A Reassessment of Copy Number Variations in Congenital Heart Defects

Picturing the whole genome

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Supplemental Table S2. Heart defects in the study cohort

	All patients		SCHD patients		ICHD patients	
All types of congenital heart defects	**270**	**100%**	**87**	**32.2%**	**183**	**67.8%**
Ventricular septal defect	51	18.9%	27	31.0%	24	13.1%
Aortic coarctation and arch abnormality	42	15.6%	11	12.6%	31	16.9%
Tetralogy of Fallot	39	14.4%	10	11.5%	29	15.8%
Transposition of the great arteries	37	13.7%	0	0%	37	20.2%
Functionally univentricular heart	27	10.0%	10	11.5%	17	9.3%
Atrial septal defect	14	5.2%	8	9.2%	6	3.3%
Left ventricular outflow tract abnormality	11	4.1%	4	4.6%	7	3.8%
Double outlet right ventricle	11	4.1%	2	2.3%	9	4.9%
Right ventricular outflow tract abnormality	8	3.0%	2	2.3%	6	3.3%
Atrioventricular septal defect	7	2.6%	2	2.3%	5	2.7%
Isomerism	6	2.2%	6	6.9%	0	0%
Pulmonary vein abnormality	5	1.9%	1	1.1%	4	2.2%
Ebstein malformation	4	1.5%	3	3.4%	1	0.5%
Truncus arteriosus	4	1.5%	1	1.1%	3	1.6%
Pulmonary atresia intact septum	2	0.7%	0	0%	2	1.1%
Congenital corrected transposition	1	0.4%	0	0%	1	0.5%
Cor triatriatum	1	0.4%	0	0%	1	0.5%

Supplemental Table S3. Pathogenic CNVs in the study cohort

Pathogenic copy number variants in individuals with SCHD	Type of congenital heart defect
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – deletion (MIM 188400)	Atrial septal defect
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – deletion (MIM 188400)	Ventricular septal defect
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – deletion (MIM 188400)	Ventricular septal defect
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – deletion (MIM 188400)	Tetralogy of Fallot
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – deletion (MIM 188400)	Tetralogy of Fallot
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – deletion (MIM 188400)	Tetralogy of Fallot
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – deletion (MIM 188400)	Functionally univentricular heart
22q11.2 recurrent region (central, B/C-D) (ISCA-37516) - deletion	Ventricular septal defect
22q11.2 recurrent region (distal type I, D-E/F) (ISCA-37397) – deletion (MIM 611867)	Aortic coarctation
22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (ISCA-37446) – duplication (MIM 608363)	Ventricular septal defect
7q11.23 recurrent (Williams-Beuren syndrome) region (ISCA-37392) – deletion (MIM 194050)	LVOT abnormality
7q11.23 recurrent (Williams-Beuren syndrome) region (ISCA-37392) – deletion (MIM 194050)	LVOT abnormality
7q11.23 recurrent (Williams-Beuren syndrome) region (ISCA-37392) – deletion (MIM 194050)	LVOT abnormality
7q11.23 recurrent (Williams-Beuren syndrome) region (ISCA-37392) – deletion (MIM 194050)	LVOT abnormality
17q21.3 recurrent region (ISCA-37420) – deletion (MIM 610443)	Atrial septal defect
17p11.2 recurrent (SMS/PLS) region (ISCA-37418) - duplication (MIM 610883)	Functionally univentricular heart
4p16.3 terminal (Wolf Hirschhorn syndrome) region (ISCA-37429) – deletion (MIM 194190)	Atrial septal defect

All CNV-US were mapped to reference genome GRCh37 (hg19)

Supplemental Table S4. CNV-US in the study cohort and subgroups

CNV-US	Subgroup	CNV-US	Subgroup
chr1:17241750-17393588dup	ICHD	chr10:88004601-88065186del	SCHD
chr1:45993451-46050273dup	SCHD	chr10:128458646-128823028del	ICHD
chr1:86488537-87236743dup	SCHD	chr11:33192074-33421736dup	SCHD
chr1:92464376-92606671dup	SCHD	chr11:40618648-40742235del	ICHD
chr1:100110001-100545000dup	ICHD	chr11:55050707-56931087dup	ICHD
chr1:145388355-145832995dup	SCHD	chr11:76670039-76777036dup	ICHD
chr1:165562486-166482444dup	ICHD	chr11:106050001-106260000del	ICHD
chr1:175448847-175726807dup	ICHD	chr12:21547800-21644501dup	ICHD
chr1:247740001-248565000dup	ICHD	**chr12:77616529-79689969del**	ICHD
chr2:14701626-15159618dup	SCHD	chr12:87900001-88080000dup	SCHD
chr2:44507915-44579904del	ICHD	chr13:61711359-62962420dup	SCHD
chr2:49545371-49629804del	ICHD	chr13:92966240-93046389dup	ICHD
chr2:60998688-61093639dup	ICHD	**chr13:114843912-115105238del**	ICHD
chr2:68685528-68915775dup	ICHD	**chr14:21902947-21909605dup**	ICHD
chr2:70439112-70488413del	ICHD	chr14:27650380-27799841del	SCHD
chr2:86447244-86537744dup	ICHD	chr14:35110121-35167580del	ICHD
chr2:88257759-89016165trip	ICHD	**chr14:41234593-41536386del**	ICHD
chr2:101521192-101659259dup	SCHD	**chr14:53326238-54313294dup**	ICHD
chr2:106878050-108441524dup	SCHD	**chr15:22755001-23085000del**	ICHD
chr2:112650001-112740000del	ICHD	**chr15:22765628-23208842dup**	ICHD
chr2:149079154-149313760dup	SCHD	**chr15:22765628-23167699del**	ICHD
chr2:186857026-187327501del	ICHD	**chr15:22765628-23208842dup**	ICHD
chr2:236075658-236458404trip	ICHD	chr15:24005491-24470088dup	ICHD
chr3:4337407-4357235del	SCHD	**chr15:29872834-30019045dup**	ICHD
chr3:30882231-30974326dup	ICHD	chr15:51739647-51791693trip	ICHD
chr3:60431642-60690267dup	SCHD	**chr15:95701920-97765966dup**	SCHD
chr3:108850038-108948062dup	SCHD	chr16:258392-462341dup	SCHD
chr3:169521817-170020490dup	ICHD	**chr16:5030678-5546770del**	ICHD
chr3:192385902-192488655dup	SCHD	chr16:7830001-8055000dup	ICHD
chr4:120033531-120113986dup	ICHD	**chr16:14968855-16292181del**	ICHD
chr4:131146744-132525235dup	ICHD	**chr16:29656684-30197290del**	ICHD
chr4:135455435-137460949dup	ICHD	**chr16:86409444-86509316del**	ICHD
chr4:135700662-135829279dup	SCHD	**chr17:9981738-10410275dup**	SCHD
chr4:187171324-187294087dup	ICHD	**chr17:15257416-15482813dup**	SCHD
chr4:187333416-187518707dup	ICHD	**chr17:18148172-18662098dup**	SCHD
chr5:1005001-1290000dup	SCHD	chr17:58372095-58588996dup	ICHD
chr5:68595931-68635696trip	SCHD	chr18:23904986-23996644dup	SCHD
chr5:122233184-122489348dup	ICHD	**chr18:39451438-39554147dup**	ICHD
chr5:151095022-151482286dup	ICHD	chr18:50883661-51084413dup	SCHD
chr5:180119112-180218463dup	ICHD	chr18:65727205-66532484dup	SCHD
chr6:4269700-4465244del	ICHD	chr18:75104351-75387552dup	ICHD
chr6:17670001-17805000dup	SCHD	chr18:77733413-77762403dup	ICHD

chr6:86004058-86204900dup	SCHD	**chr19:15850613-15978604dup**	SCHD
chr6:90315001-90510000dup	ICHD	chr19:23778647-23950181del	ICHD
chr6:91188432-91351703dup	SCHD	**chr19:58980970-59092515del** mos	SCHD
chr6:140957317-141785879dup	ICHD	**chr20:67778-439387dup**	ICHD
chr6:162130733-162799322del	SCHD	chr20:9736328-9968799dup	ICHD
chr7:9600001-9780000del	SCHD	chr20:14928568-15182995del	SCHD
chr7:11221210-12462629dup	SCHD	**chr20:32820001-33045000trip**	ICHD
chr7:12300173-12462629del	ICHD	**chr20:47471691-47625126del**	SCHD
chr7:24335739-24416109del	ICHD	**chr21:43014314-48090258del**	ICHD
chr7:40152590-40256612dup	ICHD	**chr21:47591379-47671404dup**	ICHD
chr7:55305001-55440000del	ICHD	chr22:25102007-25247453dup	ICHD
chr7:69330737-69584704del	SCHD	**chrX:61091-437220del**	ICHD *
chr7:81972080-82369067dup	ICHD	chrX:481940-638810dup	ICHD
chr7:133070210-133120414del	ICHD	chrX:908162-1259089trip	ICHD
chr7:151800001-151905000dup	ICHD	chrX:6467006-8131751dup	ICHD *
chr8:62035047-62172054del	ICHD	chrX:6467006-8131751del	SCHD *
chr8:77880001-78240000dup	ICHD	chrX:7515001-8130000dup	ICHD
chr8:140830000-141140000dup	SCHD	chrX:17388654-17417102dup	SCHD *
chr8:142131562-142255482dup	SCHD	chrX:19491688-19601181dup	ICHD
chr9:195001-405000dup	ICHD	chrX:22944987-23031936del	SCHD
chr9:210001-540000dup	ICHD	chrX:83974189-84378746dup	ICHD *
chr9:12515544-13415849del	SCHD	**chrX:130610000-130950000dup**	ICHD
chr9:107409506-107729796dup	ICHD	**chrX:130631863-130960558dup**	ICHD *
chr9:107409509-107769094dup	ICHD	chrX:138183513-138735042dup	ICHD *
chr10:1201103-1273934dup	ICHD	chrX:148886475-149084873dup	ICHD *
chr10:65690000-66491000dup	SCHD	**chrY:61091-819199del**	ICHD
chr10:84054763-84073574del	ICHD	chrY:23730419-24426917del	SCHD

CNV-US potentially related to CHD pathogenesis based on the elements studied are marked in bold.
X-chromosomal CNV-US occurring in females are marked with *.
All CNV-US were mapped to reference genome GRCh37(hg19).

Supplemental Table S5. Candidate CHD protein-coding genes in CNV-US

CNV-US	Protein-coding gene	Interpretation	
Chr1:45993451-46050273dup	*NASP*	Chromatin	-
Chr2:70439112-70488413del	*TIA1*	FGF	-
Chr2:101521192-101659259dup	*NPAS2*	TF	-
Chr7:69330737-69584704del	*AUTS2*	Ras, histone	Potentially linked to mild heart defects[1]
Chr7:151800001-151905000dup	*KMT2C*	Histone	Kleefstra syndrome 2 (MIM 617768) ; candidate CHD gene[2]
Chr13:114843912-115105238del	*CHAMP1*	TF	-
Chr14:21902947-21909605dup	*CHD8*	CHD panel, WNT, chromatin	Interacts with CHD7[3] ; expressed during rat postnatal cardiac development[4]
Chr14:53326238-54313294dup	*FERMT2*	WNT, TGFβ, sarcomere	-
Chr15:22755001-23085000del	*CYFIP1*	Ras	-
Chr15:22765628-23167699del	*CYFIP1*	Ras	-
Chr15:29872834-30019045dup	*TJP1*	Hippo	Role in formation of gap junctions in rat cardiomyocytes[5] ; association of ZO-1 with Cx43 in cardiac myocytes[6] ; Cx43 knockout mice exhibit conotruncal malformations and coronary artery defects[7]
Chr16:14968855-16292181del	*MYH11*	CHD panel	Related to thoracic aortic aneurysm / aortic dissection and PDA[8] ; role in mesenchymal and endothelial cell differentiation, associated with valvulogenesis and endothelial to mesenchymal transition[9]
Chr16:29656684-30197290del	*MAPK3*	BMP, FGF, histone	Linked to cardiac hypertrophy in transgenic mouse[10]
	MAZ	TF	Transcriptional regulator of muscle-specific genes in cardiac myocytes[11]
Chr18:39451438-39554147dup	*PIK3C3*	Cilium	Essential role in regulating autophagy and heart function[12]
Chr19:58980970-59092515del	*TRIM28*	Ras	Regulator of cardiomyocyte differentiation in murine embryonic stem cells[13] ; regulates sprouting angiogenesis in zebrafish[14]
Chr20:32820001-33045000trip	*ITCH*	Notch	-
Chr20:47471691-47625126del	*ARFGEF2*	Ras, cilium	Linked to vascular development in zebrafish[15]
Chr21:43014314-48090258del	*PKNOX1*	TF	PBX-related genes are candidates for CHD[16]
	ZBTB21	TF	Potential role in CHD pathogenesis in Down syndrome[17]

TF = transcription factor ; BMP = bmp signaling pathway ; WNT = wnt signaling pathway ; Notch = notch signaling pathway ; TGFβ = transforming growth factor β receptor signaling pathway ; Hippo = hippo signaling ; FGF = fibroblast growth factor receptor signaling pathway ; Ras = ras protein signal transduction ; Histone = histone modification ; Chromatin = chromatin remodeling.
All CNV-US were mapped to reference genome GRCh37 (hg19).

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Supplemental Table S7. LncRNA genes of interest in CNV-US

CNV-US	lncRNA of interest with TPM 2 (TPM10) in developing human heart
Chr1:86488537-87236743dup	lnc-ODF2L-32, lnc-SELENOF-2
Chr1:145388355-145832995dup	LIX1L-AS1
Chr1:165562486-166482444dup	lnc-TMCO1-1, lnc-UCK2-1
Chr2:88257759-89016165trip	lnc-RPIA-2
Chr2:101521192-101659259dup	lnc-TBC1D8-7
Chr2:106878050-108441524dup	ST6GAL2-IT1
Chr2:186857026-187327501del	LINC01473
Chr3:169521817-170020490dup	SEC62-AS1
Chr5:1005001—1290000dup	**lnc-SLC12A7-5**
Chr5:122233184-122489348dup	lnc-PPIC-1
Chr5:151095022-151482286dup	lnc-ATOX1-1, lnc-G3BP1-1, lnc-GLRA1-1
Chr6:4269700-4465244del	**lnc-ECI2-2**
Chr7:151800001-151905000dup	lnc-KMT2C-1
Chr8:142131562-142255482dup	lnc-SLC45A4-2, lnc-SLC45A4-3
Chr9:210001-540000dup	lnc-DOCK8-1
Chr9:12515544-13415849del	lnc-NFIB-1
Chr9:107409506-107729796dup	lnc-NIPSNAP3B-1
Chr9:107409509-107769094dup	lnc-NIPSNAP3B-1
Chr12:77616529-79689969del	lnc-ZDHHC17-20
Chr14:41234593-41536386del	LINC02315
Chr15:22765628-23208842dup	**lnc-NIPA1-2**
Chr15:22765628-23167699del	**lnc-NIPA1-2**
Chr15:22765628-23208842dup	**lnc-NIPA1-2**
Chr15:95701920-97765966dup	LINC01197, LINC02157, lnc-NR2F2-1, lnc-NR2F2-2, lnc-NR2F2-15, lnc-PGPEP1L-60, NR2F2-AS1
Chr16:14968855-16292181del	lnc-ABCC1-1, lnc-C16orf45-1, **lnc-C16orf45-4**
Chr16:29656684-30197290del	lnc-ASPHD1-1, lnc-CDIPT-1, lnc-PPP4C-10, lnc-PPP4C-11
Chr16:86409444-86509316del	FENDRR
Chr17:9981738-10410275dup	lnc-ADPRM-2
Chr17:15257416-15482813dup	lnc-CDRT4-4
Chr17:18148172-18662098dup	lnc-MIEF2-1, **lnc-TBC1D28-1**, lnc-TBC1D28-6
Chr19:15850613-15978604dup	UCA1
Chr20:67778-439387dup	**NRSN2-AS1**
Chr20:32820001-33045000trip	ITCH-IT1, lnc-EIF2S2-4
Chr21:43014314-48090258del	COL18A1-AS1, COL18A1-AS2, DIP2A-IT1, ITGB2-AS1, **LINC00205**, LINC00316, LINC00479, LINC01424, LINC01679, lnc-C2CD2-1, lnc-COL6A1-1, lnc-CRYAA-2, **lnc-FAM207A-2**, lnc-FAM207A-10, **lnc-LRRC3-5**, **lnc-LSS-1**, lnc-PTTG1IP-7, lnc-RSPH1-1, **lnc-SLC19A1-7**, lnc-WDR4-1, lnc-WDR4-2, lnc-WDR4-4, lnc-YBEY-5, LRRC3-DT, PICSAR, TSPEAR-AS1, TSPEAR-AS2
Chr21:47591379-47671404dup	lnc-YBEY-5
ChrX:61091-437220del	**LINC00685**, lnc-PLCXD1-5, lnc-PLCXD1-6
ChrX:130610000-130950000dup	FIRRE
ChrX:130631863-130960558dup *	FIRRE

lncRNA genes expressed in developing human heart tissue reaching TPM10 are marked in bold.
X-chromosomal CNV-US occurring in females are marked with *.
CNV-US were mapped to reference genome GRCh37 (hg19).