), workup after SCA revealed that SCA resulted from acute myocardial infarction; we found that they carried PLN-p.Arg14del (n=3), MYBPC3-p.Trp792fsX17 (n=1) or MYBPC3-p.Arg943X (n=1). Investigation into the cause of SCA in the five remaining cases yielded the diagnoses HCM (MYBPC3-p.Trp792fsX17 [n=1]); IVF (two cases) (PLN-p.Arg14del [n=1], MYBPC3-p.Trp792fsX17 [n=1]); one case was already known to have ARVC (PKP2-p.Arg79X), while in the last case the patient died before a diagnosis was made (MYBPC3-p.Trp792fsX17).
DISCUSSION

We here demonstrate that six founder mutations associated with SCA in the setting of familial cardiomyopathy or primary electrical disease are in aggregate more prevalent in an unselected cohort of 1440 SCA victims from the community as compared to non-SCA controls. This finding provides proof-of-concept for the notion that rare genetic variants contribute to SCA risk in the community.

The six mutations studied here were selected because they are among the most prevalent SCA-associated founder mutations in the Netherlands. For instance, the phospholamban gene mutation PLN-p.Arg14del is the most commonly encountered cardiomyopathy-associated mutation in the Netherlands and is identified in 10-15% of Dutch patients with DCM or ARVC. Similarly, the MYBPC3-p.Trp792fsX17 mutation, is found in 17% of index patients with HCM. Yet not all 6 mutations were found in the cohort of SCA patients tested. While this may be related to the size of the SCA cohort, this is also likely explained by the geographic origin of these mutations in relation to the ARREST study region and/or migration patterns. In line with this, the MYBPC3-p.Pro955fsX95 and the Chr7q36 IVF risk-haplotype, that were not found in ARREST, are thought to originate in regions in the Netherlands that are more to the south and to the east of the ARREST study region.

The geographic clustering of founder mutations necessitates that studies investigating the contribution of these mutations to SCA risk on the community level make use of controls that are drawn from the same geographic region as the cases. For this reason we genotyped a set of Dutch European descent blood donors (n=1379) originating from the Amsterdam area, as is ARREST. We also compared the SCA cases to control individuals from the Genome of the Netherlands study, a dataset of 500 whole-genome-sequenced individuals from different regions of the Netherlands. Considering the fact that gradients may exist in the population frequency of such founder mutations, even in a small country such as the Netherlands, the blood donor population from the Amsterdam area likely represents the best-matched control set. Compared to both control populations the yield of mutation carriers is larger in the SCA cohort than in the general population. It is clear that the study and control sets used in this study are not large enough to allow for the comparison of frequency in cases and controls per variant.

Our finding that rare genetic variants are more prevalent in SCA patients is consistent with the notion that the variants we studied are pathogenic and contribute importantly to SCA in young individuals without acquired causes for SCA. Such individuals, who suffer SCA despite seemingly full health, are typically referred to a Cardiogenetics clinic. Indeed in the four young PLN-p.Arg14del patients a clearly recognizable phenotype typical for PLN-p.Arg14del (reduced QRS voltages on the ECG) was observed and all four were referred to a Cardiogenetics clinic where the PLN mutation was identified.
Yet, we found that four of the eight SCA patients who carried the PLN-p.Arg14del mutation were of older age. These patients were not referred to a Cardiogenetics clinic, probably because SCA is not an unexpected occurrence at their age. In three of these patients, acute myocardial infarction was most likely the immediate cause of SCA. Moreover, these patients were not found to suffer from DCM, and there was no clear evidence to suggest that carriership of PLN-p.Arg14del has contributed to SCA in these patients. However, pathophysiological changes imposed by the PLN-p.Arg14del mutated protein may interact with acute myocardial infarction to increase the likelihood of VF and SCA, as PLN is crucially involved in maintaining cellular calcium homeostasis and calcium overload, present during acute myocardial infarction, may evoke cardiac arrhythmia/VF and SCA. Thus, while our study shows that rare genetic variants contribute to SCA risk in the community, it also confirms findings from previous studies that such variants may have reduced penetrance (absence of a phenotype in carriers of such variants) and a wide clinical spectrum.

In neither of the two young MYBPC3-p.Trp792fsX17 carriers was the pathogenic mutation found upon referral to the Cardiogenetics department. This may be attributed to the lack of an identifiable cardiac phenotype (IVF) in one and a non-MYBPC3-associated phenotype (ARVC) in the other, as a result of which MYBPC3 was not sequenced in these patients. This further highlights the general difficulties of assigning causality to identified genetic variants due to an incomplete penetrance and diverse clinical spectrum observed in mutation carriers.

Our findings provide support to the utility of pre-symptomatic DNA testing in the community for rare SCA-associated mutations. For instance, the PLN mutation that is clearly pathogenic (2282031326) was found, besides in young individuals who underwent Cardiogenetic follow-up, also in older individuals who were not referred to a Cardiogenetics clinic. The pathogenicity of such mutations argues in favour of screening for these mutations in older SCA patients as well, so that their relatives may also receive timely testing and/or treatment to prevent SCA.

However, issues of incomplete penetrance and variability in disease expression present obstacles to design guidelines for DNA testing in SCA victims in the community. With the current protocols DNA testing is largely limited to SCA patients with a high likelihood for carriership (e.g., because of young age, family history or clinical suspicion of a particular disease) and to genes implicated in a particular phenotype. As a result mutations with a clear disease-causing potential but reduced penetrance or variable expression will be missed (e.g., the four older PLN-p.Arg14del carriers and the young MYBPC3-Trp792fsX17 carriers in our study). Thus, mutation-carrying relatives of these patients will not be identified either, thus missing the opportunity for early detection and treatment of subclinical cardiac disease with the associated risk of SCA in these relatives.

On the other hand, broad genetic testing in all SCA patients, regardless of likelihood of carriership, clearly poses medical, ethical and logistical concerns. This is particularly true...
if comprehensive testing of large gene panels is conducted, as unavoidably many genetic variants with unclear clinical significance will be discovered in this scenario.

A possible compromise could be to specifically test only for the presence of a set of founder mutations with proven pathogenicity in all SCA. For instance, the PLN-p. Arg14del mutation is not unique to the Netherlands as it belongs to the “European-shared” founder mutation category and was also found in Germany and in the United States, suggesting a possible common ancestor between these populations. In hot spots for this mutation in these countries, specific screening for this mutation in SCA patients may be considered. In combination with other local identified founder mutations.

Clearly, we have only begun to understand the role of rare genetic variants in susceptibility to SCA in the community. Much more work is needed to identify the role of these variants in the light of possible interactions with other concomitant genetic or acquired factors that increase SCA risk. Our study is limited due to the selected number of known mutations that we studied. Future studies, with a more unbiased approach will help to obtain a more comprehensive insight into the role of rare variants in SCA risk in the community. In summary, our study provides proof-of-concept for the notion that rare genetic variants contribute to SCA risk in the community.

ACKNOWLEDGEMENTS

We acknowledge the support from the “Netherlands CardioVascular Research Initiative”: the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences (PREDICT project). We would like to thank Dr. Pieter Postema for his help with the postal code map of the Netherlands.
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References


### Supplementary Table 1: Probe sequence; in brackets is the alternative allele

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr</th>
<th>Mutation</th>
<th>Genomic position (hg19)</th>
<th>c.DNA</th>
<th>Probe sequence</th>
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<td>IVF risk-haplotype</td>
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<td></td>
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