ARTICLE

New population-based exome data are questioning the pathogenicity of previously cardiomyopathy-associated genetic variants

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Cardiomyopathies are a heterogeneous group of diseases with various etiologies. We focused on three genetically determined cardiomyopathies: hypertrophic (HCM), dilated (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). Eighty-four genes have so far been associated with these cardiomyopathies, but the disease-causing effect of reported variants is often dubious. In order to identify possible false-positive variants, we investigated the prevalence of previously reported cardiomyopathy-associated variants in recently published exome data. We searched for reported missense and nonsense variants in the *NHLBI-Go Exome Sequencing Project* (ESP) containing exome data from 6500 individuals. In ESP, we identified 94 variants out of 687 (14%) variants previously associated with HCM, 58 out of 337 (17%) variants associated with DCM, and 38 variants out of 209 (18%) associated with ARVC. These findings correspond to a genotype prevalence of 1:4 for HCM, 1:6 for DCM, and 1:5 for ARVC. PolyPhen-2 predictions were conducted on all previously published cardiomyopathy-associated missense variants. We found significant overrepresentation of variants predicted as being benign among those present in ESP compared with the ones not present. In order to validate our findings, seven variants associated with cardiomyopathy were genotype d in a control population and this revealed frequencies comparable with the ones found in ESP. In conclusion, we identified genotype prevalences up to more than one thousand times higher than expected from the phenotype prevalences in the general population (HCM 1:500, DCM 1:2500, and ARVC 1:5000) and our data suggest that a high number of these variants are not monogenic causes of cardiomyopathy.

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INTRODUCTION

Cardiomyopathy is a diverse group of cardiac disorders characterized by mechanical and/or electrical dysfunction of the cardiac muscle. The diseases are associated with significant morbidity and mortality and are a known risk factor for sudden cardiac death.^{1–3} Over time, several classification systems have evolved based on etiology, anatomy, physiology, or histopathological expression.⁴ In newer classification systems, major types include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Hypertrophic cardiomyopathy is characterized by a non-dilated, hypertrophic left ventricle with variable degrees of diastolic dysfunction, whereas DCM is characterized by dilated ventricular cavities and systolic dysfunction.^{4–7} In ARVC, progressive fibrofatty replacement of the normal cardiac tissue predisposes to ventricular tachycardia and sudden death.^{8,9} The prevalence of these three cardiomyopathies in the general population has been estimated to be 1:500, 1:2500, and 1:5000, respectively.³

Inherited cardiomyopathy has traditionally been considered a monogenic disorder and to date hundreds of variants in 84 genes have been associated with these syndromes. However, some associations are based on weak family phenotype–genotype co-segregation and/or the absence of the variant in a limited number of controls.

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Until recently, there has only been limited knowledge regarding the genetic variation in the general population, especially with regard to low-frequency variants. This was changed in June 2011 when whole exome data from the *NHLBI GO Exome Sequencing Project* (ESP) was published (latest update June 2012).¹⁰ In order to identify possible false-positive cardiomyopathy variants reported in the literature, we aimed to investigate the prevalence of previously cardiomyopathy-associated variants in the new ESP exome data and compare the prevalence of these variants with the expected prevalences of monogenic cardiomyopathies in the same population.

METHODS

In ESP, next-generation sequencing of all protein coding regions in 6500 individuals, including both European Americans (4300 individuals) and African Americans (2203 individuals), from different population studies were carried out.¹⁰ No clinical data were available on the ESP population, nor at request. By literature search, we found inclusion and exclusion criteria on 9/12

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cohorts used in ESP. None of these has specifically included persons with cardiomyopathies or other heart diseases and at least two cohorts have excluded such patients.

The databases ARVD/C Genetic Variants database (last update April 2012)¹¹ and The Human Gene Mutation Database (updated June 2012)¹² were searched for missense and nonsense cardiomyopathy-associated variants involving the three major types; HCM, DCM, and ARVC. All genes in ARVD/C Genetic Variants database were evaluated and in HGMD the search term 'Cardiomyopathy' was used. In total, 84 genes associated with cardiomyopathy were identified. Genes were then evaluated one by one and the ones associated with any of the above-mentioned cardiomyopathies were selected. Additionally, we included the recently reported DCM-associated TTN nonsense variants published by Herman *et al*¹³ in order to include all genes so far associated with DCM. All identified variants were then systematically searched for in ESP. Only variants classified by one of the databases as being pathogenic/disease causing were included in the analyses. Variants of unknown pathogenicity or variants classified as 'disease-causing mutation?' are marked with 'b' in Tables 1-3, but in order to make a conservative approach, these variants were excluded from our calculations. Due to lack of data regarding variants positioned in promoters, introns and UTRs regions in ESP, these could not be included.

In addition to taking all identified variants associated with HCM, DCM, and ARVC, into account for the calculation of genotype prevalences, we also did a more conservative approach. Based on the frequencies of HCM, DCM, and ARVC in the general population (1:500, 1:2500, and 1:5000, respectively), the estimated number of individuals in the ESP data that can be expected to be affected by HCM, DCM, and ARVC are ~13, 3, and 2, respectively. These values roughly represent the number of times a given variant with complete penetrance can be present in the exome database and still theoretically be the cause of monogenic forms of the respective cardiomyopathies.

The literature was searched for functional data and family co-segregation of all the cardiomyopathy-associated variants identified in the ESP population. Positive functional data were defined as any *in vivo* or *in vitro* model, demonstrating results differing from the wild-type model. Co-segregation was defined as at least two family members in two generations both having the phenotype and the genotype.

Additionally, we conducted a PolyPhen-2 prediction¹⁴ on all previously reported missense variants. Variants were, by PolyPhen-2, predicted to be 'benign', 'possible damaging', or 'probably damaging'. As nonsense variants cannot be evaluated by PolyPhen-2, we classified these as of 'unknown pathogenicity'. In an analysis, we evaluated differences in distributions of the four categories of pathogenicity between the variants identified in ESP *vs* variants not identified in ESP with the use of Fisher's exact test. A *P*-value <0.05 was considered as statistical significant. In case of a statistical significant difference, we also evaluated the difference in proportions of variants being predicted as benign for variants identified in ESP *vs* variants not identified in ESP, also with the use of Fisher's exact test.

Using a Taqman assay as previously described,¹⁵ we genotyped seven variants with a pathogenic association and a prevalence in the proportion of ESP with European American ancestry high enough (10:6500) to have a modest chance of being detected in our own control population (N=534). The control population of Northern European ancestry consisted of men and women between the age of 55–75 years with no history of arrhythmias or other cardiac diseases and with available ECGs as previously described.¹⁶ The ECGs from geno-positive controls were evaluated by two independent experienced ECG readers with regard to the 2010 task force ECG criteria for ARVC¹⁷ and with regard to the Cornell¹⁸ and the Sokolow–Lyon criteria for ventricular hypertrophy.¹⁹

RESULTS

Hypertrophic cardiomyopathy

In the ESP population, we identified 94 out of 687 variants previously associated with HCM (14%). Ninety-tree missense and one nonsense variants were identified, affecting 1672 individuals in total (homozygote = 76, heterozygote = 1596). Eighteen variants with family co-segregation analyses and 16 variants with functional

characterization different form wild-type were identified in ESP. On average, the genes investigated were sequenced in 6286 individuals, corresponding to a genotype prevalence of 1:4 (1672:6286). PolyPhen-2 analysis of the 94 HCM-associated variants present in ESP predicted 39 (41%) to be probably damaging, 14 (15%) to be possibly damaging, and 40 (43%) to be benign. Only one nonsense variant was found in ESP and classified as being of unknown pathogenicity (Table 1). Of the remaining 593 HCM-associated variants not present in ESP, 324 (55%) were predicted to be probably damaging, 108 (18%) possibly damaging and 107 (18%) were predicted to be benign. Fifty-four nonsense variants were classified as being of unknown pathogenicity. This difference in the distribution of the four categories of pathogenicity was statistical significant both for the overall comparison (P < 0.0001) and when comparing the proportion of variants predicted to be benign for variants identified in ESP vs variants not identified in ESP (43% vs 18%, respectively, P < 0.0001).

Fourteen of the 94 variants were identified in \geq 13 individuals, though above our conservative cutoff value. These variants affected a total of 1474 individuals, which is equivalent to a HCM genotype prevalence of 1:4 (1474:5810). If variants predicted to be benign by Polyphen-2 (43%) were additionally excluded, the genotype prevalence was 1:7. The cardiomyopathy-associated variants identified in the ESP population are listed in Table 1.

Two variants (*MYBPC3* p.V896M and *MYH7* p.M982T) were, based on our criteria, selected for genotyping in our control population. Five individuals were heterozygous carriers of the *MYBPC3* p.V896M variant and three carried the *MYH7* p.M982T variant. This corresponds to genotype prevalences of 0.94 and 0.56%, respectively, which are comparable to those found in ESP (0.96 and 0.44%, respectively; Table 4).

Dilated cardiomyopathy

In DCM, we found 58 out of 337 variants previously associated with DCM (17%). Two out of the 58 variants were nonsense variants. Both nonsense variants (LAMA4 p.R1073X and VSP13A p.R3135X) were only found in a single individual and both were heterozygous for the variant. A total of 1043 individuals were affected. On average, the genes investigated have been screened in 6314 individuals, and this results in a DCM genotype prevalence of 1:6 (1043:6314). Four variants with convincing segregation analyses were identified and 26 variants were found to have functional effects. PolyPhen-2 analysis of the 58 DCM-associated variants predicted 26 (45%) to be probably damaging, 11 (19%) possibly damaging, and 19 (33%) variants were predicted to be benign whereas two nonsense variants were classified as being of unknown pathogenicity (Table 2). Of the remaining 279 DCM-associated variants, not present in ESP, 134 (48%) were predicted to be probably damaging, 43 (15%) possibly damaging, and 56 (20%) were predicted to be benign. Forty-six nonsense variants were classified as being of unknown pathogenicity. This difference in the distribution of the four categories of pathogenicity was statistical significant both for the overall comparison (P = 0.013) and when comparing the proportion of variants predicted to be benign for variants identified in ESP vs variants not identified in ESP (33 vs 20%, respectively, P = 0.039).

Thirty-five out of the 58 variants were identified in three or more individuals, though above our conservative cutoff value. These variants affected a total of 963 individuals giving a genotype prevalence of 1:7 (963:6334). If variants predicted to be benign by Polyphen-2 (33%) were additionally excluded, the genotype prevalence was 1:10. The DCM-associated variants identified in the ESP population are listed in Table 2.

			Europear	European Americans—g	genotype	African A	African Americans—ge	genotype	AIF	-genotype	a,		
			Minor/		Major/	Minor/		Major/	Minor/	Minor/	Major/	Family co-segregation/	
Gene	Variant	Amino acid	minor	major	major	minor	major	major	minor	major	major	functional effect ^a	Polyphen-2 prediction
ACTCI		I		T	I			I		l			
ACTNZ	c.1484C>T	T495M	0	-	4299	0	0	2203	0	-	6502	Yes/NA	Benign
ANKRDI	c.368C > T c.838A > G	T123M 1280V	00	01 00	4298 4297	00	чC	2202 2203	00	നന	6500 6500	No/Yes No/Yes	Benign Benign
CALM3			P '	° '		P '	° '		P ') 			
CALR3	c.218G > A	R73Q К82Р	00	0 6	4300	00		2202	00	- r - r	6502 6490	No/No	Probably damaging Benian
CASQ2			P	, 5	100	P	°	001	>	2	001	-	
CAV3			I			I		I				I	
COA5			0		000	0			0				
CTV12	C.049C>I	S46R		⊃ m	4300 4290		ΗC	22U2 2199		(r	2000	VPS/NA	Probably damaging
	c.190C>T	R64C	0	50	4291	0	0	2199	0	\sim	6490	No/NA	Possibly damaging
	c.299G>A	R 100H	0	7	4286	0	0	2199	0	7	6485	NA/NA	Possibly damaging
DES		I		l				I				I	
IPH2	c 1513G > A	G505S	0	19	2356		28	030	0	47	3286	Yes/No	Beniøn
KLF10	c.610G>A	A204T	0) —	4299	0	0	2203	0	~	6502	NA/Yes	Benign
	c.674G>A	S225N	0	1	4299	0	0	2203	0	1	6502	NA/Yes	Benign
MKPLS	r 166G \ A ^b	G56R	33	693	3574	14	256	1033	47	070	 5507	No/NA	<u> </u>
MYH7	c.77C>T	A26V	0	1000	4299	0	002	2203	e P	2	6502	NA/NA	Benign
	c.115G>A	N39M	0	(4299	0	00	2203	0	(6502	NA/NA	Probably damaging
	C. 458G > A	V3ZUM A326P	00	N -	4298 1200		00	2203		N -	6501 6502	No/NA Na/Na	Probably damaging Renian
	c.1988G>A		00		4299	00	00	2203	00		6502	NA/NA	Benign
	c.2183C>T		0	0	4298	0		2202	0	ς,	6500	Yes/NA	Benign
	c.2359C>T	R787C	00		4299	00	0-	2203	00		6502 6502		Possibly damaging
	C.2389G > A				4300			2002			6502	Yes/Yes	Fossibiy uaniaging Reniøn
	c.2585C>T ^b		0	0	4300	0		2202	0		6502	NA/NA	Benign
	c.2608C > T		00	, ,	4299	0	00	2203	0	- 0	6502	NA/NA	\geq
	C.29451>C			۲ ۲	4281		ηc	2200		77	6481 6502	NA/NA NA/NA	Possibly damaging Ranian
	c.3981C>A		0		4298	0	0	2202	0		6500	Yes/NA	Possibly damaging
	c.4052C>T		00	0,	4298	00	00	2203	00	ء 2	6501	NA/NA	Benign
	C.4258C>1				4299			2203			6502		Probably damaging
	c.4423C>T ^b		0		4299	0	0	2203	00		6502	NA/NA	Probably damaging
	c.4472C>G ^b	S1491C	00	66	4201	00	13	2190	00	112	6391	NA/NA	
	C.4909G>A	A16371	00	0	4299 1005		ے م	2198		مو	6497 6498		Benign Prohahlv damaging
	c.5536C>T	R1846C		7	4299			2203		7	6502	NA/NA	Probably damaging
	c.5561C>T	T1854M	0		4299	0	0	2203	0		6502	NA/NA	Possibly damaging
MYBPC3	c.13G>C	G5R	00	۲ ر	4152	00	ო	1964	00	10	6116	No/NA	\geq
	C.184A>C	102F		n –	4200			2193 2191		η -	0479 6463		Benign Prohahlv damaøing
	c.461T>C	1154T	00	10	4149	0	20	2020	00	- 0	6169	NA/NA	Benign
	c.478C>T	R160W	0	1	4150	0	1	2025	0	0	6175	NA/NA	
	c.529C>T c.624G>C	R177C 0208H	00	сл н-	4198 4214	00	00	2065 2112	00	- L	6263 6326	NA/NA NA/NA	Probably damaging Probably damaging
	c.646G > A	A216T	0	-1	4203	0	9	2068	0	7	6271	NA/NA	Benign
	$c.649A > G^{b}$	S217G	0	10	4149	0	0	2073	0	12	6267	NA/NA	Possibly damaging
	c.682G>A	D228N	D	-	4193	0	D	2093	0	-	6286	NA/NA	Benign

Table 1 Variants associated with hypertrophic cardiomyopathy present in the ESP population

European Journal of Human Genetics

		Polyphen-2 prediction	Possibly damaging Possibly damaging	Erouauly ualitaging Benign	Benign Dossibly damaging	Probably damaging	Possibly damaging	Probably damaging	Benign	Probably damaging Probably damaging	Probably damaging	Benign Probably damaging	Possibly damaging	Probably damaging	Possibly damaging	Probably damaging Reniøn	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Benign	Benign	Benign	Benign	Unknown	Probably damaging Possibly damaging	Benign	Probably damaging	Probably damaging		— Ranign	Probably damaging	Frobably dairiaging		Possibly damaging		
	Family co-segregation/	functional effect ^a	No/NA NA/NA	NA/NA		NA/NA	NA/NA	NA/NA NA/NA	NA/NA	Yes/NA Yes/NA	NA/NA	No/No Yes/NA	NA/NA	Yes/NA NA/NA	NA/NA	Yes/NA NA/NA	NA/NA		NA/NA	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA NA/NA	NA/NA	NA/NA NA/Yes	NAYYes	NA/NA	Yes/Yes Vec/Vec			NA/Yes			NA/Yes	I	
e	Major/	major	5057 5967	6018 6018	6086 6307	6335	6374	6216	6197	6360 6418	6420	6403 6306	6175	6136	6309	5990 5990	6195	6384	6332	6180	6078 6078	6091	0110 6389	6452 6162	6002	6114 6497	6498	6498	6464 2170			6491 6491			5926 		
AII—genotype	Minor/	major	1145	63	100	2 1 (C)	ى م	n —	0	4 -1	17	22	40	- α	(N	·	- u	26	1	11	∼ -		1		ε	ы	م 	1 77	Ì	۳ ا	120	ი 		316 		
AI	Minor/	minor	20 0 0		00		00	00	0	00	00	00	00		00	00		00		00	00	00	00	00	00	00	00	-	0 -	•	0		>		14		
genotype	Major/	major	1851 1894	1909	1972 2161	2111	2124	2047	2037	2125 2159	2155	2146 2098	2006	2027	2098	1946 1981	2038	2141	2069	2007	1947	1951	190/ 2144	2187	1881	1973 2203	2203	2203	2186 2170		2202	2201			1754 —		
African Americans—genotype	Minor/	major	223 0	62		n c	ഗ വ	nΟ	- 1	- 0	14	1 1	(⊃	0,	чС		00	95	0 4	00	0 -	- 0	0 0	00	00		- 	0	ì	-	- CI C	>		302		
African /	Minor/	minor	000		00		00	00	0	00	00	00	00		00) C		00	0 (00	00	00		00	00	00	00	-	0-	•			>		14		
-genotype	Major/	major	3206 4073	4109	4114	4224	4250	4241 4169	4160	4235 4259	4265	4257 4208	4169	4101 4151	4211	3954 4009	4157	4243	4263	4173	4131	4140	4245	4265	4121	4141 4294	4295	4795 	4278 4288		 4298	4290	4237		4172 —		
European Americans—£	Minor/	major	922 1		0 0	10	00	7		m –	1 (7)	\ 0	ന	хс)		·	ц Ц	0 N	10	11	~ ~	⊃ ⊢		+ t	ε	ы	Ω		1	`	10,	n		14	I	
European	Minor/	minor	69 0	00	00		00	00	0	00	00	00	00) C	00	э с	00	00		00	00	00	00	00	00	00	00	-	00	°	0		>		0		
		Amino acid	S236G G263R	G278E	G279A	G416S	A429V	E44.1N T457M	R458H	G490R R502W	G507R	A5221 E542Q	D605N	E019K	V757M	A774T	W792R	HUTSA	A833V	P873H	T957S	T9581	E1017K	T1046M	W1214X	G1248R A13T	N47K	E134A —	A87V A95F	1	 1246M	Y20C			R4344Q 		
		Variant	c.706A > G ^b c.787G > A	c.833G > A	c.836G > C	c.1246G>A	c.1286C>T	c.1371G>A c.1370C>T	c.1373G > A	c.1468G>A c.1504C>T	c.1519G>A	c.1564G>A c.1624G>C	c.1813G>A ^b	C.1855G>A	c.2269G>A	c.2311G>A	c.2374T>C	C.2429G>A	c.2498C>T ^b	c.2618C>A	c.2870C>G	c.2873C>T	c.2002U > 1 c.3049G > A	c.3137C>T	c.3641G>A	c.3742G>A c.37G>A	c.141C>A	Λ	c.260C>T	`		c.59A>G	C.34010>A		c.13031G>A		
		Gene																								2 TAW		MY13	MYLK2	MY06	TMDAM	MYPN	NDUFAF1	NDUFVZ	OBSCN PRK4G2	RAFI	SLC25A3 SLC25A4

Table 1 (Continued)

European Journal of Human Genetics

921

			European	European Americans—genotype	şenotype	African /	African Americans—genotype	tenotype	Ali	AII—genotype	9)		
			Minor/	Minor/	Major/	Minor/	Minor/	Major/	Minor/	Minor/	Major/	Family co-segregation/	
Gene	Variant	Amino acid	minor	major	major	minor	major	major	minor	major	major	functional effect ^a	Polyphen-2 prediction
SRI	c.334T>C	F112L	0	-	4299	0	31	2172	0	32	6471	NA/NA	Benign
TAZ													
TCAP	c.316C>T	R106C	0	36	4263	0	11	2191	0	47	6454	NA/NA	Probably damaging
	c.458G>A	R153H	0	2	4294	0	0	2198	0	2	6492	Yes/Yes	Benign
TNNC1			I		I								
TNNI3	c.244C>T	P82S	0	1	3801	0	70	1652	0	71	5453	NA/NA	Benign
	c.484C>T	R162W	0	1	4156	0	0	1953	0	1	6109	NA/Yes	Probably damaging
	c.586G>A	D196N	0	1	4157	0	0	1974	0	1	6131	NA/NA	Probably damaging
TNNT2	$c.83C > T^b$	A28V	0	4	4296	0	0	2203	0	4	6499	NA/NA	Benign
	c.230C>T	P77L	0	1	4299	0	0	2203	0	1	6502	NA/NA	Benign
	c.732G>T	E244D	0	0	4300	0	1	2202	0	1	6502	Yes/Yes	Benign
	c.740A > G	K247R	ω	121	4176	58	540	1605	61	661	5781	NA/Yes	Benign
	c.832C>T	R278C	0	Ð	4294	0	1	2202	0	9	6496	Yes/Yes	Probably damaging
	c.857G>A	R286H	0	1	4298	0	0	2201	0	1	6499	NA/NA	Probably damaging
TPM1	c.515T>C	1172T	0	0	4300	0	1	2202	0	-1	6502	NA/NA	Benign
TTN													
NCL	c.829C>A	L277M	0	1	4299	0	0	2203	0	1	6502	NA/Yes	Benign
^a NA indicates ^b Likely disease	^a NA indicates no data available. ^b uikely disease-causing mutation, but with questionable pathogenicity.	It with questionable p	pathogenicity.										

Two variants (*CSRP3* p.W4R and *MYH6* p.A1004S) were selected for genotyping in our control population. Six individuals were heterozygote carriers of the *CSRP3* p.W4R variant and two carried the *MYH6* p.A1004S variant. The prevalences were thus comparable to the ones in ESP (1.12 *vs* 1.07% and 0.37 *vs* 0.26%, respectively; Table 4). One individual carrying the *CSRP3* p.W4R variant fulfilled the Cornell ECG criteria for ventricular hypertrophy; however, this individual died at the age of 73 and was never diagnosed with cardiomyopathy. The ECGs from the rest of the genotype-positive individuals were normal and without signs of ventricular hypertrophy.

Arrhythmogenic right ventricular cardiomyopathy

Thirty-eight out of 209 variants associated with ARVC (18%) were found in the ESP population. One nonsense and 37 missense variants were identified, affecting a total of 1404 individuals. Only one variant with convincing family co-segregation and three variants with functional characterization different from wild-type were identified in ESP. Twenty-eight of the 38 variants were identified in two or more individuals. On average, the genes investigated in ARVC have been sequenced in 6354 individuals thus corresponding to an ARVC genotype prevalence of 1:5 (1407:6354). PolyPhen-2 analysis of the 38 ARVC-associated variants predicted 14 (37%) to be probably damaging, 3 (8%) to be possibly damaging, and 20 (53%) were predicted to be benign whereas one nonsense variant was classified as being of unknown pathogenicity (Table 3). Of the remaining 171 ARVC-associated variants, not present in ESP, 77 (45%) were predicted to be probably damaging, 14 (8%) possibly damaging, and 21 (12%) were predicted to be benign. Fifty-nine nonsense variants were classified as being of unknown pathogenicity. This difference in the distribution of the four categories of pathogenicity was statistical significant both for the overall comparison (P < 0.0001) and when comparing the proportion of variants predicted to be benign for variants identified in ESP vs variants not identified in ESP (53 vs 12%, respectively, P<0.001).

Twenty-eight variants were present in two or more individuals, though above our conservative cutoff value, and this still corresponded to an ARVC genotype prevalence of 1:5 (1393:6359). If variants predicted to be benign by Polyphen-2 (53%) were additionally excluded, the genotype prevalence was 1:11. The ARVC-associated variants identified in the ESP population are listed in Table 3.

Three variants (*PKP2* p.D26N; *DSG2* p.V158G; and *DSP* p.V30M) were genotyped in the control population and five individuals were heterozygote carriers of the *PKP2* p.D26N variant, nine of *DSG2* p.V158G, and five of *DSP* p.V30M. One individual was carrier of both the *DSG2* p.V158G and the *DSP* p.V30M variant. The variant frequencies were comparable to those found in ESP (0.94 vs 1.37%; 1.69 vs 1.58%; and 0.94 vs 0.37%, respectively; Table 4). ECG's from geno-positive individuals were normal and without signs of ARVC or ventricular hypertrophy.

DISCUSSION

The present study identified a high prevalence of cardiomyopathyassociated genetic variants in recently published population-based exome data. Fourteen percent of all previously HCM-associated variants and 18% of all DCM- and ARVC-associated variants were identified in ESP. Thus, a much higher prevalence of cardiomyopathyassociated genetic variants were identified in ESP than expected from the phenotype prevalences in the general population.

In order to validate the marked overrepresentation of variants associated with HCM, DCM, and ARVC in ESP, we genotyped seven variants in seven different genes associated with cardiomyopathy in a

			European	European Americans—g	genotype	African American s-		-genotype	AIF	AII—genotype	0		
			Minor/	Minor/	Major/	Minor/	Minor/	Major/	Minor/	Minor/	Major/	Family co-segregation/	
Gene	Variant	Amino acid	minor	major	major	minor	major	major	minor	major	major	functional effect ^a	Polyphen-2 prediction
ARCCO	I	I		I				I				I	
ACTCI												I	
_	c.26A>G	Q9R	0	7	4293	0	0	2203	0	7	6496	NA/Yes	Benign
	c.2323C>T	Н775Ү	0	1	4299	0	0	2203	0	-1	6502	NA/NA	Benign
ANKRD1	c.197G>A	R66Q	0	б	4291	0	0	2203	0	б	6494	No/No	Benign
	c.313C>T	P105S	0	4	4295	0	0	2203	0	4	6498	No/Yes	Probably damaging
	c.319G>1	V10/L	00		4300	00	5.0	2164	00	50 4	6464	No/Yes	Benign
0.010	C.02/U>1	AZ/0V	D	DC:	0074	D	4	Z IYY	D	7C	0449	INO/ TES	Demign
										I	I		
		01510	<	C	0001		-			-	2100		
AD	400G > A	G1540		- ת	4200 1206					Ξ¢	0400 6106	NA/Vac	Drohahlv damaging
CSRP3	C.101 > C	W4R		46	4247		- (2197		48	6444	NA/Yes	Possibly damaging
	c.148G>A	A50T	0	20	4291	0	11	2198	0	ာက	6489	NA/NA	Possibly damaging
	c.206A > G	K69R	0		4292	0	0	2199	0		6491	NA/Yes	Possibly damaging
	c.214G>A ^b	G72R	0	2	4291	0	0	2199	0	5	6490	NA/NA	Probably damaging
CTF1	H 000	000	('		('	00	('			- - - -
	c.893C>1	S298L	00		4298	00	- 1	2202	00	7 (7	0069	NA/Yes	Probably damaging
	C. 334G > A	D312N		⊃	4500 1200		< C	2003		~ -	0490 6500	NA/Vec	Probably damaging
	C 1375G / A	V/459I			4299	00	153	2048	50	154	2000	NA/Yes	r iouauiy uamaging Renion
DMD	c.5016T>A	N1672K	0	ى ب	4295	7	244	1951	7	249	6246	NA/NA	Possibly damaging
,	c.9682T>C	F3228L	0	0	4300	0		2201	0	1	6501	NA/NA	Probably damaging
DNAJC19													
	ר פ∩זה ∕ ∆ ^b	MSORV		`		0	0	2003		^	6501	No/NA	— Ranian
	c.1003A > G	T335A		<u>م</u> 1	4094			1863		<u>م</u> 7	5957	No/NA	Probably damaging
DSP	c.5498A>T ^b	E1833V	0	112	4188	0	6	2194	0	121	6382	Yes/NA	Probably damaging
	c.5513G>A	R1838H	0 0	സ	4297	00	00	2203	00	സ	6500	No/NA	Probably damaging
	C.6881C>G	A22946 G2375R	э с	C	4297	00	00	2203	00	n –	6502	NO/NA No/NA	Probably damaging
)	'		9	,		,	'			
N		[I	
FLT1	c.162G>C	R54S	0	Q	4295	0	1	2202	0	9	6497	No/NA	Probably damaging
PR7													
												1	
MA2													
LAMA4	c.3217C>T	p.R1073X	0	1	4299	0	0	2203	0	-1	6502	No/Yes	Unknown
	c.349G>A	D117N	00	ကို	4122	00	51	1994	00	84	6116	NA/Yes	Benign
	C.566C>I	S I 89L T350I	00	N	4298	00	00	2203	00	N -	6501 6502	Yes/Yes NA/NA	Benign Possibly damaging
	c.1051A>G	T351A	00	- LO	4295	00	00	2203	00	- LO	6498	NA/NA	enign Benign
	c.2092G > A ^b	A698T	0	9	4294	0	0	2203	0	9	6497	NA/NA	Probably damaging
LMNA	c.565C>T	R189W	00		4299 4299	00	00	2203	00		6502 6502	No/NA	Possibly damaging Probably damaging
MURC	c.384C > G	N128K		10	4299		വം	2198		· D י	6497	Yes/Yes	Probably damaging
	c.458T > C	L153P P32AI	00	0-	4300 1799	00	LC	2202 2108	00	<u>н</u> и	6502 6197	No/Yes	Probably damaging Benian
<i>MYBPC3</i>	c.961G>A	V321M	00	-4	4246	00	n —	2157	00	വ	6403 6403	NA/NA	Probably damaging
	c.977G > A ^b	R326Q	00	32	4233	00	00	2161	00	32	6394	NA/NA	Possibly damaging
-	Ω.1δ14A > G	DOUDE	D	-	47/T	D	D	2002	D	-	6/TQ	NA/NA	rossibiy damaging

Table 2 Variants associated with dilated cardiomyopathy present in the ESP population

European Journal of Human Genetics

Minu Minu <th< th=""><th>Motor Motor <th< th=""><th></th><th></th><th></th><th>Europear</th><th>European Americans—_i</th><th>genotype</th><th>African A</th><th>African Americans – genotype</th><th>genotype</th><th>All</th><th>AII—genotype</th><th>0)</th><th></th><th></th></th<></th></th<>	Motor Motor <th< th=""><th></th><th></th><th></th><th>Europear</th><th>European Americans—_i</th><th>genotype</th><th>African A</th><th>African Americans – genotype</th><th>genotype</th><th>All</th><th>AII—genotype</th><th>0)</th><th></th><th></th></th<>				Europear	European Americans— _i	genotype	African A	African American s – g enotype	genotype	All	AII—genotype	0)		
Value Anio acid Into majo	Anine acid maje male				Minor/	Minor/	Major/	Minor/	Minor/	Major/	Minor/	Minor/	Major/	Family co-segregation/	
C.1875/F. T.297 C T.203 C Second NMM Perestricture C.18765/F. N.1906K 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 2203 0 1 200 NMM Ponabily C.2690G5/F N1182X 0 1 2203 0 1 2203 0 1 200 NMM Ponabily Pon	P FIGTO 0 2203 0 2202 0 2203 2203	Gene	Variant	Amino acid	minor	major	major	minor	major	major	minor	major	major	functional effect ^a	Polyphen-2 prediction
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	T Knosk C <thc< th=""> C C C</thc<>	<i>МҮН6</i>	c.824T>A ^b	1275N	00	с ,	4297	0	0,	2203	00	ω	6500	NA/NA	
C.43166/5 M.1440F 0 1 4.293 0 2.203 0 1 6502 NMM Preshib C.43065/5 M.1866H 0 1 4.293 0 1 6502 NMM Preshib C.23065/5 M.66H 0 1 4.293 0 1 6502 NMM Preship C.23065/5 M.66H 0 1 4.293 0 1 6502 NMM Preship C.43065/5 M.11961 0 1 4.293 0 1 2.203 0 1 6602 NMM Preship C.53845/5 M.11961 0 1 4.209 0 2.203 0 1 6602 NMM Preship C.53845/5 M.1961 0 1 4.209 0 1 7 6493 NMM Preship C.53845/5 M.1961 0 1 4.219 0 1 4.219 0 0	C Aliator C 2003 <		c.1/02C>1 ^v c.3010G>T	R568C A1004S) C	1	4299 4289	0 C		2202) C	20	6501 6491	NA/NA No/NA	>
C.45055-PR TIGDZA 0 3 4570 0 3 6500 NMMA Probability C.45055-PR TIGDGA 0 3 4297 0 2233 0 3 6500 NMMA Probability C.55905-FR TIGDGA 0 3 4297 0 1 4299 0 1 6602 NMMA Probability C.59605-AF TIGSGA 0 1 4299 0 1 2203 0 1 6602 NMMA Probability C.59605-AF TIJ95M 0 1 4299 0 1 2203 0 1 6602 NMMA Probability C.59605-AF TIJ95M 0 1 4299 0 1 4299 0 1 6602 NMMA Probability	Pristoz Construction		c.4318G>C	A1440P	0		4299	0	0	2203	0		6502	NA/NA	Possibly damaging
C.23905-7 Viscal Mark Viscal Frank Combine Frank Combine Frank </td <td>Production C <thc< th=""> C C C</thc<></td> <td></td> <td>c.4505G > A^b</td> <td>R1502Q</td> <td>0</td> <td>n</td> <td>4297</td> <td>0</td> <td>0</td> <td>2203</td> <td>0</td> <td>m</td> <td>6500</td> <td>NA/NA</td> <td>Probably damaging</td>	Production C <thc< th=""> C C C</thc<>		c.4505G > A ^b	R1502Q	0	n	4297	0	0	2203	0	m	6500	NA/NA	Probably damaging
C.236963-N FUIDION D 24208 D 2 6502 NAMA Preadaby C.538A5-A T1121 0 1 4299 0 0 2203 0 1 6602 NAMA Preadaby C.538A5-A T1121 0 1 4299 0 0 2203 0 1 6602 NAMA Preadaby C.538A5-A N0587 0 1 4299 0 0 2 2201 0 1 6602 NAMA Preadaby 0 2 6435 NAMA Preadaby 0 2 6435 <t< td=""><td>M R100FN 0 2 4208 0 1 2203 0 1 6601 MNM Freedally 7 720C 0 1 4299 0 0 2203 0 1 6602 NNM Freedally 7 7105 0 1 4299 0 0 2203 0 1 6602 NNM Freedally 7 7105 0 1 4299 0 0 2203 0 1 6602 NNM Freedally 6 7652C 0 1 4299 0 0 2203 0 17 6493 NNM Freedally 6 550C 1 0 2199 0 17 6493 NNM Freedally Freedally</td><td>MYH7</td><td>c.2890G > C^b</td><td>V964L</td><td>0</td><td>9</td><td>4294</td><td>0</td><td>0</td><td>2203</td><td>0</td><td>9</td><td>6497</td><td>NA/NA</td><td>Probably damaging</td></t<>	M R100FN 0 2 4208 0 1 2203 0 1 6601 MNM Freedally 7 720C 0 1 4299 0 0 2203 0 1 6602 NNM Freedally 7 7105 0 1 4299 0 0 2203 0 1 6602 NNM Freedally 7 7105 0 1 4299 0 0 2203 0 1 6602 NNM Freedally 6 7652C 0 1 4299 0 0 2203 0 17 6493 NNM Freedally 6 550C 1 0 2199 0 17 6493 NNM Freedally	MYH7	c.2890G > C ^b	V964L	0	9	4294	0	0	2203	0	9	6497	NA/NA	Probably damaging
C. C. STORDS-T M RDBKT C. C. STORDS-T M RDBKT M RDBKT </td <td>T File T Constraint T Constraint <thconstraint< t<="" td=""><td></td><td>c.3286G > T^b</td><td>D1096Y</td><td>00</td><td></td><td>4298</td><td>00</td><td>0,</td><td>2203</td><td>00</td><td>∾ -</td><td>6501</td><td>NA/NA</td><td>Probably damaging</td></thconstraint<></td>	T File T Constraint T Constraint Constraint <thconstraint< t<="" td=""><td></td><td>c.3286G > T^b</td><td>D1096Y</td><td>00</td><td></td><td>4298</td><td>00</td><td>0,</td><td>2203</td><td>00</td><td>∾ -</td><td>6501</td><td>NA/NA</td><td>Probably damaging</td></thconstraint<>		c.3286G > T ^b	D1096Y	00		4298	00	0,	2203	00	∾ -	6501	NA/NA	Probably damaging
C.556365-Xi R18655 C.566365 R18655 R18655 R18655 R18655 R18655 R18655 R186555 R186555 <thr185555< th=""> <thr186555< th=""> <thr1865< td=""><td>No. Riskov Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov <thriskov< th=""> <thriskov< th=""> Risko</thriskov<></thriskov<></td><td></td><td>C.4983G > A</td><td></td><td></td><td>D -</td><td>4300</td><td></td><td></td><td>2022</td><td></td><td></td><td>0207 6502</td><td></td><td>Brohahlv damaring</td></thr1865<></thr186555<></thr185555<>	No. Riskov Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov I Riskov Riskov Riskov Riskov <thriskov< th=""> <thriskov< th=""> Risko</thriskov<></thriskov<>		C.4983G > A			D -	4300			2022			0207 6502		Brohahlv damaring
C.596x-Sc Y20C 0 10 4290 0 2 2001 0 12 6491 NWYes Probabily C.53355X-1 V119M 0 0 1 4279 0 2 2471 NWYes Probabily C.53355X-1 V119M 0 0 1 4290 0 4 2199 0 27 6491 NWYes Probabily C.18055X-G K650C 0 1 4298 0 1 4299 0 2 2199 0 27 6437 NWYes Probabily C.18055X-G N557C 0 1 4298 0 0 25 4277 0 127 6437 NWYes Probabily C.18055X-G Y587C 0 1 2201 0 2 2473 NWYes Probabily C.17755A X516G 0 2 2 2 2 2 2 2 2 2	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		c.5588G > A ^b	R18630			4299			2203	00		6502	NA/NA	Possibly damaging
C.3335C>1 F11121 0 21 4279 0 5 6476 Norres Probabily Probabily C.1800S>C K60N 0 61 4236 0 6 2197 0 27 6476 Norres Probabily C.175C>A K502F 0 19 4236 0 6 2195 0 27 6476 Norres Probabily C.175C>A K502F 0 19 4281 0 19 0 27 6476 Norres Probabily C.175C>A K502F 0 16 4281 0 17 6489 Norres Probabily C.1755C>A K507F 0 16 4281 0 17 6477 Norres Probabily C.1755C>A K507F 0 16 4270 0 17 6476 Norres Probabily C.1755C>A K516 0 11 4280 0 12 12	T P1115L 0 21 4275 6476 Nores Probably Probably A K600N 0 61 4236 0 476 Nores Probably Probably A K522E 0 1 4236 0 4 4236 0 4236 Probably A K522E 0 1 4239 0 1 5430 Nores Probably A K522E 0 1 4239 0 1 4239 Nores Probably A S1547 0 15 2195 0 2 6461 NONA Probably A V3871 0 11 4209 0 2 2195 0 2 6461 NONA Probably A V3871 0 11 4205 0 12 6461 NONA Probably A S156L 0 11 4205 0 12 <td< td=""><td>MYPN</td><td>c.59A > G</td><td>Y20C</td><td>0</td><td>10</td><td>4290</td><td>0</td><td>0</td><td>2201</td><td>0</td><td>12</td><td>6491</td><td>NA/Yes</td><td>Probably damaging</td></td<>	MYPN	c.59A > G	Y20C	0	10	4290	0	0	2201	0	12	6491	NA/Yes	Probably damaging
C.3583GS / N1195M 0 0 4300 0 4300 0 4300 0 4430 0 7 6439 N/Yes Propably C.604GS / K60N 0 61 4238 0 1 4238 0 1 4238 0 1 4238 0 1 4238 0 0 430 N/Yes Propably C.1955A / G52C 0 1 4238 0 1 4238 0 1 4238 0 1 4238 N/Yes Propably C.1955A / G52C 0 1 4238 0 1 4238 0 1 4238 N/Yes Propably C.1955A / G57 0 1 4238 0 1 4238 0 1 4238 N/Yes Propably C.1956A / T575/F 0 1 4238 0 0 5 2195 0 7 6492 N/Yes Propably C.1956A / T575/F 0 1 1 4298 0 0 5 2195 0	A KIOSM 0 6 4.330 0 4 2195 0 4.439 NNMess Propably Propably Propably Propably 6 5 6.432 1 4.330 0 1 4.330 0 1 6.439 NNMess Propably Propably Propably 6 5 6.437 0 1 4.236 0 1 4.305 0 1 6.439 NNMess Propably Propably 7 6.453 0 1 4.236 0 1 2.202 0 2 6.477 NNMAss Propably 7 5 2.195 0 1 2.202 0 1 2.203 0 1 2.203 NNMA Propably 7 5 2.195 0 1 2.203 0 1 2.203 NNMA Propably 7 5 2.195 0 1 2.203 NNMA Propably 8 7 5		c.3335C>T	P1112L	0	21	4279	0	9	2197	0	27	6476	No/Yes	Probably damaging
C. 130G-S-C Model	A 520E D 0 B 1 2.296 D 0 S 1 S 6430 NMMes Bengin A 552E 0 1 4236 0 16 2137 0 17 6485 NMMes Bengin A 552E 0 1 4286 0 0 5 2195 0 2 6437 NMMes Bengin A 552E 0 1 4086 0 0 5 2195 0 2 6437 NMMes Bengin A 5161 0 1 6497 0 1 5436 NMMes Bengin A 7355 0 1 6497 0 1 6497 NMMes Bengin A 7355 0 1 6497 NMMes Bengin NMMes Bengin A 74561 0 1 4205 0 0 2 6447 NMMes Bengin A 74561 0 1 4205 0 1		c.3583G > A	V1195M	0	0	4300	00	4 (2199	0 (41	6499	No/Yes	Probably damaging
C.1775CA MSDER 0 1 2187 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 16 2187 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 16 2187 0 17 6486 0 0 16 2187 0 17 6486 0 0 16 2187 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 16 2187 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0 0 17 6486 0<	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	NEBL	C.180G>C	KOUN		10	4230	00	7 0	2190	00	/9	643Z	NA/Yes	\geq
C:1955A>G VG2X	NGSZC 0 1 4080 0 1 5520 0 0 1 5520 0 0 1 5520 0 0 1 5520 0 0 0 0 0 0 0 0 0 0 0 0 1 1 <		c.0040 A	A592F		г -	4202		+ C	2187		17	6485	NA/Yes	Benign
C.1980C>A GGXK 0 3 4188 0 0 2110 0 3 6298 NMM C.1950C>A GGXK 0 2 210 0 2 2202 0 3 6298 NMM C.1750C>A V5871 0 16 4275 0 1 2202 0 2 6492 NMM C.1750C>A V5871 0 16 4275 0 2 2201 0 2 6492 NMM C.1750C>A V5871 0 16 4275 0 1 4292 0 7 6492 NMM C.21364>T S4551 0 1 1590 0 1 2202 0 7 6492 NMM C.21476>A K716A 0 1 4295 0 1 4292 0 1 2202 0 7 6492 NMM C.21476>A K716A 0 1 4299 0 1 4292 0 1 2203 NMM 2308	N R3CK 0 3 4188 0 0 2110 0 3 6288 NVMA N V571 0 16 4275 0 1 1405 1405 0 3 6288 NVMA A V5571 0 16 4275 0 2 2201 0 26 6451 NVMA G N736S 0 16 4280 0 7 6492 N/MA A S455L 0 11 4260 0 7 6492 N/MA A S455L 0 11 4209 0 12 6492 N/MA A F446K 0 11 4209 0 12 6492 N/MA A F446K 0 13 4169 0 12 6492 N/MA A F436K 0 1 2003 0 1 6492 N/MA A	NEXN	c.1955A>G	Y652C			4086	0	0	1843		, -	5929	NA/Yes	>
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	T Sidof 0 25 4275 0 1 2202 0 26 6477 NANA A V5871 0 16 4226 0 1 2202 0 26 6477 NANA G NV5871 0 16 42281 0 1 2202 0 26 6477 NANA A V5871 0 10 4201 0 5 2195 0 7 6492 NANA A R716A 0 13 1558 0 0 652 0 7 6492 NANA A R716A 0 11 4205 0 1 2504 0 1 2543 NANA A R87Q 0 1 4205 0 1 2602 0 1 6477 NANA A R87Q 0 1 1 2005 0 1 2203	PKP2	c.184C>A	Q62K	0	n	4188	0	0	2110	0	ŝ	6298	NA/NA	`
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	A S1596 0 16 4281 0 5 2198 0 21 6479 NAMA 7 85871 0 16 4280 0 5 2195 0 2 6451 NAMA 7 8455L 0 2 2195 0 7 6492 NAMA 7 8455L 0 1 15568 0 0 5 2195 0 7 6492 NAMA 7 8455L 0 1 4205 0 1 4205 0 1 6422 0 1 6492 NAMA 8 7216G 0 1 4205 0 0 1 6322 0 1 6323 NAMA 8 71279J 0 1 4169 0 1 6323 NAMA 8 71279J 0 1 4169 0 1 6492 NAMA		c.419C>T	S140F	0	25	4275	0		2202	0	26	6477	NA/NA	Benign
C:1/95G>A V38/1 0 4/0 4/260 0 2 2/201 0 4/2 0/61 N/NA C:2207A>G N736S 0 2 2/297 0 5 2/297 0 7 6/492 N/NA C:2147G>A N716Q 0 11 1550 0 7 6/492 N/NA C:2147G>A R716Q 0 11 1550 0 0 692 0 7 6/492 N/NA C:2147G>A R716Q 0 11 1550 0 1 4/292 0 1 2/282 N/NA C:2135G <a< th=""> N2791 0 11 4/299 0 1 4/299 0 1 6/202 N/NA C:0135<sg<a< th=""> N/2791 0 11 4/299 0 1 4/299 0 1 6/202 N/NA C:0135<sg< th=""> R87Q 0 11 4/299 0 1 2 6/491 N/NA C:0135<sg< th=""> R87Q 0 1 2 1</sg<></sg<></sg<a<></a<>	A V38/1 O 420 4260 O 42 6401 MONA T \$455 0 2 2201 0 42 6401 MONA A \$7163 0 1 1558 0 0 692 0 7 6492 NANA A \$7163 0 1 1590 0 0 692 0 7 6492 NANA A \$7163 0 1 1590 0 0 692 0 7 6492 NANA A \$7164 0 1 4299 0 1 2283 NANA A \$7279 0 1 4299 0 1 2283 NANA A \$72054 0 1 4299 0 1 6502 NANA A \$8270 0 1 2194 0 1 6502 NANA A		c.505A>G	S169G	00	16	4281	00	വ വ	2198	0 (21	6479	NA/NA	Benign
C.2207A>G N365 O Z 4297 O S 2195 O Z 6492 NANA C.1364C>T S456 0 3 1558 0 0 3 2285 NANA C.1364C>T S476 0 1 1558 0 0 3 2285 NANA C.2375A>G C.1347C>T S476 0 1 4205 0 1 2285 NANA C.13475A>T S416 0 1 4205 0 1 2285 NANA C.23835G>A V1279I 0 1 4205 0 1 2285 NANA C.33835G>A V1279I 0 1 4205 0 1 2283 NANA C.3835G>A V1279I 0 1 4205 0 1 2283 NANA C.3835G>A V1279I 0 1 4205 0 1 6502 NANA C.3055CPTP S835 N274 0 1 4296 0 1 6499	G N7365 O Z 4227 O 5 2195 O 7 6492 NANA A R716G 0 33 1558 0 0 692 0 1 6492 NANA A R716G 0 11 4205 0 0 692 0 1 2255 NANA A R716G 0 11 4205 0 0 692 0 1 2285 NANA A R716G 0 11 4205 0 0 12 6223 0 12 6233 NANA A R1279 0 11 4205 0 11 2205 0 11 6233 NANA A R87Q 0 11 2005 0 14 6174 NANA C2221 0 11 2005 0 14 6174 NANA C2221 0		c.1/59G>A	1/867	D	40	4260	0	N	2201	Ο	42	6461	No/NA	Possibly damaging
C:1364C>T 3:1558 0 0 5:250 0 1 C:2147G>A 87160 0 1 1558 0 0 3 2250 0 1 C:2147G>A 87160 0 1 1590 0 1 4205 0 1 2249 0 1 2249 0 1 2249 0 1 2249 0 0 1 2249 0 0 1 2249 0 0 1 2249 0 0 1 2249 0 0 1 2249 0 0 1 2265 0 1 2238 0 0 1 2238 0 0 0 1 2249 0 0 1 6238 0 0 0 1	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	POLG	 c.2207A > G	N736S	0	0	4297	0	ى	2195	0		6492	NA/NA	
c.1364C>T S455L 0 33 1558 0 0 692 0 33 2250 NAVNA c.1364C>T S455L 0 1 1590 0 0 692 0 33 2250 NAVNA c.647C>T S716L 0 1 4205 0 1 2282 NAVA c.647C>T S716L 0 1 4205 0 1 2282 NAVA c.1336G>A E446K 0 1 4205 0 1 2283 NAVA c.1336G>A E446K 0 1 4205 0 0 2233 0 1 6502 NAVA c.1335G>A V1279I 0 1 4299 0 0 1 2056 0 1 6502 NAVA c.656G>A R87Q 0 1 4299 0 0 1 6502 NAVA c.656G>A R87Q 0 1 4299 0 1 2056 0 1 6491 NAVA	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	PSENI													
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R X104 A X104 S216 0 1 1290 S216 0 1 1290 S205 0 1 1290 S205 0 1 1200 S205 0 1 1200 S205 0 1 1200 S205 0 1 1 2205 S205 NoNNA NAYes NoNNA 7 72055A 0 1 2005 0 1 6502 NONNA 7 72055A 0 1 2005 0 1 2005 0 1 6502 NONA 7 R87Q 0 1 2005 0 1 6502 NONA 6222V 0 1 2194 0 1 6502 NONA 6222V 0 1 2195 0 1 2635 NANA 7 R690C 0 1 2195 0	RBM20	c.1364C>T	S455L	00	33	1558	00	00	692	00	33	2250	NA/NA	Benign
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	A E446K 0 13 4169 0 13 4169 0 13 4169 0 13 4169 0 13 4169 0 13 4169 0 13 4169 0 13 4169 0 13 4169 0 13 4169 0 14 6702 0 14 14 14 14 14	SCN54	C.Z14/G>A	K/ 10U		11	1290 4205) -	2042		10	2282 6249	Yes/INA NA/Yes	Probably damaging
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	A V12791 0 1 4299 0 0 13 4169 0 13 4169 0 14 6174 NUNNA		c.1336G>A	5210L E446K	00		4188	00	- 0	2050	00		6238	No/NA	Probably damaging
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	S ¹⁰ P2005A 0 13 4169 0 1 2005 0 14 6174 NAVNA Image: Signed conditions Image: S		c.3835G>A	V1279I	0		4299	0	0	2203	0	ц,	6502	No/NA	Possibly damaging
C:260G>A R87Q 0 1 4290 0 1 4290 0 1 4291 0 2 6484 NAYes C:260G>A R87Q 0 17 4290 0 1 4291 0 2 6484 NAYes C:265G>T ^b C:266G>T ^b C:266G>T ^b 0 1 4295 0 4 2194 0 2 6484 NAYes C:266G>T ^b C:266G>A R370 0 1 4295 0 4 2196 0 8 6491 NAYes C:26206G>A R32069Q 0 0 4 4296 0 3 6035 NA/NA C:96206G>A R32069Q 0 0 4 2196 0 3 6035 NA/NA C:95206G>A R32069Q 0 0 1 4296 0 3 6035 NA/NA C:95206G>A R32059Q 0 1 4299 0 2 1 1 1 C:33375 R11255 0 1	A R87Q 0 1 4290 0 1 2194 0 2 6484 NAYes T R690C 0 17 4295 0 4 2194 0 2 6484 NAYes T R690C 0 17 4295 0 4 2196 0 2 6484 NAYes T R690C 0 17 4295 0 4 2196 0 8 6491 NOYes A R32069Q 0 0 4115 0 4 2196 0 8 6491 NOYes A R32069Q 0 0 4 1920 0 3 6035 NA/NA A28N 0 1 4296 0 0 2203 0 4 6499 NA/NA T R975W 0 1 4299 0 2203 0 1 6502 Yes/Yes T R1125C 0 1 2197 0 1 6502 Yes/Yes	222	c.6013C>G	P20054	0	13	4169	0	-	5002	Ο	14	61/4	NA/NA	Benign
c.2606>A R87Q 0 1 4290 0 1 2194 0 2 6484 NAYes c.5656>T ¹ 622V 0 17 4283 84 598 1521 84 615 5804 NAYes c.5656>T ¹ 622V 0 17 4283 84 598 1521 84 615 5804 NAYes c.5656>T ¹ 622V 0 17 4283 84 598 1521 84 6491 NAYes c.5656 1 1 4295 0 4 4295 0 4 1615 5603 1 1 c.96206G>A R32069Q 0 0 4 4296 0 3 6035 NA/NA c.95206G>A R32069Q 0 1 4296 0 0 1 6499 NA/NA 2	A R87Q 0 1 4290 0 1 2194 0 2 6484 NAYNes T R690C 0 1 4295 0 4 2194 0 2 6484 NAYNes R690C 0 1 4295 0 4 2196 0 8 6491 NOYNes A R32069Q 0 0 4115 0 3 1920 0 8 6491 NOYNes A R32069Q 0 0 4 4295 0 3 6035 NA/NA A R32069Q 0 0 2203 0 4 6499 NA/NA A R3750 0 1 4296 0 0 2203 0 1 6499 NA/NA T R975W 0 1 2203 0 1 6502 Yes/Yes 1 T R3135X 0 1 2197 0 1 6502 Yes/Yes 1 1 1 1	SYNEI													
c.260G>A R87Q 0 1 4290 0 1 2194 0 2 6484 NAYes c.65G>TP G22V 0 17 4295 0 4 2196 0 2 6484 NAYes c.65G>TP G22V 0 17 4295 0 4 2196 0 8 6491 NAYes c.<0563C>T R690C 0 4 4295 0 4 2196 0 8 6491 NAYes c.<0563C>TP A28V 0 0 4 1521 84 615 5804 NAYAes c96206G>A R32069Q 0 0 4 4295 0 3 6035 NA/NA c.96206G>A R32069Q 0 0 2203 0 4 6499 NA/NA c.93373C>T R975W 0 1 4299 0 0 1 6502 Yes/Yes c.23233C>T R975W 0 1 2197 0 1 6502 Yes/Yes 6502 </td <td>A R87Q 0 1 4290 0 1 2194 0 2 6484 MAYes T R690C 0 17 4295 0 4 2196 0 2 6484 NAYes T R690C 0 4 4295 0 4 2196 0 8 6491 NAYes T R32069Q 0 0 4115 0 3 1920 0 8 6491 NAYes A R32069Q 0 0 4115 0 2203 0 4 6499 NA/NA A R3205 0 0 2203 0 2203 0 4 6499 NA/NA T R975W 0 1 4299 0 2203 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6490 NA/NA</td> <td>SYNM</td> <td>I</td> <td>I</td> <td> </td> <td>I</td> <td>I</td> <td> </td> <td> </td> <td>I</td> <td> </td> <td> </td> <td> </td> <td>Ι</td> <td> </td>	A R87Q 0 1 4290 0 1 2194 0 2 6484 MAYes T R690C 0 17 4295 0 4 2196 0 2 6484 NAYes T R690C 0 4 4295 0 4 2196 0 8 6491 NAYes T R32069Q 0 0 4115 0 3 1920 0 8 6491 NAYes A R32069Q 0 0 4115 0 2203 0 4 6499 NA/NA A R3205 0 0 2203 0 2203 0 4 6499 NA/NA T R975W 0 1 4299 0 2203 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6490 NA/NA	SYNM	I	I		I	I			I				Ι	
C.903G>T 9422V 0 1/1 4283 84 936 1921 84 919 9304 NMVM Image: C.9058C>T R690C 0 4 4295 0 4 2196 0 8 6491 NOVes Image: C.9058C>T R690C 0 4 4295 0 4 2196 0 8 6491 NOVes Image: C.96206G>A R32069Q 0 0 4 115 0 3 1920 0 8 6491 NOVes C.96206G>A R32069Q 0 0 4 4296 0 3 1920 0 4 6499 NA/NA C.93375 T NA/NA 0 2203 0 4 6499 NA/NA Image: C.29236 T 1 4299 0 0 2203 0 1 6502 Yes/Ves Image: C.3373C>T R11256 0 1 2197 0 1 6502 NA/NA Image: C.94036 0 0 2203 <	T GLZV U 1/2 4.283 64 192 5604 NMMA T R690C 0 4 4295 0 4 2196 0 8 6491 NOVes T T R690C 0 4 1295 0 3 6491 NOVes T R32069Q 0 0 4115 0 3 1920 0 8 6491 NOVes A28V 0 4 4296 0 0 2203 0 4 6499 NA/NA T R975W 0 1 4299 0 0 2203 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6490 NA/NA T R3135X 0 1 2197 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6490 NA/NA	TCAP TOLOI	c.260G > A	R870	00	 -	4290	0		2194	0	21	6484	NA/Yes	Probably damaging
C:96206G>A R32069Q 0 0 4115 0 3 1920 0 3 6035 NA/NA C.83C>T ^b A28V 0 0 44 4296 0 0 2203 0 4 6499 NA/NA C.83C>T R975W 0 1 4299 0 0 2203 0 1 6502 YesYes C.3373C>T R1125C 0 1 4299 0 0 2203 0 1 6502 YesYes C.9403C>T R1125C 0 1 2293 0 1 6502 YesYes C.9403C>T R3135X 0 0 2203 0 1 6502 NA/NA	A R32069Q 0 0 4115 0 3 1920 0 0 4 6499 MA/NA A R32069Q 0 0 4 115 0 3 1920 0 4 6499 MA/NA A R320 0 1 4296 0 0 2203 0 4 6499 MA/NA T R1125C 0 1 4299 0 0 2203 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6499 MA/NA	TMPO	C.050G > 12	REGOC		7 7 1	4283 4295	α 4 C	86G 7	1261	84 0	619 8	5804 6491	NA/NA No/Yas	Benign Prohahlv damaging
C:96206G>A R32069Q 0 0 4115 0 3 1920 0 3 6035 NA/NA C.83C>T ^b A28V 0 0 4 4296 0 0 2203 0 4 6499 NA/NA C.83C>T R975W 0 1 4299 0 0 2203 0 1 6502 YesYes C.3373C>T R1125C 0 1 4299 0 0 2203 0 1 6502 YesYes C.9403C>T R1125C 0 1 4299 0 1 2197 0 1 6502 NA/NA	A R32069Q 0 4115 0 3 1920 0 3 6035 NA/NA A28V 0 4 4296 0 3 6035 NA/NA T R975W 0 1 4299 0 0 2203 0 4 6499 NA/NA T R975W 0 1 4299 0 0 2203 0 1 6502 Yes/Yes T R1125C 0 1 2203 0 1 6502 Yes/Yes T R3135X 0 1 2197 0 1 6490 NA/NA	TNNCI	- / 00001:0		>	+	001	P	+		P)			
C:96206G>A R32069Q 0 0 4115 0 3 1920 0 3 6035 NA/NA C.83C>T ^b A28V 0 4 4296 0 0 2203 0 4 6499 NA/NA C.83C>T 7 7 7 8975W 0 1 4299 0 0 2203 0 1 6502 YesYes C.3373C>T R1125C 0 1 4299 0 0 2203 0 1 6502 YesYes C.9403C>T R3135X 0 0 4293 0 1 2197 0 1 6490 NA/NA	A R32069Q 0 0 4115 0 3 1920 0 3 6035 NANA -	TNNI3													
	T R975W 0 1 4299 0 0 2203 0 1 6502 Ves/Ves T R1125C 0 1 4299 0 0 1 6502 Ves/Ves T R3135X 0 0 1 2197 0 1 6490 NA/NA	TTN TNNT2	C.96206G>A	R32069Q	00	0 <	4115	00	m ⊂	1920 2203	00	m <	6035 6400		Probably damaging
C.2923C>T R975W 0 1 4299 0 0 2203 0 1 6502 Yes/Yes C.3373C>T R1125C 0 1 4299 0 0 2203 0 1 6502 Yes/Yes C.9403C>T R3135X 0 0 4293 0 1 2197 0 1 6490 NA/NA	T R975W 0 1 4299 0 0 2203 0 1 6502 Yes/Yes T R1125C 0 1 4299 0 0 2203 0 1 6502 Yes/Yes T R3135X 0 0 2197 0 1 6490 NA/NA	TPM1			>	+	001	P	2		P	+			
c.2923C>T R975W 0 1 4299 0 0 2203 0 1 6502 Yes/Yes c.3373C>T R1125C 0 1 4299 0 0 2203 0 1 6502 NA/NA c.9403C>T R3135X 0 0 4293 0 1 2197 0 1 6490 NA/NA	T R975W 0 1 4299 0 0 2203 0 1 6502 Yes/Yes T R1125C 0 1 4299 0 0 2203 0 1 6502 Na/NA T R3135X 0 0 0 4293 0 1 2197 0 1 6490 Na/NA	TXNRD2	I					'			1		I	1	
c.9403C>T R3135X 0 0 1 2293 0 1 2197 0 1 6490 NAVNA	T R3135X 0 0 4293 0 1 2197 0 1 6490 NAVA	NCL	C.2923C>T	R975W	00		4299 1200	00		2203	00		6502 6502	Yes/Yes NA/NA	Probably damaging Benian
	aNA indicates no data available.	VPS13A	c.9403C>T	R3135X	00	- 0	4293	00		2197	00		6490	NA/NA	Unknown

Table 2 (Continued)

npg 924

Neuron Neuron<				European	European Americans—g	genotype	African +	African Americans-genotype	snotype	Aı	All—genotype	0)		
Votor Anone kel mot mot </th <th></th> <th></th> <th></th> <th>Minor/</th> <th>Minor/</th> <th>Major/</th> <th>Minor/</th> <th>Minor/</th> <th>Major/</th> <th>Minor/</th> <th>Minor/</th> <th>Major/</th> <th>Family co-segregation/</th> <th></th>				Minor/	Minor/	Major/	Minor/	Minor/	Major/	Minor/	Minor/	Major/	Family co-segregation/	
C-2016/S-A E107K C <thc< th=""> C C <</thc<>	Gene	Variant	Amino acid	minor	major	major	minor	major	major	minor	major	major	functional effect ^a	Polyphen-2 prediction
C30R5-A E10K 0 7 201 0 0 0 0 C37N-G* 1109M 0 1 2295 0 1 2695 0 1 2695 0 0 1 2695 0 0 1 2695 0 0 1 2695 0 0 1 2695 0 0 1 2695 0 0 1 2695 0 <td< td=""><td>DES</td><td></td><td></td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td></td><td></td></td<>	DES													
Calible II (0)M C 1 2201 C	DSC2	c.304G>A	E102K	0	7	4291	0	ŝ	2200	0	10	6491	No/Yes	Benign
C (17)(A) T (A) D T (A) D T (A) D D D C (17)(A) S (A) 0 1 2200 0 1 600 NOM C (17)(A) S (A) 0 1 2200 0 1 600 NOM C (27)(A) S (A) 0 1 2200 0 1 600 NOM C (27)(A) S (A) 0 1 2200 0 1 600 NOM C (27)(A) S (A) 0 1 200 0 1 200 NOM C (27)(A) S (A) 0 1 200 0 1 200 NOM C (10)(A) S (A) 0 1 200 0 1 200 NOM C (10)(A) S (A) 0 1 200 NOM NOM C (10)(A) S (A) 0 1 200 NOM NOM NOM NOM		$c.327A > G^b$	1109M	0	1	4295	0	1	2201	0	2	6496	Yes/NA	Benign
C17216.x16 S374N 0 4 4266 0 2 200 0 4 6469 NMM C13715-51 S324V 0 1 2.203 0 4 6499 NMM C23715-51 S324V 0 1 2.203 0 3 6.697 NMM C25715-51 S134L 0 1 2.999 0 3 6.697 NMM C16667-A VS6M 0 2 2.201 0 3 6.697 NMM C1667-A VS6M 0 1 2.093 0 3 6.997 NMM C1667-A VS6M 0 1 4090 0 1 993 NMM C11666-A VS6M 0 1 4090 0 1 993 NMM C1103A-5 T334 0 2 4090 0 2 993 NMM C1103A-5 T3340 0 1		c.1018A>G	T340A	0	1	4299	0	0	2202	0	1	6501	NA/NA	Probably damaging
C.239(T>6 T.22(V) 0 11 229 0 14 6495 MOM C.259(T>A 05844 0 11 229 0 1 6495 MOM C.259(T>A 05844 0 5 4295 0 1 2956 MOM C.259(T>A 0566(A V1566 0 5 4295 0 1 956 MOM C.259(T>A 05817 0 1 4002 0 2 1877 0 2 9595 MOM C.1015(A>6 73316 0 1 4003 0 2 1973 MOM MOM C.1015(A>6 73316 0 1 4030 0 2 1973 MOM MOM C.1015(A>6 73316 0 1 4030 0 1474 0 1474 0 MOM C.1015(A>6 73316 0 1 4031 0 1474 0		$c.1721G > A^{b}$	S574N	0	4	4296	0	0	2203	0	4	6499	NA/NA	Benign
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		c.2194T>G	L732V	0	11	4289	0	ŝ	2200	0	14	6489	NA/NA	Benign
C2587G>A G653 0 5 4295 0 0 6 6 7 0 0 C2587G>A G653 0 5 4295 0 0 5 697 0 0 C4775>G V1960 0 5 402 0 1 409 0 1 995 0 0 C1675>P S134 0 5 410 0 2 1933 0 3 995 0 0 C1051A>G T3211 0 5 410 0 2 410 0 2 100 2 995 0 0 C1051A>G T3211 0 5 410 0 2 410 0 2 995 0 <td></td> <td>c.2471C>T</td> <td>S824L</td> <td>0</td> <td>1</td> <td>4299</td> <td>0</td> <td>2</td> <td>2201</td> <td>0</td> <td>ю</td> <td>6500</td> <td>No/NA</td> <td>Probably damaging</td>		c.2471C>T	S824L	0	1	4299	0	2	2201	0	ю	6500	No/NA	Probably damaging
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		c.2587G>A	G863R	0	Ð	4295	0	-1	2202	0	9	6497	NA/NA	Probably damaging
Light Circle Vision D Sign Circle Vision D Sign Circle Vision D Sign Circle Vision V	DSG2	c.166G>A	V56M	0	29	4082	0	2	1876	0	31	5958	NA/NA	Probably damaging
C581C>15 S194. 0 1 408 0 1 408 0 1 566 NMM c.59(1) 733M 0 1 4140 0 2 3673 NMM c.50(1) 733M 0 2 4140 0 2 3677 NMM c.1051A-5 733M 0 2 4140 0 2 3677 NMM c.1051A-5 733M 0 1 4140 0 2 1873 0 2 5977 NMM c.1174G>M M323 0 1 4130 0 2 141 NMM c.1174G>M M323 0 1 4130 0 2 141 NMM c.1174G>M M331 0 1 4131 0 2 141 NMM c.1350C>M M313 0 1 4132 0 2 141 NMM c.1350C>M M3147<		c.473T>G	V158G	0	65	4059	0	6	1864	0	74	5923	Yes/NA	Benign
		$c.581C > T^b$	S194L	0	1	4098	0	0	1858	0	1	5956	NA/NA	Probably damaging
ColdityA T3211 0 2 4105 0 1872 0 2 9977 NMM C.1003Ay-G T3211 0 5 4094 0 0 1883 0 2 9977 NMM C.1003Ay-G T3314 0 1 4150 0 2 1883 0 2 996 NMM C.1174G>A A517V 0 1 4150 0 2 1873 0 2 996 NMM C.1174G>A A517V 0 1 4150 0 2 1873 0 2 996 NMM C.1350C>T A517V 0 1 4150 0 2 1393 0 2 996 NMM C.1350C>T A517V 0 1 4130 0 1 1 1<00 2 606 NMM C.1350C>T A517V 0 1 1 <th1< th=""> <th1<0< th=""> 1<1<00</th1<0<></th1<>		$c.716T > C^b$	V239A	0	1	4140	0	2	1908	0	m	6048	NA/NA	Probably damaging
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		c.961T>A	F321I	0	2	4105	0	0	1872	0	2	5977	NA/NA	Probably damaging
C1051A-5 ⁶ SS51d 0 10 4090 0 11 4093 0 11 4093 0 11 4093 0 11 4093 0 11 4093 0 11 4093 0 11 4093 0 11 4093 0 11 4093 0 11 4093 0 2 6066 NMM c.1478A50 F F 4132 0 1 1333 0 2 6066 NMM c.1476A50 F F 4132 0 1 1333 0 2 6046 NMM c.21376A F F 2 6433 0 1 3 2 649 NMM c.21376A F F 4293 0 1 4 4 3 649 NMM NMM c.21376A N608H 0 1 4 4 2 1 4 4		c.1003A>G	T335A	0	Ð	4094	0	0	1863	0	2	5957	No/NA	Probably damaging
C1174G>A V3321 0 17 4033 0 17 4033 0 19 5966 NMM C.1915GO-F A537 0 1 1490 0 1 1490 0 1 1440 0 1 1440 0 2 6686 NMM C.1915GO-F A5137 0 1 4194 0 2 6698 NMM C.1915GO-F 65387 0 1 4194 0 2 6492 NMM C.2137G>A 65387 0 1 4094 0 72 1249 0 1 9929 NMM C.2137G>A K580 0 1 4094 0 72 1249 0 1 9929 NMM C.2137G>A K580 0 1 4094 0 2 6691 NMM C.2159G5A K680 0 1 4299 0 1 4299 NMM		$c.1051A > G^{b}$	S351G	0	0	4090	0	24	1807	0	24	5897	NA/NA	benign
C.1478A-S ⁶ M433 0 1 4150 0 1 1336 0 2 6086 MMM C.131506-7 ¹ A517V 0 2 4174 0 2 6114 MMO C.131506-7 ¹ K317V 0 2 4174 0 2 6114 MMO C.131506-7 K317V 0 2 4124 0 2 6086 MMM C.2137G-A K318V 0 411 4084 0 72 1929 16 692 6587 MMM C.2137G-A K3865 0 411 4084 0 0 1 4999 MMM C.2159G-A M5661 0 1 4094 0 2 6499 MMM C.24205-A K608H 0 1 429 0 1<1		c.1174G>A	V392I	0	17	4093	0	2	1873	0	19	5966	No/NA	Benign
C.1550C> 7 $A517$ 0 0 174 0 21 16114 NMN C.1976C-A 6538R 0 2 1646 NMN C.1976C-A 6538R 0 2 1646 NMN C.27347-5 633R 0 2 1645 NMN C.234346-7 6812C 0 1 4084 0 0 1942 0 1 9929 NMN C.234346-7 6812 0 1 4084 0 0 1845 0 1 9929 NMN c.234346-7 6817 0 1 4084 0 0 2 6495 NMN c.23436-7 88084 0 1 4253 0 2 6495 NMN c.16966-A M5667 0 1 3 4293 0 1 6393 NMN c.2336-P R9084 0 1 2 2 2 1 </td <td></td> <td>$c.1478A > G^{b}$</td> <td>N493S</td> <td>0</td> <td>1</td> <td>4150</td> <td>0</td> <td>1</td> <td>1936</td> <td>0</td> <td>2</td> <td>6086</td> <td>NA/NA</td> <td>Probably damaging</td>		$c.1478A > G^{b}$	N493S	0	1	4150	0	1	1936	0	2	6086	NA/NA	Probably damaging
C.1912G>A GG38R 0 2 4132 0 1914 0 2 6046 NMM C.21370-A E713K 16 620 6558 0 72 1929 16 622 6587 NMM C.21370-A E713K 16 620 6558 0 72 1929 16 622 6587 NMM C.27391-G V320G 0 11 4084 0 0 1 5229 NMM C.2865-A V30M 1 3 4295 0 0 216 6387 NMM C.2865-A N30M 1 3 4295 0 11 4299 NMM C.24226-A R808H 0 11 4299 0 12 6439 NMM C.24326-A R808H 0 11 2203 0 11 6502 NMM C.24375-A R808H 0 11 2203 0		c.1550C>T ^b	A517V	0	0	4174	0	21	1940	0	21	6114	NA/No	Probably damaging
c.2137G>A E713K 16 6.20 6558 0 72 1929 16 692 6587 NMM c.2343G>T 6812C 0 1 4084 0 0 1 9529 NMM c.2343G>T 6812C 0 1 4084 0 0 1 9529 NMM c.2865>A V30M 0 16 423 0 0 1 9529 NMM c.8865>A V30M 0 16 423 0 0 1 3 499 NMM c.8865>A N30H 0 1 4094 0 1 3 6499 NMM c.1696G 0 1 4299 0 1 2 6499 NMM c.247265 R1848G 0 1 2 2 6501 NMM c.247365 R308H 0 1 2 2 2 0 1 6	_	c.1912G>A	G638R	0	2	4132	0	0	1914	0	2	6046	NA/NA	Probably damaging
c.2434G>T G812C 0 1 4084 0 1845 0 1 5929 NAMA c.2434G>T 6812C 0 1 4094 0 6 1942 0 1 5929 NAMA c.2759T>G V30M 0 16 4253 0 0 1 5929 NAMS c.288G>A N30M 0 1 3 4295 0 0 1 6499 NAMS c.688G>A A566T 0 1 3 4295 0 0 1 3 6499 NAMS c.1696G>A A566T 0 1 4299 0 1 2 6499 NAMS c.2243G>A R908H 0 1 4299 0 1 2 6491 NAMS c.2243G>A R908H 0 1 4299 0 1 2 6491 NAMS c.2243G>A R9186H 0		c.2137G>A	E713K	16	620	6558	0	72	1929	16	692	6587	NA/NA	Benign
c.2759T>G V320G 0 41 4094 0 6 1942 0 47 6036 NMM c.886>A V30M 0 16 4253 0 0 2169 0 16 6422 NMMs c.886>A A56T 0 5 4295 0 0 2169 0 16 6422 NMMs c.16966A A56T 0 5 4298 0 0 16 6429 NMM c.16966A A56T 0 5 4298 0 0 16 439 NAM c.24236A R808H 0 11 4299 0 10 11 6602 NAM c.27236A R1775I 0 1 4299 0 1 2199 0 11 6602 NAM c.21366A N1775I 0 1 4299 0 1 6502 NAM c.21366A N1775I		c.2434G>T	G812C	0	1	4084	0	0	1845	0	1	5929	NA/NA	Probably damaging
c.88G>A V30M 0 16 4253 0 0 16 6422 NMMes c.688G>A D230N 1 3 4295 0 0 16 6422 NMMes c.688G>A D230N 1 3 4295 0 0 2203 0 1 3 6499 NMMs c.1686G>A D230N 1 3 4295 0 0 2203 0 1 6602 NMMs c.1436C>M R00H 0 11 4299 0 1 2203 0 1 6602 NMMs c.2723G>M R00H 0 1 4299 0 1 2203 0 1 6602 NMMs c.23745 R1751 0 1 4299 0 0 1 6502 NMMs c.33245 R17756 0 1 4299 0 0 2 6491 NMM c.332		c.2759T>G	V920G	0	41	4094	0	9	1942	0	47	6036	NA/NA	Benign
c.688G>A D230N 1 3 4296 0 0 2203 1 3 6499 NMM c.16966>A A566T 0 5 4295 0 0 2 6498 NMM c.16966>A A566T 0 2 4295 0 0 2 6498 NMM c.24425 <p< td=""> R808H 0 1 4293 0 1 2203 0 1 6499 NMM c.23725 R4158G 0 1 4299 0 1 2202 0 14 6489 N/M c.23725 R1458G 0 1 4299 0 1 2203 0 1 6489 N/M c.33726 R1751 0 1 4299 0 1 2203 0 1 6489 N/M c.321265 N17751 0 1 4299 0 1 6502 N/M c.3121056</p<>	DSP	c.88G>A	V30M	0	16	4253	0	0	2169	0	16	6422	NA/Yes	Benign
C.1696G>A A56f 0 5 429 0 2203 0 5 6498 NAVA C.2422G>T R808C 0 1 4293 0 1 6501 NAV8 C.2422G>T R808H 0 1 4293 0 1 6502 NAV8 C.2423G>A R308H 0 1 4293 0 1 4293 No/N C.2213G>A R308H 0 1 4293 0 1 4293 No/N C.2213G>A R1458G 0 1 4293 3 166 2034 3 167 6332 No/N C.2324G>T R1775I 0 1 4299 0 1 2199 0 1 6502 No/N C.2123G>C N1471 0 1 4299 0 2203 0 1 6502 No/N C.2123G>C N4171 0 1 4299 0		c.688G>A	D230N	1	с	4296	0	0	2203	1	с	6499	NA/NA	Probably damaging
c.242C5T R808C 0 2 4298 0 0 2 6501 NM%s c.2423G5A R808H 0 1 4299 0 1 2033 0 1 6602 NMMs c.2433G5A R808H 0 1 4299 0 1 2203 0 1 6602 NMA c.2433G5A R308H 0 1 4299 0 1 2203 0 1 6602 NMA c.2313G5A R1458G 0 1 4299 0 1 2203 0 1 6602 NMA c.533G5A R1458G 0 1 4299 0 0 2 6431 N/M<		c.1696G>A	A566T	0	5	4295	0	0	2203	0	D	6498	NA/NA	Probably damaging
$c.2423G>A$ R808H01 4299 01 4299 01 6502 NMM $c.2723G>A^0$ R908H013 4287 01 2203 01 6489 N/MA $c.2733G>A^0$ R908H013 4287 01 2202 014 6489 N/MA $c.23815G>A$ 013 4287 01 4298 3166 6332 N/MA $c.233246>T$ R175B01429900220301 6502 N/MA $c.533246>T$ R175B01429900220301 6502 N/MA $c.71236>A$ A143T01429900220301 6502 N/MA $c.12196>A$ V407I01429900220301 6502 N/MA $c.71236>A$ A143T01429900220301 6502 N/MA $c.12196>A$ V407I01429900220301 6502 N/MA $c.71236>A$ A143T01429900201 6502 N/MA $c.12196>A$ VV01220301 6502 N/MA $c.1476>TD26N024/2490026477N/MAc.184C>AD26N<$		c.2422C>T	R808C	0	0	4298	0	0	2203	0	2	6501	NA/Yes	Probably damaging
c.2723G>A ^b R908H 0 13 4.287 0 1 2.202 0 14 6.489 No/NA c.2815G>A G939S 0 1 4.287 3 166 2.034 3 167 6.332 NA/NA c.2815G>A G939S 0 1 4.298 3 166 2.034 3 167 6.332 NA/NA c.3324G>T R1775I 0 1 4.299 0 1 6502 NA/NA c.5123GS>A V4071 0 1 4.299 0 2.033 0 1 6502 NA/NA c.7123GS>A V4071 0 1 4.299 0 0 1 6502 NA/NA c.7123GS>A V4071 0 1 4.299 0 1 6502 N/NA c.7123GS>A V4071 0 1 4.299 0 1 6502 N/NA c.7427G>NB A188 0		c.2423G>A	R808H	0	1	4299	0	0	2203	0	1	6502	NA/NA	Probably damaging
C.2815G>A G3395 0 1 4298 3 166 2034 3 167 6332 N/NA C.437ZC>G R145BG 0 1 4299 0 4 2199 0 22 6481 N/NA C.437ZC>G R145BG 0 1 4299 0 0 2 6481 N/NA C.5324G>T R17751 0 1 4299 0 0 2 6481 N/NA C.5324G>T R143T 0 1 4299 0 0 2 0 1 6502 N/NA C.1219G>A V4071 0 1 4299 0 2 0 1 6502 N/NA C.1219G>A A143T 0 1 4299 0 2 1 6502 N/NA C.1219G>A A143T 0 1 4299 0 2 6 6 1 0 1 6 6 <td></td> <td>c.2723G>A^b</td> <td>R908H</td> <td>0</td> <td>13</td> <td>4287</td> <td>0</td> <td>1</td> <td>2202</td> <td>0</td> <td>14</td> <td>6489</td> <td>No/NA</td> <td>Possibly damaging</td>		c.2723G>A ^b	R908H	0	13	4287	0	1	2202	0	14	6489	No/NA	Possibly damaging
c.4372C>G R1458G 0 18 4282 0 4 2199 0 22 6481 NANA c.5324G>T R1775I 0 1 4299 0 0 22 6481 NANA c.5123G>C 62375R 0 1 4299 0 0 2203 0 1 6502 NANA c.7123G>C 62375R 0 1 4299 0 0 2203 0 1 6502 NANA c.1219G>A V4071 0 1 4299 0 0 2203 0 1 6502 NANA c.1219G>A V4071 0 1 4299 0 2203 0 1 6502 NANA c.1219G>A A143T 0 1 4299 0 1 6502 NANA c.76G>A D26N 0 1 2208 0 1 6477 NANA c.1847 0		c.2815G>A	G939S	0	1	4298	m	166	2034	с	167	6332	NA/NA	Benign
c.5324G>T R1775I 0 1 4299 0 2203 0 1 6502 NoNA c.7123G>C G2375R 0 1 4299 0 0 2203 0 1 6502 NoNA c.7123G>A V407I 0 1 4299 0 0 2203 0 1 6502 NoNA c.1219G>A V407I 0 1 4299 0 0 2203 0 1 6502 NoNA c.1219G>A V407I 0 1 4299 0 0 2203 0 1 6502 NoNA c.427G>A ^b A143T 0 1 4298 0 0 2203 0 1 6501 NoNA c.76G>A D26N 0 3 4044 0 4 2068 0 6112 NANA c.184C>A Q62K 0 1 2203 0 2110 0 2298 NANA c.184C>T S169G 0 1 2202 0		c.4372C>G	R1458G	0	18	4282	0	4	2199	0	22	6481	NA/NA	Benign
c.7123G>C G2375R 0 1 4299 0 2203 0 1 6502 NANA c.1219G>A V4071 0 1 4299 0 0 2203 0 1 6502 NANA c.1219G>A V4071 0 1 4299 0 0 2203 0 1 6502 NANA c.427G>A ^b A143T 0 1 4299 0 0 2203 0 1 6501 NONA c.742G>A ^b A143T 0 5 2068 0 1 6501 NONA c.7565A M24C 0 5 4044 0 4 2068 0 5 6477 NANA c.184C>A Q62K 0 16 4281 0 1 2202 0 6477 NANA c.184C>T S169G 0 16 2202 0 2102 0 2648 NANA c.1114G>C ^b A372P 0 1 2202 0 21 6477 NA		c.5324G>T	R1775I	0	1	4299	0	0	2203	0	1	6502	No/NA	Benign
c.1219G>A V4071 0 1 4299 0 2 2 0 1 6502 No/NA c.427G>A ^b A143T 0 1 4298 0 0 1 6502 No/NA c.427G>A ^b A143T 0 1 4298 0 0 2203 0 1 6501 No/NA c.745G>A D26N 0 56 4044 0 4 2068 0 1 6501 No/NA c.184C>A Q62K 0 3 4188 0 0 1 2058 0 1 6477 NANA c.184C>A Q62K 0 16 4281 0 1 2202 0 26 6477 NANA c.5056>G S169G 0 16 4281 0 1 2202 0 26 6477 NANA c.1114G>C ^b A372P 0 16 4292 0 1 2202 0 1 6477 NANA c.1114G>C ^b A337P 0 </td <td></td> <td>c.7123G>C</td> <td>G2375R</td> <td>0</td> <td>1</td> <td>4299</td> <td>0</td> <td>0</td> <td>2203</td> <td>0</td> <td>1</td> <td>6502</td> <td>NA/NA</td> <td>Probably damaging</td>		c.7123G>C	G2375R	0	1	4299	0	0	2203	0	1	6502	NA/NA	Probably damaging
c.427G>A ^b A143T 0 1 4298 0 2203 0 1 6501 No/NA c.76G>A D26N 0 56 4044 0 4 2068 0 6112 NA/NA c.184C>A Q62K 0 56 4044 0 4 2068 0 6112 NA/NA c.184C>A Q62K 0 3 4188 0 0 2110 0 3 6298 NA/NA c.184C>A Q62K 0 25 4275 0 1 2202 0 26 6477 NA/NA c.5055>G 0 16 4281 0 5 2198 0 26 6477 NA/NA c.1114G>C ^b A372P 0 16 4294 0 21233 0 1 6502 NA/NA c.1114G>C ^b A372P 0 6 4299 0 1 20202 0 1 6502 NA/NA c.1375C>T R413X 0 1 4295 0	JUP	c.1219G>A	V407I	0	1	4299	0	0	2203	0	1	6502	No/NA	Benign
c.76G>A D26N 0 56 4044 0 4 2068 0 60 6112 NANA c.184C>A 062K 0 3 4188 0 0 2110 0 3 6298 NANA c.184C>A 062K 0 3 4188 0 0 2110 0 3 6298 NANA c.114G>C 5140F 0 25 4275 0 1 2202 0 21 6477 NANA c.1114G>C A372P 0 16 4281 0 5 2198 0 26 6477 NANA c.1114G>C A372P 0 16 4294 0 0 2108 0 6 6497 NANA c.1114G>C A372P 0 6 4294 0 0 2103 0 6 6497 NANA c.1114G>C A372P 0 4300 0 1 2202 0 1 6502 NANA c.1465G>A G489F 0		c.427G>A ^b	A143T	0	1	4298	0	0	2203	0	1	6501	No/NA	Possibly damaging
Q62K 0 3 4188 0 0 2110 0 3 6298 NANA \$\$I40F 0 25 4275 0 1 2202 0 26 6477 NANA \$\$I40F 0 25 4275 0 1 2202 0 26 6477 NANA \$\$I69G 0 16 4281 0 5 2198 0 21 6497 NANA \$\$A372P 0 6 4294 0 0 2203 0 6 6497 NANA \$\$A372P 0 6 4294 0 0 2203 0 6 6497 NANA \$\$A13X 0 0 4300 0 1 2202 0 1 6502 NANA \$\$A433X 0 6 6 6497 NANA \$\$G489X 0 1 2202 0 1 6497 NANA	PKP2	c.76G>A	D26N	0	56	4044	0	4	2068	0	60	6112	NA/NA	Possibly damaging
S140F 0 25 4275 0 1 2202 0 26 6477 NANA S169G 0 16 4281 0 5 2198 0 21 6479 NANA A372P 0 6 4294 0 5 2198 0 6 6497 NANA R413X 0 6 4294 0 0 1 6502 No/NA G489R 0 1 2202 0 1 6497 No/NA G489R 0 1 2202 0 1 6497 No/NA T526M 0 20 2202 0 1 6497 NA/NA		c.184C>A	Q62K	0	с	4188	0	0	2110	0	с	6298	NA/NA	Benign
S169G 0 16 4281 0 5 2198 0 21 6479 NANA A372P 0 6 4294 0 0 20 6 6497 NANA R413X 0 6 4294 0 0 1 6502 No/NA G489R 0 1 2202 0 1 6497 NANA T526M 0 20 2 2202 0 1 6497 NANA		c.419C>T	S140F	0	25	4275	0	1	2202	0	26	6477	NA/NA	Benign
A372P 0 6 4294 0 0 2203 0 6 6497 NANA R413X 0 0 4300 0 1 2202 0 1 6502 No/NA G489R 0 1 4295 0 1 2202 0 1 6497 NANA T526M 0 20 22 0 1 6497 NANA		c.505A>G	S169G	0	16	4281	0	Ð	2198	0	21	6479	NA/NA	Benign
R413X 0 0 4300 0 1 2202 0 1 6502 No/NA G489R 0 1 4295 0 0 2202 0 1 6497 NA/NA T526M 0 20 28 2175 0 48 6455 NA/NA		$c.1114G > C^{b}$	A372P	0	9	4294	0	0	2203	0	9	6497	NA/NA	benign
G489R 0 1 4295 0 0 2202 0 1 6497 NA/NA T526M 0 20 4280 0 28 2175 0 48 6455 NA/NA		c.1237C>T	R413X	0	0	4300	0	1	2202	0	1	6502	No/NA	Unknown
T526M 0 20 4280 0 28 2175 0 48 6455 NANA		c.1465G>A	G489R	0	1	4295	0	0	2202	0	1	6497	NA/NA	Benign
		c.1577C>T	T526M	0	20	4280	0	28	2175	0	48	6455	NA/NA	Possibly damaging

Questioning cardiomyopathy-associated genetic variants C Andreasen $et \ al$

925



			Europear	European Americans—genotype	șen otype	African ,	African Americans—genotype	enotype	A	All—genotype	(P		
			Minor/	Minor/	Major/	Minor/	Minor/	Major/	Minor/	Minor/	Major/	Family co-segregation/	
Gene	Variant	Amino acid	minor	major	major	minor	major	major	minor	major	major	functional effect ^a	Polyphen-2 prediction
	$c.1592T > G^b$	1531S	0	42	4258	0	0	2203	0	42	6461	NA/No	Benign
	c.1759G>A	V587I	0	40	4260	0	2	2201	0	42	6461	No/NA	Possibly damaging
	c.2062T>C	S688P	0	0	4300	0	2	2201	0	2	6501	NA/NA	Probably damaging
	c.2431C>A	R811S	0	Ð	4295	0	0	2203	0	2	6498	NA/NA	Benign
	c.2434G>A ^b	D812N	0	0	4300	0	1	2201	0	1	6502	NA/NA	Benign
	$c.2615C > T^b$	T872I	0		4299	0	0	2203	0	1	6502	NA/NA	Probably damaging
RYR2													
TGFβ3													
TMEM43	$c.718C > T^b$	R240C	0	0	4300	0	1	2202	0	1	6502	NA/NA	Probably damaging
NTT	c.26542C>T	Н8848Ү	0	34	4146	0	ო	2011	0	34	6157	NA/NA	Benign
	c.50846T>C	I16949T	0	1	4091	0	0	1839	0	1	5930	NA/NA	Benign
	c.55735G>A	A18579T	0	1	4116	0	0	1917	0	1	6033	NA/NA	Probably damaging
	c.99872T>C	M33291T	0	13	4130	0	0	1929	0	13	6059	NA/NA	Benign
^a NA indicates ^b Likely diseas	^a NA indicates no data available. ^b Likely disease-causing mutation, but with questionable pathogenicity.	ut with questionable	pathogenicity.										

Table 3 (Continued)

				ESP no	pulation	Control population
				Loi po	pulation	Genotype
				Genotype	frequency	frequency
				(%	%)	(%)
	Amino		Disease	African	European	Northern
Gene	acid	rs#	association	Americans	Americans	European
CSRP3	W4R	rs45550635	DCM	0.09	1.07	1.12
DSG2	V158G	_	ARVC	0.48	1.58	1.69
DSP	V30M	rs121912998	ARVC	0.00	0.37	0.94
МҮВРСЗ	V896M	rs35078470	HCM	0.30	0.96	0.94
МҮН6	A1004S	rs143978652	DCM	0.05	0.26	0.37
MYH7	M982T	rs145532615	HCM	0.14	0.44	0.56
PKP2	D26N	rs143004808	ARVC	0.19	1.37	0.94

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; ESP, Exome Sequencing Project; HCM, hypertrophic cardiomyopathy.

second population with clinical data available and no history of arrhythmias or other cardiac diseases. Thirty-four out of the 534 control subjects carried at least one of the variants. The seven genotyped variants were present with frequencies comparable with those found in ESP (Table 4), and all geno-positive controls, except from one individual, had ECGs without any signs of cardiomyopathy (eg, no hypertrophy or signs of ARVC). Thus, overrepresentation of cardiomyopathy-associated variants in ESP does not seem to be a major problem. In a recent paper,²⁰ we also established that prevalences of four other variants genotyped in a control population were comparable to those of ESP. These results thus indicate that ESP consists of individuals representative of the general population.

A control population with available echocardiograms would have been preferable, but such a control population was not available. However, symptoms and signs of cardiomyopathy do not usually appear beyond the age of 50–60 years in these diseases,^{21–23} and also 75–95% of ARVC and HCM patients display ECG abnormalities.^{24,25} This indicates that our control population is well suited since it consists of 534 people all above the age of 55 with no reported signs of cardiovascular diseases. It is of course possible that a small fraction of the control population might develop cardiomyopathy in a very late age and that variant carriers are displaying reduced penetrance. However, this is not very likely, since we found a high number of carriers of the seven genotyped variants, and the fact that all geno-positive individuals except one had ECGs without any signs of cardiomyopathy and no history of cardiac diseases.

A genotype prevalence of 1:4 for HCM, 1:6 for DCM, and 1:5 for ARVC is unlikely to be caused by reduced or age-related penetrance. Even when taking into consideration a penetrance as low as 20% (reported for some genotypes), it would still result in genotype prevalences being massively overrepresented.

PolyPhen-2 predicted a statistically significant higher proportion of the variants present in ESP to be benign compared with the variants not present in ESP (43 *vs* 18% for HCM, 33 *vs* 20% for DCM, and 53 *vs* 12% for ARVC). This analysis further questions the pathogenic role of at least some of the variants present in ESP.

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In the lack of phenotypic data available on the ESP population, we defined a cutoff value based on the expected prevalences of the respective cardiomyopathies in the same population. In this definition, variants with prevalence above this cutoff were assumed not to be monogenic causes of cardiomyopathy. However, taking this conservative cutoff into account revealed genotype prevalences similar to the ones obtained when including all cardiomyopathy-associated variants. Such a cutoff is of course somewhat arbitrary because of uncertainty regarding true prevalences of the cardiomyopathies in the general population (ESP) and because variants with reduced penetrance or recessive inheritance are not taken in to account. However, most variants listed in the ARVC database and in HGMD are reported as monogenic, autosomal dominant causes of the cardiomyopathies.

Interpretation of the significance of the cardiomyopathy-associated variants with prevalences below our cutoff and thus present in a very low frequency in the ESP data is much less straightforward. These rare variants may be monogenic causes of cardiomyopathy, disease-modifiers, or benign. A small number of studies have associated genetic variation with increased susceptibility for cardiomyopathy in a non-monogenic manner.^{26–28} For this reason, we can only exclude high-prevalent variants as monogenic causes of cardiomyopathy, but we cannot make a conclusion about possible disease-modifying effects.

It is noteworthy that four genes associated with HCM in the HGMD database (COX15, OBSCN, SRI, and VCL) only had one variant that has been associated with cardiomyopathy (COX15 p.R217W, OBSCN p.4344Q, SRI p.F112L, and VCL p.L277M). These four variants were also present in ESP and both OBSCN p.4344Q and SRI p.F112L had prevalences above our defined cutoff values. Similarly, in five genes associated with DCM only one variant was identified in each gene (DSG2 p.T335A, FLT1 p.R54S, POLG p.N736S, TMPO p.R690C, and VPS13A p.R3135X) and all of these were also present in ESP. Only DSG2 p.T335A and VPS13A p.R3135X were below our cutoff value. Our data suggest that the genes OBSCN, SRI, FLT1, POLG, and TMPO require a revaluation regarding their disease causation with HCM and DCM.

A number of variants with functional effects or family cosegregation were identified in ESP. Functional characterization and family co-segregation analyses within families are valuable tools in determining the pathogenicity of identified sequence variants. However, small family sizes and reduced penetrance often hampers segregation analyses. In addition, functional characterization in model systems may not be representative of *in vivo* human physiology and an observed difference in a model system may not be of clinical importance. As an example, the *CSRP3* (alternative symbol *MLP*) p.W4R variant has been associated with cardiomyopathy in functional systems,^{29,30} but lack of family co-segregation has also been reported.³¹

Genetic screening is gaining ground in the identification of patients and family members at an increased risk of cardiomyopathies. Identification of a misclassified genetic variant in cardiomyopathy patients might lead to erroneous risk stratification, misdiagnosis of family members and this could have potentially devastating clinical consequences. It is therefore important that variants being reported as causative of cardiomyopathies are truly disease causing.

In conclusion, we identified a massive overrepresentation of previously cardiomyopathy-associated genetic variants in new population-based exome data. With genotype prevalences up to one thousand times higher than expected from the phenotype prevalence in the general population, we suspect a high number of these genetic variants to be only modest disease-modifiers or even non-pathogenic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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