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Supplementary information

Genomic frontiers in congenital heart disease

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Supplementary Table 1 | **Damaging variants identified in 132 definitive and candidate CHD-associated genes reported in CHD and control cohorts[1,2]**

Gene name	Control cohorts				CHD cohort			
	gnomAD		SFARI		PCGC			
	Rare LOF	Rare damaging missense	Damaging missense DNV	LOF DNV	Rare LOF	Rare damaging missense	Damaging missense DNV	LOF DNV
AGPS	6	80	0	0	0	9	1	0
AKAP6	22	8	0	0	5	0	0	0
AMBRA1	11	106	0	0	1	10	0	1
ANK3	29	142	0	0	4	5	0	2
ANKRD11	10	9	0	0	1	0	0	6
ATG2A	37	1	0	0	4	0	0	0
ATP8B2	19	153	0	0	0	11	0	0
CACNA1C	22	318	0	0	0	20	2	0
CACNA1H	45	722	0	0	0	39	3	0
CAD	43	466	0	0	3	27	3	0
CDK13	15	10	0	0	1	3	6	1
CHD4	18	285	0	0	0	13	7	0
CHD7	7	274	0	0	12	17	4	15
CLUH	21	175	1	0	0	17	4	0
COL1A2	16	300	0	0	0	17	0	0
COL4A3BP	13	14	0	0	3	1	0	0
CTNNB1	2	29	0	0	3	2	0	3
CYFIP1	33	11	0	0	4	1	0	0
DGKD	27	118	0	0	0	11	1	0
FAM135A	38	65	0	0	5	2	0	0
FARSB	21	39	0	0	3	5	1	0
FBN1	13	465	1	0	0	30	3	0
FBN2	37	739	0	0	5	36	2	1
FLT4	10	119	0	0	12	9	1	2
FRYL	58	31	0	2	8	3	0	3
GANAB	20	157	0	0	1	11	2	1
GATA4	7	121	0	0	2	9	0	2
HDAC7	11	12	0	0	3	0	0	1
JAG1	6	179	0	0	5	14	1	3
JAG2	7	159	0	0	0	15	1	0
KAT6B	13	217	0	0	1	15	0	2
KMT2A	4	366	0	0	1	13	2	5
KMT2B	19	204	0	0	0	14	0	1
KMT2D	22	416	0	0	12	30	6	15
LAMA5	83	156	0	0	7	8	1	0
LRP1	18	755	1	0	0	42	4	0

LRP5	38	491	1	0	0	24	0	0
MACF1	107	397	0	0	0	21	0	0
MAPK8IP3	11	26	0	0	3	2	0	0
NF1	55	137	0	0	4	10	1	0
NOTCH1	9	297	0	0	12	34	4	4
NSD1	9	380	1	0	4	22	5	8
PIAS3	8	8	0	0	3	0	0	0
PLXND1	20	29	0	0	4	3	0	0
PTPN11	3	76	0	0	0	20	17	0
RBFOX2	6	5	0	0	3	1	0	3
RYR2	65	951	0	0	5	49	2	0
RYR3	77	1186	1	0	5	51	4	2
SCN5A	23	540	2	0	0	27	2	0
SLIT3	34	162	0	0	1	11	1	1
SMAD2	3	60	0	0	1	10	4	2
SMARCC1	13	22	0	0	6	2	0	0
SOS1	5	99	0	0	0	9	5	0
SPTBN1	13	90	0	0	1	10	0	1
SSH2	17	10	0	0	3	0	0	0
TAB2	2	17	0	0	1	0	0	4
TBX18	1	88	0	0	1	10	0	1
TBX5	2	69	0	0	3	5	1	1
TCF12	32	23	0	1	5	0	1	1
TENM4	16	518	0	0	4	19	2	0
TMTC2	21	89	0	1	0	8	0	0
TNS1	28	409	0	0	0	22	1	0
TSC1	12	187	0	0	1	14	1	1
UBAP2	58	1	0	0	5	0	0	0
WHSC1	7	190	0	0	1	11	1	2
ZMIZ1	6	24	0	0	3	4	0	2
KDR	16	111	0	0	5	9	0	0
BCAR1	15	3	0	0	3	0	0	0
PLEKHO1	13	4	0	0	3	0	0	0
SMAD5	4	62	0	1	0	11	1	0
KMT2E	24	371	1	0	0	20	1	0
COL27A1	38	294	0	0	0	19	1	0
FOXO1	0	126	0	0	0	10	1	0
SOS2	15	95	0	0	3	4	1	0
CHD8	12	179	0	0	0	12	1	0
CLSPN	34	2	0	0	4	0	0	0
CLCN7	29	120	0	0	0	8	1	0
ABCA2	28	257	0	0	0	17	2	0

ADNP	3	9	0	0	0	0	0	4
INO80	6	261	0	0	0	14	1	0
ITPR1	24	410	0	0	0	21	2	0
DYRK1A	9	1	0	0	0	0	0	3
LTBP4	42	237	0	0	0	18	1	0
TCF7L2	11	212	0	0	0	12	0	1
SOX13	11	127	0	0	0	9	1	0
ANKHD1	18	33	0	0	4	1	0	0
ARHGAP29	20	9	0	0	3	0	0	0
ATL2	15	72	0	0	3	5	0	0
ATP13A1	13	92	1	0	2	11	0	0
ATP2B1	7	165	0	0	0	13	0	0
ATP2C1	13	76	0	0	0	9	0	0
COL11A1	34	418	1	0	4	23	0	0
COL3A1	12	224	0	0	0	20	0	0
COL6A1	23	190	0	0	4	8	0	0
COPS6	4	7	0	0	3	1	0	0
CTDP1	17	11	0	0	3	1	0	0
MEGF8	54	42	0	0	6	2	0	0
EIF6	8	30	0	0	3	1	0	0
ENAH	14	113	0	0	0	8	0	0
FAM160A2	23	1	0	0	3	0	0	0
FBLN1	23	140	0	0	0	9	0	0
GNA12	13	80	0	0	0	9	0	0
GOT2	13	61	0	0	0	8	0	0
HERC1	44	180	0	0	2	14	0	0
PIK3C2B	41	116	0	0	3	9	0	0
ITGB1	22	119	0	0	0	8	0	0
KANK2	14	24	0	0	3	0	0	0
KCNH2	23	273	0	0	0	15	0	0
PTPRF	24	18	1	0	0	8	0	0
QSER1	20	0	0	0	5	0	0	0
KIF13A	24	105	0	0	3	4	0	0
RAD54L2	6	113	0	0	0	8	0	0
MAGI1	28	17	0	0	4	1	0	0
MBD6	17	13	0	0	3	0	0	0
MESDC2	20	2	0	0	3	0	0	0
SLC12A2	18	224	1	0	3	13	0	0
MYO18A	30	346	0	1	2	20	0	0
NFATC4	21	27	0	0	3	1	0	0
NKX2-5	6	52	0	0	3	2	0	0
NNT	16	274	0	0	0	18	0	0

PAN2	24	12	0	0	4	0	0	0
USP25	30	25	0	0	5	2	0	0
SLC4A2	14	114	1	0	3	10	0	0
SIPA1L2	20	181	0	0	0	15	0	0
SMARCA4	11	120	0	0	0	8	0	0
SMURF1	10	59	0	0	3	1	0	0
SSH1	39	40	0	0	4	2	0	0
WDR70	27	67	0	0	4	2	0	0
SULF1	26	292	0	0	0	21	0	0
TCF7L1	11	153	0	0	0	11	0	0
TMOD3	15	34	0	0	3	2	0	0
ZC3H3	24	15	0	0	3	1	0	0

CHD, congenital heart disease; DNV, de novo variant; gnomAD, Genome Aggregation Database; LOF, loss of function; PCGC, Pediatric Cardiac Genomics Consortium; SFARI, Simons Foundation for Autism Research Initiative.

References

1. Jin, S. C. et al. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nat. Genet.* **49**, 1593–1601 (2017).
2. Karczewski, K. J. et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* **581**, 434–443 (2020).

Supplementary Table 2 | **Gene ontology terms associated with 132 definitive and candidate congenital heart disease-associated genes**

Category	**Gene class (number)**	**Gene ontology terms**	**Definitive and candidate genes**
Gene regulation	Chromatin modification (21)	Chromosome organization	*CHD4, CHD7, CHD8, COPS6, CTNNB1, HDAC7, INO80, KAT6B, KMT2A, KMT2B, KMT2D, KMT2E, NSD1, RAD54L2, SMARCA4, SMARCC1, TCF7L1, TCF7L2, WDR70, WHSC1, ZMIZ1*
	Transcription factor (11)	DNA-binding transcription factor activity	*ADNP, FOXO1, GATA4, NFATC4, NKX2-5, SMAD2, SMAD5, SOX13, TBX18, TBX5, TCF12*
	mRNA processing (7)	mRNA processing, translation factor activity, RNA binding, mRNA binding	*CDK13, CLUH, DYRK1A, EIF6, PAN2, RBFOX2, ZC3H3*
	DNA binding (3)	DNA binding	*CLSPN, MBD6, MYO18A*
Signalling	Extracellular matrix (12)	Extracellular matrix	*COL11A1, COL1A2, COL27A1, COL3A1, COL4A3BP, COL6A1, FBLN1, FBN1, FBN2, LAMA5, LTBP4, SULF1*
	Cilia (1)	Cilium	*AMBRA1*
	Cytoskeleton (18)	Cytoskeleton organization, cytoskeleton	*ABCA2, ANK3, ATP2C1, BCAR1, CTDP1, CYFIP1, ENAH, ITGB1, KIF13A, LRP1, MACF1, NF1, SPTBN1, SSH1, SSH2, TMOD3, TNS1, TSC1*
	Signal transduction (32)	Signal transduction	*AKAP6, ARHGAP29, CACNA1C, DGKD, FLT4, GNA12, ITPR1, JAG1, JAG2, KANK2, KDR, LRP5, MAGI1, MAPK8IP3, MEGF8, MESDC2, NOTCH1, PIAS3, PIK3C2B, PLXND1, PTPN11, PTPRF, RYR2, SIPA1L2, SLC12A2, SLIT3, SMURF1, SOS1, SOS2, TAB2, TENM4, UBAP2*
Other	Ion binding, transmembrane transport, oxidoreductase activity (27)	None	*AGPS, ANKHD1, ANKRD11, ATG2A, ATL2, ATP13A1, ATP2B1, ATP8B2, CACNA1H, CAD, CLCN7, FAM135A, FAM160A2, FARSB, FRYL, GANAB, GOT2, HERC1, KCNH2, NNT, PLEKHO1, QSER1, RYR3, SCN5A, SLC4A2, TMTC2, USP25*