Supplementary Materials

Reassessment of genes associated with dilated and hypertrophic cardiomyopathy in a Chinese Han population

Yang Sun[1,2,#], Hong Wang[1,2,#], Man Huang[1,2], Ke Li[1,2], Xiuli Song[1,2], Lei Xiao[1,2], Jiaqi Dai[1,2], Linlin Wang[1,2], Yanghui Chen[1,2], Dongyang Wu[1,2], Ting Yu[1,2], Rui Li[1,2], Fei Ma[1,2], Zongzhe Li[1,2], Peng Chen[1,2], Hong Wang[1,2], Yan Wang[1,2], Zhongsheng Sun[3], Li Jin[4], Dao Wu Wang[5], Guangzhi Chen[1,2,#], Dao Wen Wang[1,2,]

[#]These authors contributed equally.

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Figures S1 to S3.
Tables S1 to S6.

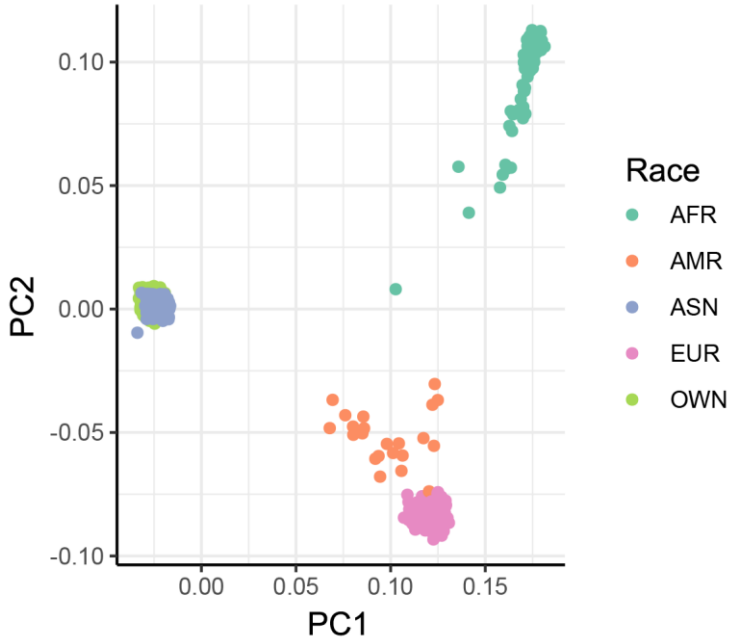

Figure S1. Principle analysis of the study cohort. Principle Component (PC) analysis based on common variants and data from 100 genome projects revealed that the current study cohort belongs to the Asian population. AFR, African; AMR, American; ASN, Asian; EUR, European; OWN, the current study population.

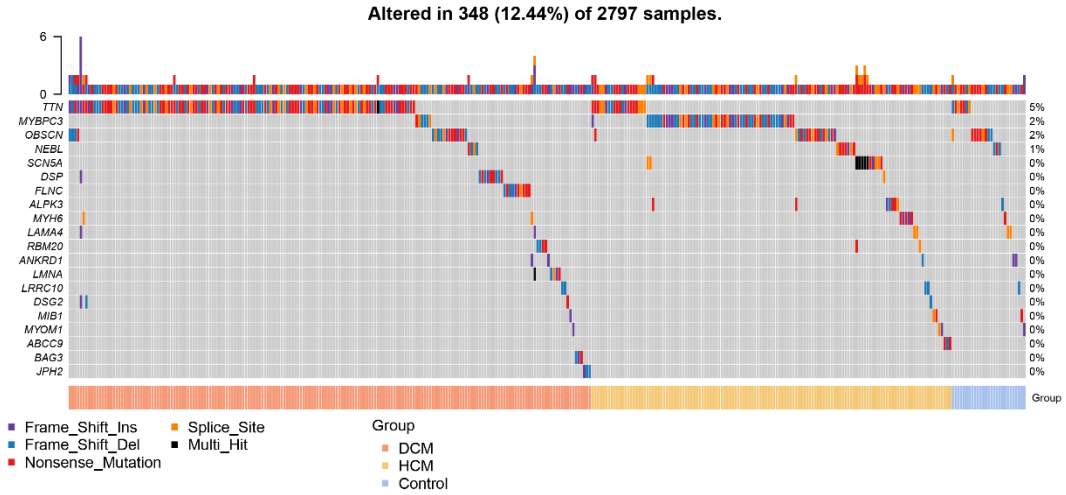

Figure S2. Overall landscape of truncating variants in cardiomyopathy genes from the ClinGen Expert panel.

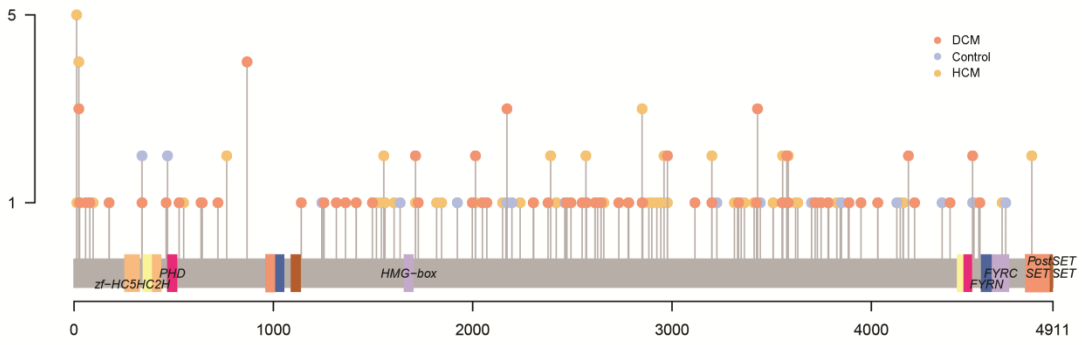

Figure S3. Distribution of rare variants in DCM, HCM and control cohorts. The lollipop plot shows the variants distribution of three cohorts, where the red points indicate DCM, the yellow points indicate HCM and the blue points indicate control. The X axis represents the length of KMT2C protein, the boxes indicate the protein domains and the Y axis represents the number of individuals carrying certain variants. Maftools was used to generate the plot.

Table S1. Cardiomyopathy genes in the ClinGen expert panels

Gene Symbol	Classification
DCM genes	
ABCC9	Limited
ACTC1	Moderate
ANKRD1	Limited
BAG3	Definitive
CSRP3	Limited
CTF1	Limited
DES	Definitive
DSG2	Limited
DSP	Strong
DTNA	Limited
EYA4	Limited
FLNC	Definitive
GATAD1	Limited
ILK	Limited
JPH2	Moderate
LAMA4	Limited
LDB3	Limited
LMNA	Definitive
LRRC10	No Known Disease Relationship
MIB1	No Known Disease Relationship
MYBPC3	Limited
MYH6	Limited
MYH7	Definitive
MYL2	Limited
MYL3	Disputed
MYPN	Limited
NEBL	Limited
NEXN	Moderate
NKX2-5	Limited
NPPA	No Known Disease Relationship
OBSCN	Limited
PDLIM3	Disputed
PKP2	Disputed
PLEKHM2	Limited
PRDM16	Limited
PSEN1	Disputed
PSEN2	Limited
RBM20	Definitive
SCN5A	Definitive
SGCD	Limited

TBX20	Limited
TCAP	Limited
TNNC1	Definitive
TNNI3	Moderate
TNNI3K	Limited
TNNT2	Definitive
TPM1	Moderate
TTN	Definitive
VCL	Moderate
HCM genes	
ACTA1	No Known Disease Relationship
ACTC1	Definitive
ACTN2	Moderate
ALPK3	Strong
ANKRD1	Limited
CACNB2	No Known Disease Relationship
CALR3	Limited
CASQ2	No Known Disease Relationship
CSRP3	Moderate
DSP	No Known Disease Relationship
FLNC	Definitive
FXN	Definitive
JPH2	Moderate
KCNQ1	No Known Disease Relationship
KLF10	Limited
LAMP2	Definitive
MYBPC3	Definitive
MYH6	Limited
MYH7	Definitive
MYL2	Definitive
MYL2	Definitive
MYL3	Definitive
MYLK2	Limited
MYOM1	Limited
MYOZ2	Limited

Table S2. Comparison of truncating variants in DCM and HCM curated genes

Gene Symbol	DCM	HCM	Control	P values (DCM vs Con)	P values (HCM vs Con)	Phenotypes
TTN	128 (12.1)	17 (1.4)	7 (1.4)	<0.001	1	DCM
OBSCN	17 (1.6)	16 (1.4)	9 (1.8)	0.999	0.696	DCM
DSP	11 (1.0)	0 (0.0)	0 (0.0)	0.046	NA	DCM, HCM
FLNC	10 (0.9)	0 (0.0)	0 (0.0)	0.061	NA	DCM
LMNA	5 (0.5)	0 (0.0)	0 (0.0)	0.279	NA	DCM
MYBPC3	6 (0.6)	55 (4.7)	0 (0.0)	0.203	< 0.001	DCM, HCM
NEBL	4 (0.4)	7 (0.6)	3 (0.6)	0.864	1	DCM
RBM20	4 (0.4)	2 (0.2)	0 (0.0)	0.389	0.867	DCM
BAG3	3 (0.3)	0 (0.0)	0 (0.0)	0.554	NA	DCM
DSG2	3 (0.3)	1 (0.1)	0 (0.0)	0.554	1	DCM
JPH2	3 (0.3)	0 (0.0)	0 (0.0)	0.554	NA	DCM
ANKRD1	2 (0.2)	1 (0.1)	2 (0.4)	0.837	0.461	DCM, HCM
LAMA4	2 (0.2)	2 (0.2)	2 (0.4)	0.837	0.758	DCM
LRRC10	2 (0.2)	2 (0.2)	1 (0.2)	1	1	DCM
MYH6	2 (0.2)	4 (0.3)	1 (0.2)	1	0.983	DCM, HCM
MYPN	2 (0.2)	0 (0.0)	0 (0.0)	0.817	NA	DCM
TPM1	2 (0.2)	0 (0.0)	0 (0.0)	0.817	NA	DCM
CSRP3	1 (0.1)	0 (0.0)	0 (0.0)	1	NA	DCM
DTNA	1 (0.1)	0 (0.0)	0 (0.0)	1	NA	DCM
MIB1	2 (0.2)	1 (0.1)	1 (0.2)	1	1	DCM
NKX2-5	1 (0.1)	1 (0.1)	0 (0.0)	1	1	DCM
PDLIM3	1 (0.1)	1 (0.1)	1 (0.2)	1	1	DCM
ACTN2	0 (0.0)	2 (0.2)	0 (0.0)	NA	0.867	HCM
ALPK3	0 (0.0)	7 (0.6)	1 (0.2)	0.712	0.472	HCM
CALR3	0 (0.0)	1 (0.1)	1 (0.2)	0.712	1	HCM
MYOM1	1 (0.1)	2 (0.2)	1 (0.2)	1	1	HCM

NA, not available.

Table S3. Candidate genes associated with DCM in SKAT-O based on rare variants

Gene Symbol	P values	Het in Case	Hom in Cases	Het in Control	Hom in Control
TTN	0.01382	879	3	350	0
MUC16	0.007195	303	0	187	0
KMT2C	0.040845	76	0	21	0
RYR2	0.046119	70	0	19	0
FN1	0.015441	59	0	24	0
FBN1	0.005868	53	0	9	0
RBM20	0.025595	45	0	9	0
MYLK2	0.018111	25	0	6	0
SLC26A1	0.003867	23	0	19	0
FBLN2	0.010814	21	0	23	0
TPCN1	0.039986	19	0	2	0
PSEN1	0.03488	17	0	4	0
KCNJ11	0.043339	15	0	5	0
CYP2D6	0.001124	13	2	21	0
FHL2	0.0245	12	0	0	0
TPM1	0.03115	12	0	0	0
NOS3	0.015966	11	0	12	0
ABCC9	0.023156	10	0	13	0
CYP2B6	0.006786	8	0	13	0
CTSB	0.037812	7	0	7	0
TLR9	0.003154	7	0	13	0
PNPLA2	0.04617	6	0	8	0

ADRB2	0.018346	6	0	4	0
IL2RA	0.023192	6	0	9	0
SLC25A46	0.024636	6	0	6	0
SLC39A8	0.012496	4	0	2	0
TOR1AIP1	0.005845	3	0	8	0
GPR34	0.028256	2	0	1	2
RIT1	0.04057	1	0	3	0
NDUFB9	0.04057	1	0	3	0
HDDC3	0.04057	1	0	3	0
MMP7	0.000271	1	0	4	0
PPCS	0.000498	0	0	5	0
CMTM7	0.001038	0	0	5	0
COX15	0.001735	0	0	4	0

Het, heterozygous; Hom, homozygous.

Table S4. Candidate genes associated with HCM in SKAT-O based on rare variants

Gene Symbol	P values	Het in Case	Hom in Cases	Het in Control	Hom in Control
MYBPC3	3.31E-05	114	1	16	0
KMT2C	0.021949	87	1	21	0
RYR2	0.016796	85	0	19	0
SCN5A	0.012554	74	0	22	0
MYH7	2.45E-05	81	0	7	0
SPEG	0.01745	54	0	39	1
FBLN2	0.011419	50	0	23	0
TMPO	0.000651	45	0	7	0
PLB1	0.048316	44	0	32	0
TPO	0.000679	42	0	10	0
FN1	0.020509	37	0	24	0
UBR1	0.026555	31	0	16	0
VEGFA	0.003178	28	0	3	0
P2RX7	0.040109	21	0	2	0
MYO6	0.026497	15	0	11	0
MYLK2	0.042832	11	0	6	0
MAP2K1	0.035007	10	0	6	0
CYP2B6	0.007018	9	0	13	0
HSPB7	0.023003	9	0	5	0
MMP1	0.008083	7	0	11	0
PDLIM3	0.04251	6	0	8	0

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TIMP4	0.015865	5	0	4	0
CAPN12	0.014787	5	0	8	0
DHRS7C	0.03653	5	0	5	0
MMP7	0.047744	4	0	4	0
MEF2A	0.023904	3	0	4	0
MYL7	0.025874	2	0	3	0
RIT1	0.030055	1	0	3	0
AVIL	0.018174	1	0	3	0
RASD1	0.030055	1	0	3	0
CACNG8	0.004404	0	0	3	0
HSPA8	0.013381	0	0	2	0
RETN	0.013381	0	0	2	0
TNNT3	0.013381	0	0	2	0
HSPD1	0.004404	0	0	3	0

Table S5. Candidate genes associated with DCM in SKAT-O based on rare deleterious variants

Gene Symbol	P values	Het in Cases	Homo in Cases	Het in Control	Homo in Control
TTN	7.36E-06	310	0	82	0
SLC6A6	0.003466	1	920	1	473
FBN1	0.005735	27	0	2	0
SLC26A1	0.008959	18	0	9	0
FPGT-TNNI3K	0.017109	13	1	0	0
TNNI3K	0.017109	13	1	0	0
FHL2	0.031141	11	0	0	0
PSEN1	0.037798	17	0	3	0
VWF	0.047972	33	0	10	0
RBM20	0.049391	15	0	1	0
SDHA	0.049759	14	0	1	0

Table S6. Candidate genes associated with HCM in SKAT-O based on rare deleterious variants

Gene Symbol	P values	Het in Cases	Homo in Cases	Het in Control	Homo in Control
MYBPC3	1.18E-05	85	1	7	0
MYH7	1.49E-05	76	0	5	0
SCN5A	0.010746	65	0	17	0
MYO6	0.019801	9	0	6	0
RYR2	0.022698	57	0	11	0