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Genetic basis of sudden death after COVID-19 vaccination in Thailand



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BACKGROUND Severe acute respiratory syndrome coronavirus 2 vaccination reduces morbidity and mortality associated with coronavirus disease 2019 (COVID-19); unfortunately, it is associated with serious adverse events, including sudden unexplained death (SUD).

OBJECTIVE We aimed to study the genetic basis of SUD after COVID-19 vaccination in Thailand.

METHODS From April to December 2021, cases with natural but unexplained death within 7 days of COVID-19 vaccination were enrolled for whole exome sequencing.

RESULTS Thirteen were recruited, aged between 23 and 72 years; 10 (77%) were men, 12 were Thai; and 1 was Australian. Eight

(61%) died after receiving the first dose of vaccine, and 7 (54%) died after receiving ChAdOx1 nCoV-19; however, there were no significant correlations between SUD and either the number or the type of vaccine. Fever was self-reported in 3 cases. Ten (77%) and 11 (85%) died within 24 hours and 3 days of vaccination, respectively. Whole exome sequencing analysis revealed that 5 cases harbored *SCN5A* variants that had previously been identified in patients with Brugada syndrome, giving an *SCN5A* variant frequency of 38% (5 of 13). This is a significantly higher rate than that observed in Thai SUD cases occurring 8–30 days after COVID-19 vaccination during the same period (10% [1 of 10]), in a Thai SUD cohort studied before the COVID-19 pandemic (12% [3 of 25]), and in our in-house exome database (12% [386 of 3231]).

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CONCLUSION These findings suggest that *SCN5A* variants may be associated with SUD within 7 days of COVID-19 vaccination, regardless of vaccine type, number of vaccine dose, and presence of underlying diseases or postvaccine fever.

KEYWORDS COVID-19; Vaccination; Genetics; Sudden unexplained death (SUD); *SCN5A*

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Introduction

Coronavirus disease 2019 (COVID-19) is a devastating infectious disease that has had resulted in health, social, and economic disasters worldwide. Vaccines are 1 intervention that is known to reduce the risk of severe disease and death. Unfortunately, serious adverse events after immunization with any type of COVID-19 vaccine have been demonstrated.¹ These include fulminant myocarditis,² cardiac arrhythmia,³ and sudden unexplained death (SUD).⁴ Although fatal cases with postmortem investigations have been reported,⁴ few studies have investigated the genetic basis of SUD after COVID-19 vaccination.

Methods

From April to December 2021, all cases of unexplained death occurring within 7 days of COVID-19 vaccination were sent for medicolegal investigation by forensic pathologists of the National Forensic Network comprising 9 medical centers throughout Thailand. All cases tested negative for severe acute respiratory syndrome coronavirus 2 by reverse transcription polymerase chain reaction. No consent from relatives was required because the autopsy was legally mandated. Those in whom the cause of death was found to be natural were sent for genetic studies. The research reported in this article adhered to Helsinki Declaration guidelines.

Genetic testing was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (institutional review board no. 264/62). Postmortem blood was obtained for genomic DNA extraction; then, whole exome sequencing (WES) was performed as described previously.⁵ Briefly, the sequencing libraries were enriched using a SureSelect Human All Exon V7 kit (Agilent Technologies [Santa Clara, CA]) here for SureSelect Human All Exon V7 kit and were sequenced using Illumina HiSeq 4000 (Illumina, San Diego, CA) for Illumina HiSeq 4000 device. The only unequivocal, major genetic locus responsible for Brugada syndrome (BrS) is *SCN5A-SCN10A*,^{6,7} and its common variants could have susceptible effects on the phenotype.⁸ We therefore used minor allele frequencies of <5% as a filtering criterion for this *SCN5A-SCN10A* locus. Minor allele frequencies of <1% were used for all other genes. In addition, to be considered pathogenic, variants had to be reported in the literature in patients with BrS, cardiac arrhythmias, cardiomyopathies, or SUD.

Results

Thirteen cases comprising 10 men (77%) and 3 women (23%), aged between 23 and 72 years, were recruited (Table 1); 12 were Thai and 1 was Australian. Underlying

diseases were reported in 5 patients, but none were arrhythmia. No cases had a history of SUD in family members. Eight (61%), 4 (31%), and 1 (8%) died after receiving the first, second, and third doses of vaccine, respectively. The total number of individuals receiving 1, 2, and 3 doses of COVID-19 vaccines in Thailand during the same period were 51,295,617 (49%), 46,145,566 (44%), and 7,002,986 (7%) doses, respectively. There was no significant correlation between the number of vaccine and SUD (Online Supplemental Table S1). SUD occurred after all types of vaccines used in Thailand, with 7 (54%), 2 (15%), 2 (15%), 1 (8%), and 1 (8%) deaths after receiving ChAdOx1 nCoV-19 (AstraZeneca), BBIBP-CorV (Vero Cells) (Sinopharm [Beijing]), CoronaVac (Sinovac), BNT162b2 (Pfizer/BioNTech), and mRNA-1273 (Moderna), respectively (Table 1). During the same period in Thailand, the number of administered doses of vaccines were 41,839,326 (41%), 14,091,514 (14%), 27,607,314 (27%), and 17,587,080 (18%) for AstraZeneca, Sinopharm, Sinovac, and Pfizer/BioNTech, respectively (no formal data for Moderna). There was no significant correlation between the type of vaccine and SUD (Online Supplemental Table S2). Fever after vaccination was noted in the self-reported web-based registry in 3 cases (23%). Ten (77%) and 11 (85%) deaths occurred within 24 hours and 3 days of vaccination, respectively. In 6 cases (46%), the autopsy identified no explainable causes of death. Another 6 were found to have cardiac causes including coronary atherosclerosis in 4 (31%), dilated cardiomyopathy (DCM) in 1 (8%), and arrhythmogenic right ventricular dysplasia in 1 (8%). The remaining case had thalassemia, leading to hemochromatosis and liver cirrhosis.

Five cases harbored variants in *SCN5A* (Table 1); 4 were men, aged between 23 and 46 years, who died within 3 days of the last COVID-19 vaccination. Only 2 of our 5 SUD cases with *SCN5A* variants reported fever. Six other SUD cases in our cohort harbored variants in other genes, which were previously reported to be associated with cardiac arrhythmias, cardiomyopathies, or SUD. Two had no variants, consistent with the filtering criteria.

The frequency of *SCN5A* variants in our cohort was 38% (5 of 13). For comparative purposes, we thereafter determined the frequency of *SCN5A* variants in Thai SUD cases occurring 8–30 days after COVID-19 vaccination during the same period. The rate in these SUD cases that occurred after 7 days was considerably lower (1 of 10 [10%]; Online Supplemental Table S3), as were the rates in a Thai cohort of SUD before the COVID-19 pandemic (3 of 25 [12%]),⁹ and in our in-house exome database enrolling patients and their parents with various rare diseases (186 of 3231 [12%]), after applying the same filtering criteria

Table 1 Clinical and genetic characteristics of Thai cases with SUD within 7 d of COVID-19 vaccinations

No	Gender	Age (y)	Ethnic	Underlying disease	Type of vaccine*	Self-reported side effects	Days of death after vaccination	Forensic impression and autopsy findings	Gene†	DNA changes	Amino acid changes	Type of mutation	Zygoty	gnomAD (alleles)	Thai exomes (6462 alleles)	Reported in patients in PubMed or ClinVar	PubMed or ClinVar no.	ACMG (A)	SIFT (S)	Polyphen (P)	mCAP (m)
I. Cases with variants in <i>SCN5A</i> (n = 5) [‡]																					
1	M	23	Thai	None	SV-AZ	Fever, headache, fatigue	1	Unexplained	<i>SCN5A</i>	c.3269C>T	p.Pro1090Leu	Missense	Hetero-	411/245980	84	BrS	16344400, 15996170		Y		
									<i>SCN10A</i>	c.1157T>G	p.Phe386Cys	Missense	Hetero-	129/251388	16	BrS, LQTS	28407228, 24998131		Y	Y	Y
2	M	33	Thai	Schizophrenia with clonazepam, diazepam, fluoxetine	SV-AZ	None	1	Unexplained	<i>SCN5A</i>	c.3578G>A	p.Arg1193Gln	Missense	Hetero-	1414/272838	323	BrS, atrioventricular block, and DCM	16344400, 19808398				
3	M	43	Thai	Asthma, gout	SV-SV-PZ	Fever, myalgia	1	DCM	<i>SCN5A</i>	c.833A>G	p.His278Arg	Missense	Hetero-	1/152256	0	BrS	29202755		Y	Y	Y
4	M	46	Thai	Hyperthyroidism	SV	None	3	Unexplained	<i>SCN5A</i>	c.3578G>A	p.Arg1193Gln	Missense	Hetero-	1414/272838	323	BrS, atrioventricular block, and DCM	16344400, 19808398				
5	F	28	Thai	None	SV	None	7	Arrhythmogenic right ventricular dysplasia	<i>SCN5A</i>	c.3068G>A	p.Arg1023His	Missense	Hetero-	72/279064	2	BrS, LQTS	16344400, 25935074				Y
II. Cases with variants in non- <i>SCN5A</i> genes (n = 6)																					
6	M	35	Thai	None	SP	Fever, pain in both knees	1	Unexplained	<i>SCN3B</i>	c.328G>A	p.Val110Ile	Missense	Hetero-	77/251476	13	BrS, sudden death of the young	23257389, 27435932, 30662450			Y	Y
7	M	36	Thai	Alcoholic hepatitis	SV-AZ	None	1	Unexplained	<i>MYBPC3</i>	c.2807C>T	p.Thr936Met	Missense	Hetero-	10/247610	0	LVHT	28798025		Y	Y	Y
8	M	38	Thai	None	SP-SP	None	1	Coronary atherosclerosis	<i>SLC22A5</i>	c.865C>T	p.Arg289Ter	Null	Hetero-	4/251492	0	PCD and SCD	30863740, 26828774	Y			
									<i>SLC22A5</i>	c.1022G>A	p.Arg341Gln	Missense	Hetero-	6/251448	2	PCD and HCM	ClinVar: VCV000 650541.1		Y	Y	Y
9	M	72	Thai	None	AZ	Chest pain	1	Coronary atherosclerosis	<i>TTN</i>	c.20165-1G>A	N/A	Null	Hetero-	6/244112	0	DCM	ClinVar: VCV0010 53732.1				
									<i>DNMT3A</i>	c.939G>A	p.Trp313Ter	Null	Hetero-	0	2	DCM in Tatton-Brown-Rahman syndrome	32435502				
10	F	53	Thai	B-thalassemia [§]	AZ	None	1	Thalassemia with liver cirrhosis	<i>TTN</i>	c.6668A>T	p.His2223Leu	Missense	Hetero-	17/251140	48	CM	23861362				Y
11	F	59	Thai	None	AZ	None	1	Coronary atherosclerosis	<i>TTN</i>	c.18530T>G	p.Leu6177Arg	Missense	Homo-	26/273246	12	SCD	28704380				

III. Cases with no candidate variants (n = 2)

12	M	34	Thai	None	AZ	None	1	Unexplained
13	M	56	Australian	None	MD	None	4	Coronary atherosclerosis

ACMG = The American College of Medical Genetics and Genomics; BrS = Brugada syndrome; CM = cardiomyopathy; COVID-19 = coronavirus disease 2019; DCM = dilated cardiomyopathy; F = female; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; LVHT = left ventricular hypertabulation; M = male; PCD = primary carnitine deficiency; SCD = sudden cardiac death; SUD = sudden unexplained death; Y = yes.

*Vaccines: AZ: ChAdOx1 nCoV-19 (AstraZeneca); MD: mRNA-1273 (Moderna); PZ: BNT162b2 (Pfizer/BioNTech); SP: BBIBP-CorV (Vero Cells) (Sinopharm [Beijing]); SV: CoronaVac (Sinovac).
 †Transcripts used: *SCN5A* (NM_001099404.2), *SCN10A* (NM_006514.3), *SCN3B* (NM_018400.4), *MYBPC3* (NM_000256.3), *SLC22A5* (NM_003060.4), *TTN* (NM_001256850.1), *DNMT3A* (NM_022552.5).

‡In the last 4 columns, (A): pathogenic; (S) deleterious; (P): damaging; (m): pathogenic.

§Compound heterozygous for p.Glu27Lys and p.Phe42Leufs*19 in the *HBB* gene.

(Figure 1A). The odds ratios for *SCN5A* variants and SUD in these other groups and that of the present study are shown in Figure 1B. Evidence from our present study supports the hypothesis that SUD within 7 days of COVID-19 vaccination is associated with *SCN5A* variants.

Discussion

This study aimed to identify associations between genetic variants and SUD that occurred within 7 days of COVID-19 vaccination. A total of 13 variants in 7 genes were identified by WES in 11 of 13 cases (85%), compared with approximately one-third to one-half of the diagnostic yield of WES for patients with previously undiagnosed diseases.^{10,11} This suggests that SUD after COVID-19 vaccination may have a genetic susceptibility more commonly identified by WES, compared with other rare and undiagnosed diseases.

Four *SCN5A* variants were found in 5 cases. All have previously been identified in patients with BrS. Two variants—c.833A>G in case 3 and c.3068G>A in case 5—had low allele frequencies: 0 and 2 alleles, respectively, out of 6462 alleles in our in-house exome database. Case 3 also had DCM, which could possibly have resulted from *SCN5A* variants,¹² suggesting that *SCN5A* c.833A>G (p.His278Arg) is a severe loss-of-function variant. The frequency of *SCN5A* c.3269C>T (p.Pro1090Leu) identified in case 1 is 0.013 (84 of 6462) in our database. In addition to carrying the *SCN5A* variant, case 1 harbored a c.1157T>G (p.Phe386Cys) variant in *SCN10A*, previously found in patients with BrS (Table 1). Variants in *SCN5A* and *SCN10A* are a major SUD risk locus.⁶ Although the *SCN5A* c.3578G>A (p.Arg1193Gln) variants found in cases 2 and 4 have an allele frequency of 0.049 (323 of 6462) in our database, these have previously been demonstrated to encode a protein with aberrant function contributing to various cardiac arrhythmias, including long QT syndrome and BrS.¹³ It was also previously identified in 2 of 25 (8%) Thai SUD cases.⁹ Moreover, case 2 had schizophrenia and was prescribed with clonazepam, diazepam, and fluoxetine. Psychotropic drugs are associated with sudden death of cardiac origin,¹⁴ especially diazepam, which causes a faster block and unblock of Na⁺ channels,¹⁵ and may therefore aggravate abnormalities caused by the aberrant *SCN5A* variant. Taken together, these lines of evidence suggest that all 4 *SCN5A* variants had a contributory role in the SUD of these 5 cases.

Six other SUD cases in our cohort harbored variants in 5 other genes. Three cases carried likely pathogenic variants in *TTN*, a huge gene encoding a 34,350 -amino acid protein in which mutations are known to cause cardiomyopathies.¹⁶ The heterozygous splice site c.20165-1G>A variant identified in case 9 was previously reported in the ClinVar database in an individual with DCM.¹⁷ Case 9 was also heterozygous for a nonsense variant, c.939G>A (p.Trp313Ter) in *DNMT3A*, mutations in which cause Tatton-Brown-Rahman syndrome, a syndrome with possible cardiac abnormalities, inherited in an autosomal dominant manner.¹⁸ Case 10 with underlying beta thalassemia was heterozygous for the

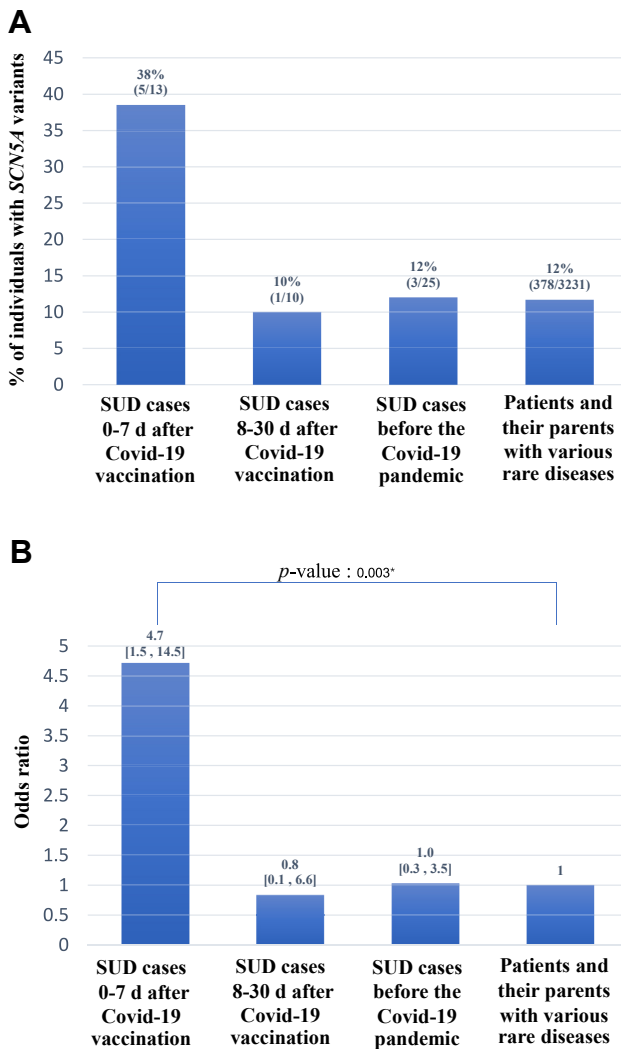


Figure 1 A: Frequencies of *SCN5A* variants in our cohort with sudden unexplained death (SUD) cases within 7 days of coronavirus disease 2019 (COVID-19) vaccination, in Thai SUD cases during 8–30 days after COVID-19 vaccination during the same period, in a Thai cohort of SUD before the COVID-19 pandemic, and in our in-house exome database enrolling patients and their parents with various rare diseases. B: The odds ratios and 95% confidence intervals for *SCN5A* variants and SUD in study groups, compared with the in-house exome controls as a reference. The asterisk indicates that the *P*-value reaches statistical significance of less than .05.

c.6668A>T (p.His2223Leu) variant in *TTN* previously reported in a patient with cardiomyopathy.¹⁹ Case 11 was homozygous for the *TTN* c.18530T>G (p.Leu6177Arg) variant, which was recently identified heterozygously in a 25-year-old Thai male with SUD.⁹ Cases 6, 7, and 8 harbored variants in *SCN3B*, *MYBPC3*, and *SLC22A5*, which were previously associated with BrS,²⁰ left ventricular hypertrabeculation,²¹ and autosomal recessive primary carnitine deficiency with hypertrophic cardiomyopathy and sudden death,²² respectively.

The association between *SCN5A* variants and SUD within 7 days of COVID-19 vaccination (Figure 1) might be due to COVID-19 vaccination unmasking fatal arrhythmia in individuals with *SCN5A*. Fever is a well-known trigger for

arrhythmia in BrS.²³ A possible mechanism might therefore include an indirect effect of the vaccine in which an individual with a susceptible pathogenic *SCN5A* variant had vaccine-induced fever and malaise serving as a precipitating factor leading to fatal arrhythmias.²⁴ Nonetheless, since fever did not seem to play a major role in our study, the other possibility is a direct effect. The vaccine may cause myocarditis in the right ventricular outflow tract area, which in turn unmasks the preexisting aberrant conduction in individuals with *SCN5A*²⁵ and leads to death. It is important to note that the possible association of genetic variants and SUD after COVID-19 vaccination in our study while plausible is primarily hypothesis generating and must be independently confirmed by other studies.

Conclusion

Our study suggests that *SCN5A* variants could be associated with SUD within 7 days of COVID-19 vaccination, regardless of vaccine type, number of vaccine dose, and presence of underlying diseases or postvaccine fever. Given the observational nature of our study, these findings should be further explored and confirmed in surveillance programs in other settings. Until then, it seems prudent to closely monitor individuals who harbor variants in *SCN5A*, and possibly in other genes that predispose to cardiac arrhythmias or cardiomyopathies, for 7 days after the administration of COVID-19 vaccines, regardless of preexisting underlying diseases and the presence of vaccination-associated fever.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2022.07.019>.

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