ORIGINAL ARTICLE

A Prospective Study of Sudden Cardiac Death among Children and Young Adults

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ABSTRACT

BACKGROUND

Sudden cardiac death among children and young adults is a devastating event. We performed a prospective, population-based, clinical and genetic study of sudden cardiac death among children and young adults.

METHODS

We prospectively collected clinical, demographic, and autopsy information on all cases of sudden cardiac death among children and young adults 1 to 35 years of age in Australia and New Zealand from 2010 through 2012. In cases that had no cause identified after a comprehensive autopsy that included toxicologic and histologic studies (unexplained sudden cardiac death), at least 59 cardiac genes were analyzed for a clinically relevant cardiac gene mutation.

RESULTS

A total of 490 cases of sudden cardiac death were identified. The annual incidence was 1.3 cases per 100,000 persons 1 to 35 years of age; 72% of the cases involved boys or young men. Persons 31 to 35 years of age had the highest incidence of sudden cardiac death (3.2 cases per 100,000 persons per year), and persons 16 to 20 years of age had the highest incidence of unexplained sudden cardiac death (0.8 cases per 100,000 persons per year). The most common explained causes of sudden cardiac death were coronary artery disease (24% of cases) and inherited cardiomyopathies (16% of cases). Unexplained sudden cardiac death (40% of cases) was the predominant finding among persons in all age groups, except for those 31 to 35 years of age, for whom coronary artery disease was the most common finding. Younger age and death at night were independently associated with unexplained sudden cardiac death as compared with explained sudden cardiac death. A clinically relevant cardiac gene mutation was identified in 31 of 113 cases (27%) of unexplained sudden cardiac death in which genetic testing was performed. During follow-up, a clinical diagnosis of an inherited cardiovascular disease was identified in 13% of the families in which an unexplained sudden cardiac death occurred.

CONCLUSIONS

The addition of genetic testing to autopsy investigation substantially increased the identification of a possible cause of sudden cardiac death among children and young adults. (Funded by the National Health and Medical Research Council of Australia and others.)

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Sudden cardiac death among children and young adults is a devastating event for the family and wider community. Coronary artery disease is the predominant cause of sudden cardiac death in older persons,[1] whereas among persons 1 to 35 years of age, sudden cardiac death is more often caused by structural heart disease, including hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, myocarditis, and primary arrhythmogenic disorders (such as the congenital long-QT syndrome, the Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia).[2-5] Many of these cardiac causes of sudden cardiac death among children and young adults have an underlying genetic basis.[6,7]

Estimates in studies of the incidence of sudden cardiac death vary widely owing to differences in the age range of the various study populations; in addition, studies are often limited by small sample size and by retrospective and non–population-based study designs. A nationwide retrospective study of sudden cardiac death in an unselected population of persons 1 to 35 years of age in Denmark showed an incidence of 2.8 per 100,000 person-years, or 1.9 per 100,000 person-years when only autopsied cases were considered.[8] A similar incidence of 1.8 per 100,000 per year was found after a review of death certificates in England and Wales.[9]

In up to one third of cases of sudden cardiac death among children and young adults, a cause of death is not found after a comprehensive autopsy examination that includes toxicologic and histologic studies; these deaths are termed unexplained sudden cardiac deaths.[3,8,10-12] Unexplained sudden cardiac death is often attributed to cardiac arrhythmia caused by cardiac ion-channel dysfunction, which is undetectable in a conventional autopsy. Noncardiac conditions may also cause sudden death that is clinically indistinguishable from sudden cardiac death. For example, patients with epilepsy have a higher rate of sudden death than persons without epilepsy, and sudden unexpected death in epilepsy is the most common cause of death related to epilepsy.[13]

Autopsy-based genetic studies of the major genes for the long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia (a four-gene "molecular autopsy" including the *KCNQ1*, *KCNH2*, *SCN5A*, and *RYR2* genes) have identified a pathogenic mutation in up to one third of unexplained sudden cardiac deaths that were referred for postmortem genetic testing.[14,15] However, in population-based, nonreferred cases of unexplained sudden cardiac death, the prevalence of pathogenic mutations in the major genes for the long-QT syndrome is significantly lower.[16,17] Furthermore, population-based studies of human genetic variation have revealed an abundance of rare variants, which has led to increasingly stringent mutation classification criteria and a lower diagnostic yield of autopsy genetic testing for unexplained sudden cardiac death.[18,19] We performed a 3-year, prospective, population-based study of sudden cardiac death among persons 1 to 35 years of age in Australia and New Zealand and focused on determining the underlying cause of death after a comprehensive autopsy examination and genetic testing.

METHODS

STUDY DESIGN AND OVERSIGHT

All major forensic pathology centers in Australia and New Zealand prospectively collected premorbid and autopsy investigation data on all cases of sudden cardiac death that occurred in persons 1 to 35 years of age from January 2010 through December 2012. Autopsy examinations were performed by the medical examiners at these centers according to the guidelines of the Royal College of Pathologists of Australasia.[20] In addition, case reports of deaths that had been investigated by a coroner were retrieved from the National Coronial Information System (for Australia) and the Case Management System (for New Zealand) and from the registries of births, deaths, and marriages in each Australian state and territory.

Coroners' autopsy reports, which included toxicologic and histologic findings, and police reports of death were reviewed to identify cases of sudden cardiac death. Sudden cardiac death was defined as a sudden unexpected death in an otherwise healthy person within 1 hour after the onset of symptoms or, when unwitnessed, within 24 hours after the person was last seen in good health. Unexplained sudden cardiac death was defined as sudden cardiac death for which no cause was identified after a complete and comprehensive autopsy examination that included histologic and toxicologic studies (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

A forensic pathologist, an adult cardiologist, and two pediatric cardiologists assessed all cases of sudden cardiac death. Cases in which the details were insufficient to define the death as sudden cardiac death and cases of sudden unexplained death in epilepsy were excluded from our study.

This study was approved by the ethics committee of each state government in Australia and in New Zealand. In 290 cases, permission from the next of kin was obtained, which allowed detailed data on the sudden cardiac death to be recorded and a blood sample to be collected at autopsy for genetic analysis. In addition, for the cases in which permission was obtained, clinical follow-up was recommended for all first-degree relatives if an inherited heart disease was suspected.[5] For cases in which permission was not obtained, only age, sex, and cause and circumstances of death were recorded; such cases were termed de-identified cases. All the authors vouch for the completeness and accuracy of the data and analyses.

DNA Collection and Genetic Analysis

DNA was isolated from samples of whole blood obtained at autopsy, as described previously.[18] The genetic analysis of DNA in cases of unexplained sudden cardiac death is summarized in Figure 1. In 51 of the 113 cases of unexplained sudden cardiac death (45%), we performed clinical-grade sequencing (i.e., a next-generation sequencing test accredited through the National Association of Testing Authorities) of the coding exons of 69, 98, or 101 cardiac disease genes on the Illumina MiSeq platform (Victorian Clinical Genetic Services). In 62 of the 113 cases (55%), commercial research-grade exome sequencing (i.e., exome-sequencing service intended for research purposes) was performed on the Illumina HiSeq2000 platform (Macrogen). Alignment, variant calling, and annotation of all sequencing data were performed at the Centenary Institute, Sydney.

Filtering and Classification of Variants

We searched for variants with a general population frequency of less than 0.1% in 59 cardiac genes common to all sequencing panels and divided the findings into four groups: conventional molecular autopsy genes (4 genes), cardiac arrhythmia genes (16), major and minor cardiomyopathy genes (16), and rare cardiomyopathy genes (23). In addition, we searched for variants in 72 epilepsy genes in the 62 exome-sequenced cases. A list of the target genes is shown in Table S1 in the Supplementary Appendix; the variant classification scheme and a description of the scheme are provided in Figure S1 and the Methods section, respectively, in the Supplementary Appendix.

Copy-Number Variation and Multiplex Ligation-Dependent Probe Amplification

Copy-number variants were detected with the use of eXome-Hidden Markov Model software[21] in 45 cases of unexplained sudden cardiac death and in 48 unrelated control exomes from patients with structural heart disease who attended the Genetic Heart Diseases Clinic, Royal Prince Alfred Hospital, Sydney. Multiplex ligation-dependent probe amplification of five long-QT syndrome genes (i.e., *SCN5A*, *KCNH2*, *KCNQ1*, *KCNE1*, and *KCNE2*) was performed, as described previously, in 71 cases.[22] Additional details of these analyses are provided in the Supplementary Appendix.

Statistical Analysis

Statistical analysis was performed with the use of IBM SPSS Statistics software, version 22 (SPSS), and SAS Studio software (SAS Institute). Continuous variables were compared with the use of unpaired Student's t-tests and are reported as means with standard deviations; categorical variables were compared with the use of chi-square tests and are reported as frequencies and percentages. P values of less than 0.05 were considered to indicate statistical significance. Univariate and multivariate logistic-regression models were used to assess variables associated with unexplained sudden cardiac death, as compared with explained sudden cardiac death (see the Methods section in the Supplementary Appendix).

RESULTS

Incidence of Sudden Cardiac Death among Children and Young Adults

From 2010 through 2012, a total of 490 cases of sudden cardiac death were identified in persons 1 to 35 years of age; 360 (73%) were identified at 11 centers in Australia and 130 (27%) at 5 centers in New Zealand. Of the 490 cases of sudden cardiac death, 198 (40%) were unexplained. During the study period, the mean combined population of Australia and New Zealand was 26.74 million persons, of whom 12.59 million were 1 to

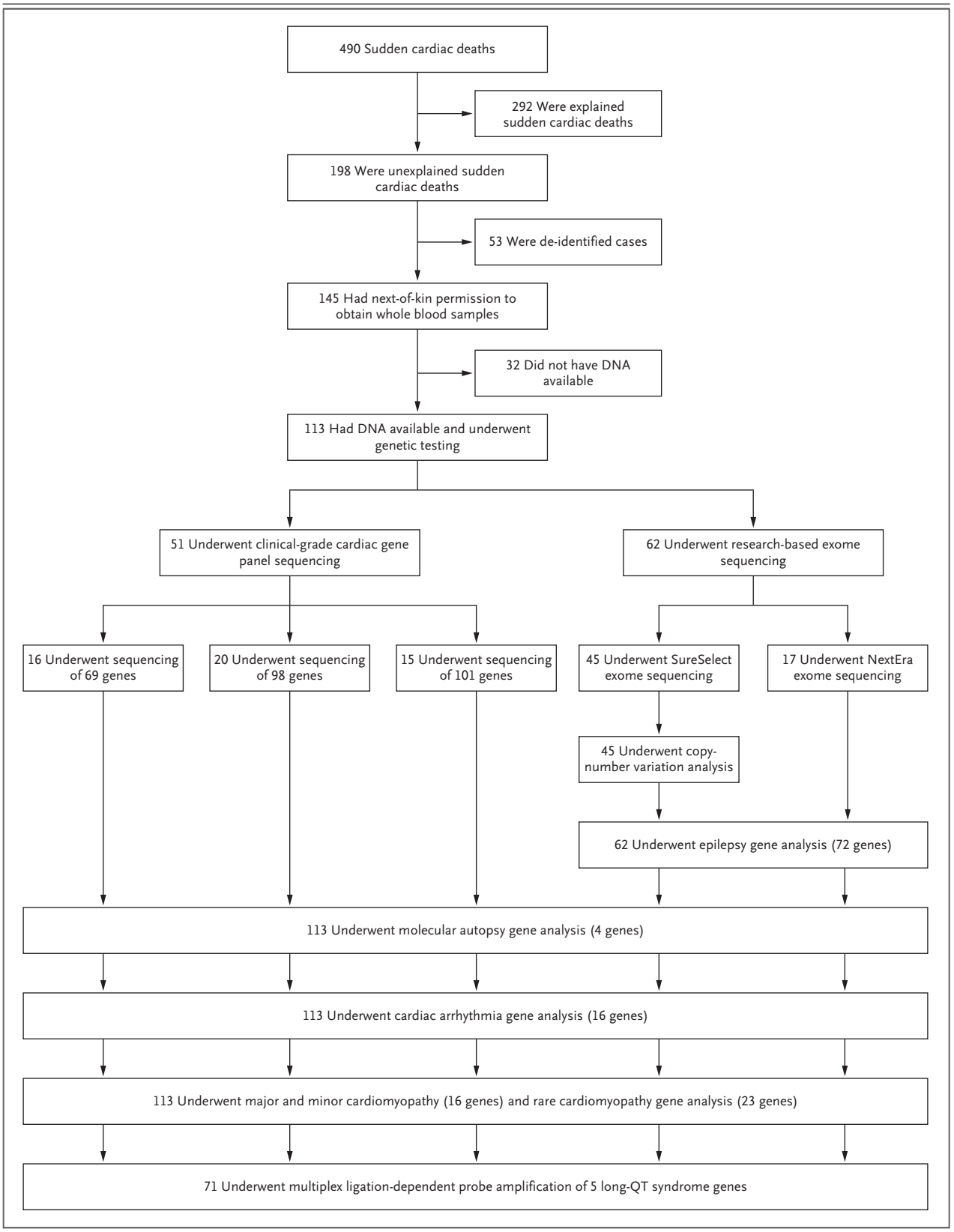
490 Sudden cardiac deaths
292 Were explained sudden cardiac deaths
198 Were unexplained sudden cardiac deaths
53 Were de-identified cases
145 Had next-of-kin permission to obtain whole blood samples
32 Did not have DNA available
113 Had DNA available and underwent genetic testing
51 Underwent clinical-grade cardiac gene panel sequencing
62 Underwent research-based exome sequencing
16 Underwent sequencing of 69 genes
20 Underwent sequencing of 98 genes
15 Underwent sequencing of 101 genes
45 Underwent SureSelect exome sequencing
17 Underwent NextEra exome sequencing
45 Underwent copy-number variation analysis
62 Underwent epilepsy gene analysis (72 genes)
113 Underwent molecular autopsy gene analysis (4 genes)
113 Underwent cardiac arrhythmia gene analysis (16 genes)
113 Underwent major and minor cardiomyopathy (16 genes) and rare cardiomyopathy gene analysis (23 genes)
71 Underwent multiplex ligation-dependent probe amplification of 5 long-QT syndrome genes

Figure 1 (facing page). Investigation of Cases of Sudden Cardiac Death.

A total of 490 cases of sudden cardiac death were identified. A diagnosis was established on the basis of conventional autopsy in 292 cases, and in 198 cases, no diagnosis was evident (unexplained sudden cardiac death). For 113 cases of unexplained sudden cardiac death, DNA from the patient was available. For these cases, massively parallel sequencing was performed on a clinical-grade cardiac gene panel (i.e., a next-generation sequencing test accredited through the National Association of Testing Authorities) in 51 cases and a commercial research-grade exome (i.e., exome-sequencing service intended for research purposes) in 62 cases. An analysis of 59 cardiac genes common to all sequencing technologies was performed on all cases. Copy-number variation analysis of exome data was performed in 45 cases with the use of SureSelect exome sequencing data (Agilent Technologies). An analysis of 72 epilepsy genes was performed in all 62 cases with the use of exome sequencing data. Multiplex ligation-dependent probe amplification analysis was performed in 71 cases of unexplained sudden cardiac death for which a sufficient amount of DNA of adequate quality were available. The NextEra exome enrichment kit is manufactured by Illumina.

35 years of age.[23] On the basis of these figures, the annual incidence of sudden cardiac death in Australia and New Zealand was 1.3 cases per 100,000 persons (95% confidence interval, 1.2 to 1.4); men and boys had a higher incidence than did women and girls (1.8 vs. 0.7 cases per 100,000 persons, P<0.001). Persons 31 to 35 years of age had the highest incidence of sudden cardiac death (3.2 cases per 100,000 persons), and persons 16 to 20 years of age had the highest incidence of unexplained sudden cardiac death (0.8 cases per 100,000 persons) (Fig. 2A).

CHARACTERISTICS, CIRCUMSTANCES, AND CAUSES OF SUDDEN CARDIAC DEATH

The demographic and clinical characteristics of patients who died from sudden cardiac arrest are provided in Table 1. A total of 72% of the patients were male, and the mean (±SD) age at death was 24±10 years. The greatest number of cases occurred among persons 31 to 35 years of age, and the least among persons 6 to 10 years of age (Fig. 2B). The most common finding at autopsy (in 40% of cases) was a structurally normal heart (i.e., no cause of death identified [unexplained sudden cardiac death]), followed by coronary artery disease (in 24% of cases), inherited cardiomyopathies that included dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (cumulatively accounting for 16% of the cases), myocarditis (7% of cases), and aortic dissection (4% of cases) (Fig. 2C). Most cases of sudden cardiac death occurred while the person was sleeping (38%) or at rest (27%), whereas sudden cardiac death during exercise (11%) or after exercise (4%) was relatively uncommon (Fig. 2D).

Unexplained sudden cardiac death was more likely than explained sudden cardiac death to have occurred in women or girls, in younger persons, and during sleep or during the nighttime hours between 6 p.m. and 6 a.m. (Table 1). A comparison of cases of unexplained sudden cardiac death and explained sudden cardiac death according to age group revealed important age-specific differences. Among 49 children 1 to 5 years of age, 37 cases of sudden cardiac death (76%) were classified as unexplained sudden cardiac death; a total of 26 of the 37 cases (70%) occurred among boys and 30 of 33 cases (91%) occurred during sleep (information was not available for all 37 cases). In contrast, among 173 persons 31 to 35 years of age, 42 cases of sudden cardiac death (24%) were classified as unexplained sudden cardiac death; a total of 24 of these 42 cases (57%) occurred among men and 10 of 31 cases (32%) occurred during sleep. Unexplained sudden cardiac death was the predominant finding in all age groups, except among persons 31 to 35 years of age, for whom coronary artery disease was the most common finding. Multivariate analysis showed that after adjustment for sex, younger age group (as compared with persons 31 to 35 years of age) and death at night were significantly and independently associated with unexplained sudden cardiac death as compared with explained sudden cardiac death. Additional details of the characteristics, circumstances, and causes of sudden cardiac death are provided in Tables S2 through S5 and in Figure S2 in the Supplementary Appendix.

GENETIC ANALYSIS OF CASES OF UNEXPLAINED SUDDEN CARDIAC DEATH

Among the 198 cases of unexplained sudden cardiac death, permission from the next of kin

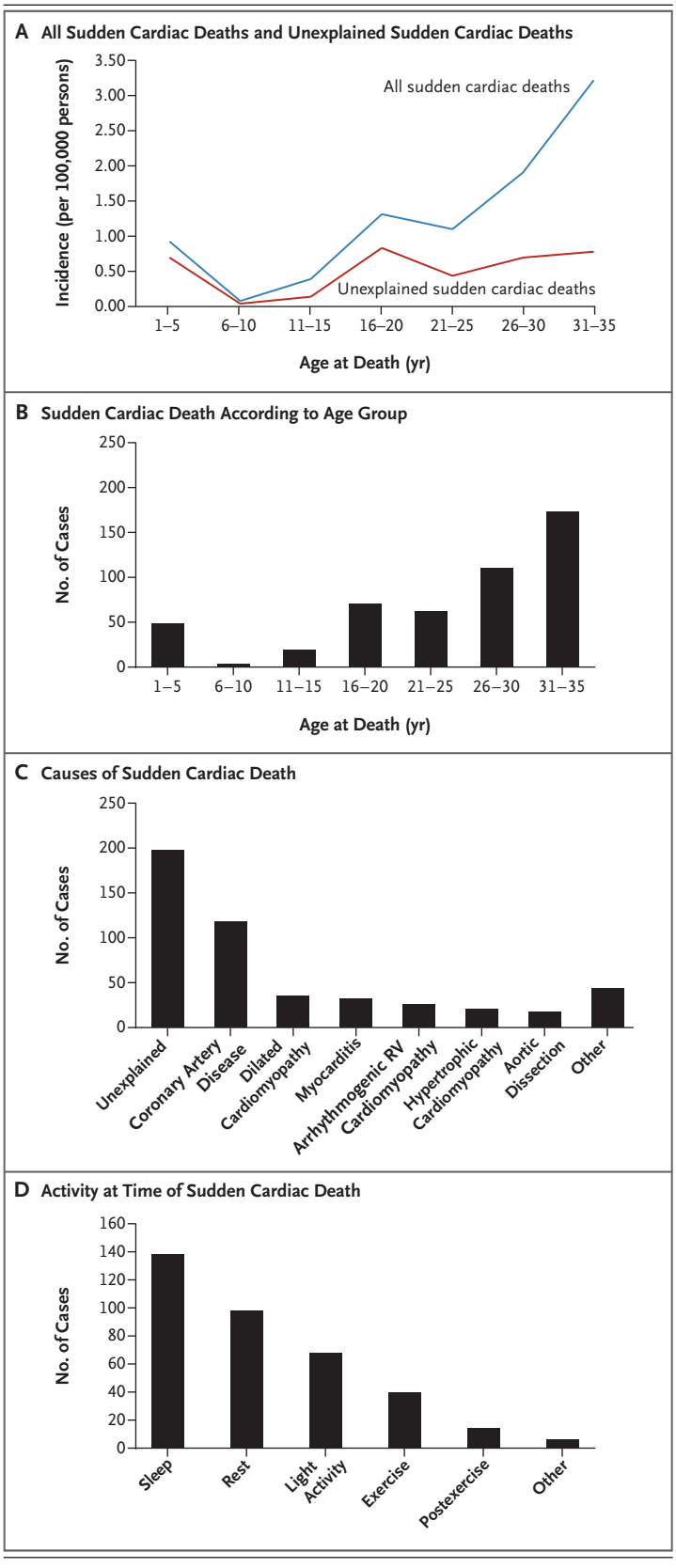

Figure 2. Incidence of Sudden Cardiac Death and Clinical and Demographic Features of the Patients.
RV denotes right ventricular.

was given and a blood sample was obtained in 113 cases (57%), and genetic analysis of at least 59 cardiac arrhythmia and cardiomyopathy genes was performed in these 113 samples (Fig. 1). In the 4 molecular autopsy genes, we found 3 pathogenic and 7 probably pathogenic variants, for a diagnostic yield of 9%. In 16 additional cardiac arrhythmia genes, we found 6 probably pathogenic variants. In 16 major and minor cardiomyopathy genes, we found 1 pathogenic and 13 probably pathogenic variants, and in 23 rare cardiomyopathy genes, we found 6 probably pathogenic variants. The 36 pathogenic and probably pathogenic variants were found in 31 cases of unexplained sudden cardiac death. In 62 cases of unexplained sudden cardiac death, exome sequencing had been performed and we found 4 probably pathogenic variants in epilepsy genes, for a diagnostic yield of 6%. Lists of the rare variants in the four groups of cardiac genes are provided in Tables S6 through S9, and a list of the rare variants in epilepsy genes in Table S10, in the Supplementary Appendix. The demographic characteristics of the patients and relevant autopsy findings in the cases of unexplained sudden cardiac death for which a pathogenic or probably pathogenic cardiac gene variant was identified (31 of the 113 cases in which genetic analysis was performed [27%]) are provided in Table 2.

We detected a mean of 4.7 copy-number variants per sample; however, none overlapped with cardiac disease genes. Multiplex ligation-dependent probe amplification of five long-QT syndrome genes in 71 of the 113 cases of unexplained sudden cardiac death did not reveal deletions or duplications. Overall, age at death, sex, or activity at the time of death was not associated with a pathogenic variant among the cases of unexplained sudden cardiac death (Table S11 in the Supplementary Appendix).

CLINICAL FOLLOW-UP IN FAMILIES OF CASES OF UNEXPLAINED SUDDEN CARDIAC DEATH

Clinical screening was performed in 91 of the 198 families in which an unexplained sudden cardiac death occurred. A total of 54 families

Table 1. Demographic Characteristics and Clinical Circumstances of the Sudden Cardiac Death Cohort.*

Variable	Sudden Cardiac Death (N=490)	Explained Sudden Cardiac Death (N=292)	Unexplained Sudden Cardiac Death (N=198)	P Value
Age — yr	24±10	27±8	20±11	<0.001
Female sex — no. (%)	137 (28)	72 (25)	65 (33)	0.048
Activity at death — no./total no. (%)				
Exercise	56/365 (15)	34/199 (17)	22/166 (13)	0.31
Sleep	139/365 (38)	59/199 (30)	80/166 (48)	<0.001
Attempted resuscitation — no./total no. (%)	297/360 (82)	168/197 (85)	129/163 (79)	0.13
Death during nighttime — no./total no. (%)†	204/349 (58)	103/199 (52)	101/150 (67)	0.004

* Plus–minus values are means ±SD.
† Nighttime was defined as the hours from 6 p.m. to 6 a.m.

could not be followed up because the families had declined follow-up or because information on the families was not available, and 53 families could not be followed up because the cases had been de-identified (Fig. S3 in the Supplementary Appendix). A definite clinical diagnosis was established in 12 of the 91 families (13%) that underwent follow-up clinical screening; inherited arrhythmogenic diseases were identified in 7 families (the long-QT syndrome in 4, catecholaminergic polymorphic ventricular tachycardia in 1, the short-QT syndrome in 1, and primary conduction disease in 1) and inherited cardiomyopathies were identified in 5 families (arrhythmogenic right ventricular cardiomyopathy in 2 and dilated cardiomyopathy, left ventricular noncompaction, or both in 3).

DISCUSSION

This 3-year prospective, population-based study of sudden cardiac death among persons 1 to 35 years of age in Australia and New Zealand identified 490 cases of sudden cardiac death, representing an incidence rate of 1.3 cases per 100,000 persons per year. The most common finding after autopsy was unexplained sudden cardiac death, which accounted for a larger proportion of cases of sudden cardiac death than did explained sudden cardiac death in younger age groups and among persons who died during nighttime hours (6 p.m. to 6 a.m.). Genetic analysis of 4 molecular autopsy genes revealed pathogenic and probably pathogenic variants in 9% of the cases of unexplained sudden cardiac death. Genetic analysis of an additional 55 cardiac genes in the cases of unexplained sudden cardiac death resulted in an overall diagnostic yield of 27%. Therefore, autopsy investigation combined with genetic testing and family screening was associated with a substantially higher likelihood of identifying a possible cause of sudden cardiac death among children and young adults than did autopsy investigation alone.

The incidence and underlying causes of death in our study varied according to age group. A total of 10% of all the cases of sudden cardiac death in our study occurred among children 1 to 5 years of age; most of these deaths occurred among infants and young children 1 to 2 years of age. Sudden cardiac death among infants and young children 1 to 2 years of age probably has shared causes with the sudden infant death syndrome, which is classified as the unexplained death of an infant younger than 1 year of age.[24-27] Children 6 to 10 years of age had the lowest rate of sudden cardiac death (0.8%), after which the risk increased, as reported previously.[28,29] The incidence of cardiomyopathy (hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy) as a cause of sudden cardiac death among children and young adults in our study was lower than that observed in previous studies[30]; this finding may reflect improved diagnosis and management in recent years, including the appropriate use of implantable cardioverter–defibrillator therapy.[31-33] Coronary artery disease was the

Table 2. Demographic Characteristics and Autopsy Findings in Cases of Unexplained Sudden Cardiac Death Associated with a Pathogenic or Probably Pathogenic Variant.*

Sample ID	Sex	Age at Unexplained Sudden Cardiac Death	Activity at Time of Death	Relevant Postmortem Findings	Gene	Amino Acid Change	Gene Panel
		yr					
NSW14A	F	24	Sleep	None	*ANK2*	Ser2976Cys	Cardiac arrhythmia
NSW20A	M	27	Unknown	Moderate perivascular myocardial fibrosis and microfocal interstitial fibrosis Signs of myocyte hypertrophy	*TPM1*	Glu54Val	Cardiomyopathy major and minor
NSW22A	M	20	Sleep	None	*TNNT2*	Arg151Gln	Cardiomyopathy major and minor
NSW28A	M	16	Sleep	Postmortem MRI suggestive of hypertrophic cardiomyopathy (not supported at autopsy) Interventricular septum thickness of 15 mm, posterior left ventricular wall thickness of 16 mm	*CSRP3*	Thr104Lys_fs*27	Cardiomyopathy rare
NSW55A	M	35	Exercise	Heart macroscopically normal Histologic findings of focal myocyte hypertrophy, disarray, and degree of perivascular fibrosis suggestive of hypertrophic cardiomyopathy	*RYR2*	Glu2169Gly	Molecular autopsy
					MYH7	Arg663His	Cardiomyopathy major and minor
NSW100A	M	17	Other	None	*PKP2*	Glu85Met_fs*26	Cardiomyopathy major and minor
NSW104A	M	35	Unknown	None	*LMNA*	Arg343Trp	Cardiomyopathy major and minor
NSW105A	M	23	Sleep	None	*AKAP9*	Gln3730Arg	Cardiac arrhythmia
NSW123A	M	27	Rest	None	*SCN5A*	Ala586_Leu587del	Molecular autopsy
NZ14A	F	24	Exercise	Focal transmural fibrosis, chronic inflammation, and pigmented macrophages in right ventricle	*PKP2*	Gln323Arg_fs*11	Cardiomyopathy major and minor
					ACTN2	Asn101Ser	Cardiomyopathy rare
NZ26A	M	17	Light activity	None	*AKAP9*	Thr1302Gln_fs*10	Cardiac arrhythmia
NZ36A	M	2	Sleep	None	*SCN5A*	Asp546Gly	Molecular autopsy
NZ38A	M	19	Exercise	Interstitial fibrosis in the sinoatrial node	*DES*	Gly437Val_fs*10	Cardiomyopathy rare
					TMEM43	Val119Met	Cardiomyopathy rare
NZ53A	M	1	Sleep	None	*RYR2*	Ile4756Val	Molecular autopsy

QLD5A	M	19	Light activity	None	*DSP*	Leu1451Pro	Cardiomyopathy major and minor
QLD33A	M	20	Rest	None	*FKTN*	Ile248Thr	Cardiomyopathy rare
QLD42A	M	34	Rest	None	*ANK2*	Tyr3936Cys	Cardiac arrhythmia
SA22A	M	28	Light activity	None	*PRKAG2*	Ser151Cys	Cardiomyopathy rare
VIC3A	F	34	Light activity	None	*ACTC1*	Ala321Thr	Cardiomyopathy major and minor
VIC11A	M	16	Light activity	None	*DSP*	Leu851Gln	Cardiomyopathy major and minor
VIC29A	M	35	Light activity	Dilated right ventricle	*RYR2*	Arg3227Pro	Molecular autopsy
VIC44A	F	31	Rest	Out-of-hospital ventricular fibrillation arrest Echo detected in ICU after the arrest showed systolic dysfunction, but the significance was unclear	*SCN5A*	Arg1896Trp	Molecular autopsy
VIC47A	M	33	Unknown	None	*RYR2*	Gly3225Ser	Molecular autopsy
					MYBPC3	Leu994Phe	Cardiomyopathy major and minor
VIC56A	M	5	Sleep	Interventricular septum thickness of 14 mm Unexplained hypertrophy	*SCN5A*	Thr220Ile	Molecular autopsy
VIC57A	M	1	Sleep	Interventricular septum thickness of 7 mm	*MYBPC3*	Arg335Cys	Cardiomyopathy major and minor
VIC72A	M	1	Sleep	None	*MYL3*	Gly74Arg	Cardiomyopathy major and minor
VIC83A	F	1	Sleep	None	*KCNH2*	Gly749Ala_fs*8	Molecular autopsy
					ANK2	Thr825Arg	Cardiac arrhythmia
WA4A	F	14	Sleep	None	*DSP*	Gly2016Arg	Cardiomyopathy major and minor
WA5A	F	27	Light activity	None	*KCNQ1*	Arg594Pro	Molecular autopsy
WA6A	F	27	Unknown	None	*MYH6*	Arg147Lys	Cardiomyopathy major and minor
WA11A	M	32	Sleep	None	*CACNA1C*	Ala174Val	Cardiac arrhythmia

* ICU denotes intensive care unit, and MRI magnetic resonance image.

most common finding among persons 31 to 35 years of age.

A clinically important finding was that the majority of sudden cardiac deaths occurred either while the person was sleeping or at rest. This observation raises questions about the efficacy of limiting physical activity as a means of reducing the risk of sudden death among children and young adults, as is sometimes recommended for competitive athletes. Death during sleep may be caused by bursts of vagal and sympathetic activity during rapid-eye-movement sleep that lead to adrenergically triggered arrhythmias, although nonadrenergic mechanisms may also be involved. Therefore, strategies to prevent sudden cardiac death among children and young adults should also focus on gaining a better understanding of the mechanisms associated with death that occurs while a person is sleeping or at rest.

The likelihood that a case of unexplained sudden cardiac death was caused by an underlying inherited disorder has led to the emerging role of genetic testing of DNA obtained at autopsy (i.e., molecular autopsy).[5,34] Establishing a clear genetic diagnosis in cases of unexplained sudden cardiac death has major implications for the identification of at-risk relatives, the initiation of strategies to prevent sudden death, and guidance with respect to reproductive options. In the current study, the diagnostic yield of 9% that was found for the four molecular autopsy genes is consistent with that found in unselected cohorts in previous studies (9 to 11%).[16,17] In retrospective studies of unexplained sudden cardiac death in selected populations, there was a higher diagnostic yield (>20%), which may represent ascertainment and referral bias.[14,15] We recently reported the genetic findings in 61 cases of sudden unexplained death in epilepsy; we found pathogenic or probably pathogenic variants in the three common genes for the long-QT syndrome in 7% of the cases and in epilepsy genes in 25% of the cases.[35] In contrast, in the current study involving persons who had no history of epilepsy, we found only 4 cases of unexplained sudden cardiac death (6%) in which the person had probable pathogenic variants in epilepsy genes, which suggests that undiagnosed genetic epilepsy is uncommon in cases of unexplained sudden cardiac death.

In the current study, in the clinical follow-up of families in which an unexplained sudden cardiac death occurred, 12 of the families (13%) had a definite clinical diagnosis established in a first-degree relative; inherited cardiomyopathies were identified in five of these families. This diagnostic yield from clinical follow-up was less than what had been reported previously[7,36] and probably reflects the population-based nature of our study, as compared with retrospective, tertiary center–based studies. A thorough clinical evaluation of surviving at-risk family members is nonetheless strongly recommended and may be supplemented by a molecular autopsy.[4,6,37,38]

Our study has several limitations. First, although every available national resource was used to identify cases of sudden cardiac death over the 3-year study period, some cases were not considered because our study did not include cases that had insufficient details to determine with certainty whether the death was sudden, and cases in which the body was found more than 24 hours after the person was last seen alive were not included. Second, various methodologic approaches to genetic analysis were used during the study, which reflects the rapid escalation in genetic technologies over the course of the study. Finally, the scope of the current study did not include cases of successfully resuscitated out-of-hospital cardiac arrest.

In conclusion, in this prospective, population-based, binational study, we found an annual incidence of sudden cardiac death of 1.3 cases per 100,000 persons 1 to 35 years of age. Unexplained sudden cardiac death accounted for 40% of the cases. Among the cases of unexplained sudden cardiac death in which genetic testing was performed, a likely cause of death was identified in 27%. Autopsy investigation combined with genetic testing and family screening was associated with a substantially higher likelihood of identifying a possible cause of death among children and young adults who had a sudden cardiac death than was autopsy investigation alone.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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