SUPPLEMENTAL MATERIAL

H. Lahm et al. Congenital heart disease risk loci identified by genome-wide association study in European patients

Supplemental Table 1. Possible causal variants in *MACROD2* and *GOSR2* gene loci

rs ID	Z score	PIP CAVIARBF	gene	cyto band	CHD subgroup
rs17677363	-5.3322	0.9999244	*GOSR2*	17q21.32	anomalies of thoracic arteries and veins
rs11874	5.40319	0.991485			
rs76774446	5.32994	0.9874922			
rs149890280	-6.37711	1	*MACROD2*	20q12.1	transposition of the great arteries
rs150246290	6.42989	1			
rs149467721	6.05662	0.5554932			
rs77094733	6.02248	0.4444939			

PIP: posterior inclusion probability, CAVIARBF: CAVIAR Bayes factor, CHD: congenital heart disease

Supplemental Table 2. Analysis of loci 12q24 and 13q32 in patients with right heart lesions

								DHM collective						meta-analysis (DHM + UK collective)				
	ChrPosID hg19	Strand	Chr	Pos	N [1]	Effect_allele	Other_allele	EAF [2]	Info [3]	BETA [4]	OR	SE [5]	*P*	meta_Effect	meta_StdErr	meta_*P*-value	Direction	Subgroup
rs7982677 (13q32)	13:92988323	+	13	92988323	3999	A	C	0,270024	0,989605	0,00695663	1.006981	0.0811229	0.931689	-0.0477	0.0522	0.3607	+-	septal defects
	13:92988323	+	13	92988323	3717	A	C	0,268711	0,989537	-0,133944	0.874639	0.133799	0.311697	-0.1339	0.1338	0.3168	--	ASDII
	13:92988323	+	13	92988323	5049	A	C	0,27035	0,989636	-0,00429724	0.995712	0.0507463	0.932507	0.0402	0.0306	0.1896	-+	all CHD
	13:92988323	+	13	92988323	3786	A	C	0,268119	0,989515	-0,146722	0.863534	0.112598	0.187516	-0.097	0.0702	0.1671	--	ASD
	13:92988323	+	13	92988323	3759	A	C	0,269706	0,989828	-0,0193519	0.980834	0.115665	0.866948	-0.0528	0.075	0.4814	--	anomalies of thoracic arteries and veins
	13:92988323	+	13	92988323	3700	A	C	0,27129	0,989499	0,127057	1.135482	0.132544	0.341485	0.0944	0.0785	0.2295	++	TGA
	13:92988323	+	13	92988323	3692	A	C	0,269495	0,989387	-0,0969594	0.907593	0.143157	0.495098	0.0123	0.0898	0.8908	-+	left heart lesions
	13:92988323	+	13	92988323	3824	A	C	0,272319	0,989156	0,174637		0.0997423	0.0828563	0.2123	0.047	$6.29x10^{-6}$	++	right heart lesions
rs11065987 (12q24)	12:112072424	+	12	112072424	3999	G	A	0,466492	1	0,055953	1.057548	0.0729835	0.443403	0.0084	0.0473	0.859	-+	septal defects
	12:112072424	+	12	112072424	3717	G	A	0,465967	1	0,114226	1.121005	0.115896	0.324546	-0.1142	0.1159	0.3243	--	ASDII
	12:112072424	+	12	112072424	5049	G	A	0,46534	1	0,00368067	1.003687	0.0453026	0.935247	-0.0281	0.0281	0.3163	--	all CHD
	12:112072424	+	12	112072424	3786	G	A	0,465927	1	0,0776794	1.080776	0.0975685	0.42613	0.0363	0.0629	0.564	-+	ASD
	12:112072424	+	12	112072424	3759	G	A	0,462623	1	-0,166374	0.846729	0.104174	0.108993	0.1428	0.0683	0.03646	++	anomalies of thoracic arteries and veins
	12:112072424	+	12	112072424	3700	G	A	0,464595	1	-0,0213772	0.978850	0.121644	0.860464	0.0905	0.0736	0.219	++	TGA
	12:112072424	+	12	112072424	3692	G	A	0,462893	1	-0,220078	0.802456	0.127457	0.0825705	0.0746	0.0825	0.3658	+-	left heart lesions
	12:112072424	+	12	112072424	3824	G	A	0,46705	1	0,119852	1.127330	0.0909645	0.187722	-0.2114	0.0443	$1.79x10^{-6}$	--	right heart lesions

[1]: sample size, [2]: effector allele frequency, [3]: info score, [4]: β=ln OR, [5]: standard error of β

Supplemental Table 3. Possible influence of rs11784 on expression of *GOSR2* and *WNT3*

rsid	chr	pos_hg19	cyto band	gene	type	gene/protein consequences	Ensembl Regulatory Build	roadmap enhancer(tissue)	GeneHancer Interactions	geneAssociationMethods	GeneHancer (GH) Identifier	Gene_By_topologically association domains	SV	SV_PMID
rs35437121	2	131769448	2q21.1	ARHGEF4	protein_coding	intronic(ARHGEF4),coding(ARHGEF4)			ARHGEF4	eQTLs,Distance	GH02J131039,GH02J131036	GPR148,AMER3,ARHGEF4,FAM168B,PLEKHB2, POTEE,CYP4F31P,MZT2A,TUBA3D	gain	25217958
rs114503684	3	141834969	3q23	TFDP2	protein_coding	intronic(TFDP2),non-coding intronic(TFDP2)	Promoter Flanking Region					GK5,TFDP2,XRN1	gain	19592680;21841781;21293372; 25217958;25503493;21179565
rs2046060	3	187852486	3q27.3	RP11-430L16.1	lincRNA	non-coding intronic(RP11-430L16.1)			LPP	C-HiC,eRNA_co-expression,eQTLs	GH03J187735,GH03J188081	LPP,AC022498.1,TPRG1	gain	17911159
rs187369228	3	189802439	3q28	LEPREL1	protein_coding	intronic(LEPREL1)			P3H2	eQTLs,C-HiC,Distance,eRNA_co-expression	GH03J189961,GH03J189983, GH03J189995,GH03J189999, GH03J190002,GH03J190010, GH03J190016,GH03J190024, GH03J190031,GH03J190033, GH03J190036,GH03J190040, GH03J190048,GH03J190053, GH03J190055,GH03J190062, GH03J190072,GH03J190075	CLDN1,CLDN16,TMEM207,LEPREL1		
rs870142	4	4648047	4p16.2	STX18-AS1	antisense	non-coding intronic(STX18-AS1)						TMEM128,LYAR,ZBTB49,NSG1,STX18,MSX1		
rs185531658	5	113136521	5q22.3	YTHDC2	protein_coding	upstream						KCNN2,TRIM36,PGGT1B,CCDC112	loss	25217958
rs146300195	5	128326845	5q23.3	SLC27A6	protein_coding	intronic(SLC27A6)			SLC27A6	eQTLs,Distance	GH05J128965	FBN2,SLC27A6,ISOC1,ADAMTS19,KIAA1024L		
rs117527287	6	85729959	6q14.3	RP3-435K13.1	pseudogene	upstream						TBX18,NT5E,SNX14		
rs148563140	8	81475406	8q21.13	RPSAP47	pseudogene	upstream						ZBTB10		
rs11065987	12	112072424	12q24.12	BRAP	protein_coding	downstream			ALDH2,ADAM1A,ATXN2	eQTLs,eRNA_co-expression,TF_co-expression,Distance	GH12J111396,GH12J111402, GH12J111424,GH12J111466, GH12J112417			
rs7982677	13	92988323	13q31.3	GPC5	protein_coding	intronic(GPC5)						GPC6,DCT,GPC5,TGDS	gain	25217958
rs138741144	17	32286564	17q12	ASIC2	protein_coding	intronic(ASIC2)		H3K9me3(Right Atrium)	ASIC2	C-HiC,Distance	GH17J033905,GH17J033906, GH17J033908,GH17J033928, GH17J033930	AC005549.3,CCL2,CCL7,CCL11,CCL8,CCL13, CCL1,ASIC2	gain	25217958
rs11874	17	45017193	17q21.32	GOSR2,RP11-156P1.2	protein_coding	intronic(GOSR2),intronic(RP11-156P1.2),3downstream(GOSR2),3utr(GOSR2)		H3K36me3(Left Ventricle)	KANSL1,CDC27,**GOSR2**	eQTLs,TF_co-expression,C-HiC,Distance	GH17J047098,GH17J046922, GH17J047274,GH17J046942, GH17J046940	**WNT3**,WNT9B,GOSR2,RP11-156P1.2,RPRML, CDC27,MYL4,ITGB3,EFCAB13,NPEPPS,NSF		
rs72917381	18	54546223	18q21.31	WDR7	protein_coding	intronic(WDR7)			WDR7	eRNA_co-expression,Distance	GH18J056889	BOD1L2,ST8SIA3,ONECUT2,FECH,WDR7,NARS		
rs150246290	20	15112880	20p12.1	MACROD2	protein_coding	intronic(MACROD2)						FLRT3,KIF16B,SNRPB2,OTOR,MACROD2	loss	21841781;25118596;25217958; 21293372;19592680;25503493

Supplemental Table 4. List of candidate genes within the LD region of associated loci

gene	chromosome	expression pattern, potential cardiac relevance	reference(s)
Figure 1	**rs185531658**	**all CHD patients**	
MCC (MCC regulator of WNT signaling pathway)	5q22.2	expressed in primitive streak, cardiac mesoderm formation	Teo et al., Stem Cells, 30;631-642 (2012)
TSSK1B (testis specific serine kinase 1B)	5q22.2	expressed in various tissue, overexpressed in heart	
YTHDC2 (YTH domain containing 2)	5q22.2	mRNA widely expressed	
Figure 2A	**rs150246290**	**transposition of the great arteries**	
MACROD2 (MACRO Domain Containing 2)	20p12.1	mRNA widely expressed	see manuscript
MACROD2-AS1 (MACROD2 anti-sense RNA1)	20p12.1	RNA widely expressed (non-protein coding)	
Figure 2B	**rs148563140**	**transposition of the great arteries**	
ZBTB10 (zinc finger and BTB containing domain 10)	8q21.13	mRNA widely expressed	
ZNF704 (zinc finger protein 704)	8q21.13	mRNA widely expressed, protein in fetal and adult heart	
PAG1 (phosphoprotein membrane anchor with glycosphingolipid microdomains 1)	8q21.13	mRNA widely expressed	
Figure 3	**rs11874**	**thoracic arteries and veins**	
ARL17B (ADP ribosylation factor like GTPase 17b)	17q21.31	mRNA widely expressed	
WNT3 (Wnt family member 3)	17q21.31-32	mRNA widely expressed, primitive streak and mesoderm formation	Liu et al., Nature Genet. 22;361-365 (1999); see manuscript
WNT9B (Wnt family member 9B)	17q21.32	mRNA widely expressed including atrioventricular node cells	Alfieri et al., Dev. Biol., 338;127 (2010)
GOSR2 (Golgi SNAP receptor complex member 2)	17q21.32	mRNA widely expressed, coronary artery disease and myocardial infaction	see manuscript
MIR5089 (micro RNA 5089)	17q21.32	RNA weakly expressed in different tissues, but not in heart	
RPRML (reprimo like)	17q21.32	mRNA widely expressed	
CDC27 (cell division cycle 27)	17q21.32	mRNA widely expressed, protein in fetal heart	
MYL4 (myosin light chain 4)	17q21.32	mRNA expressed in fetal heart and cardiomyocytes, atrial fibrillation	Orr et al., Nat. Commun., 12;11303 (2016)
Supplemental Figure 2A	**rs11065987**	**right heart lesions (TOF)**	
CUX2 (Cut Like Homebox 2)	12q24.11-12	mRNA widely expressed	Liu et al., Can J Cardiol., 33; 443-449 (2017); Lin et al., Sci Rep. 7: 40377 (2017); Sinner et al., Circulation, 130;1225-35 (2014)
MIR6760 (micro RNA 6760)	12q24.12	no data on RNA expression	
FAM109A (PH Domain Containing Endocytic Trafficking Adaptor 1)	12q24.12	no data on RNA expression	
SH2B3 (SH2B Adaptor Protein 3)	12q24.12	mRNA widely expressed, protein in heart	Wang et al., Curr Mol Med., Epub ahead of print; Keefe et al., Hypertension, 73;497-503; Hong et al., Medicine (Baltimore), 97;e13436 (2018)
ATXN2 (Ataxin 2)	12q24.12	mRNA widely expressed, protein in fetal heart	Liu et al., Oncotarget., 8(63); 106976-106988 (2017); Lv et al., J Mol Cell Cardiol., 112;1-7 (2017)
BRAP (BRCA1 Associated Protein)	12q24.12	mRNA widely expressed	Volland et al., Cardiovasc Res. Epub ahead of print

gene	chromosome	expression pattern, potential cardiac relevance	reference(s)
			(2019); Nozynski et al., Transplant Proc., 48;1746-50 (2016)
ACAD10 (Acyl-CoA Dehydrogenase Family Member 10)	12q24.12	mRNA widely expressed, protein in heart and fetal heart	
ALDH2 (Aldehyde Dehydrogenase 2 Family Member)	12q24.12	mRNA widely expressed, protein widely expressed and in heart and fetal heart	Chen et al., Adv Exp Med Biol., 1193; 53-67 (2019)
ADAM1A (ADAM Metallopeptidase Domain 1A (Pseudogene))	12q24.12-13	mRNA widely expressed	
MAPKAPK5 (MAPK Activated Protein Kinase 5)	12q24.12-13	mRNA widely expressed, protein in heart	Nawaito et al., Am J Physiol Heart Circ Physiol., 313;H46-H58 (2017); Dingar et al., Cell Signal, 22;1063-75 (2010)
MIR6761 (micro RNA 6761)	12q24.12	no data on RNA expression	
MAPKAPK5-AS1 (MAPKAPK5 Antisense RNA1)	12q24.12	RNA widely expressed	
TMEM116 (Transmembrane Protein 116)	12q24.13	mRNA widely expressed	
ERP29 (Endoplasmic Reticulum Protein 29)	12q24.13	mRNA widely expressed, protein widely expressed and in heart and fetal heart	Su et al., Pulm. Circ., 5;481-497 (2015)
NAA25 (N(Alpha)-Acetyltransferase 25, NatB Auxiliary Subunit)	12q24.13	mRNA widely expressed, protein in fetal heart	
TRAFD1 (TRAF-Type Zinc Finger Domain Containg 1)	12q24.13	mRNA widely expressed, protein in heart and fetal heart	
MIR3657 (micro RNA 3657)	12q24.13	no data on RNA expression	
Supplemental Figure 2B	**rs7982677**	**right heart lesions (TOF)**	
GPC5-AS2 (GPC5 Antisense RNA 2)	13q31.3	mRNA expressed in heart	
Supplemental Figure 2C	**rs146300195**	**right heart lesions**	
SLC27A6 (solute carrier family 27 member 6)	5q23.3	mRNA widely expressed, heart failure	Auinger et al., Br. J. Nutr., 107;1422-1428 (2012)
ISOC1 (isochorismatase domain containing 1)	5q23.3	mRNA widely expressed	
MIR4633 (micro RNA 4633)	5q23.3	RNA weakly expressed in different tissues, including heart	
MIR4460 (micro RNA 4460)	5q23.3	RNA only detectable in blood and esophagus	
Supplemental Figure 3A	**rs35437121**	**left heart lesions**	
AMER3 (APC membrane recruitment protein 3)	2q21.1	RNA weakly expressed in different tissues, protein in fetal heart and adipocytes	
ARHGEF4 (Rho guanine exchange factor 4)	2q21.1	mRNA widely expressed	
FAM168B (family with sequence similarity 168 member B)	2q21.1	mRNA widely expressed	
PLEKHB2 (pleckstrin homolgy domain containing B2)	2q21.1	mRNA widely expressed	
POTEE (POTE ankyrin domain family member E)	2q21.1	mRNA widely expressed, protein in heart	
LOC440910 (uncharacterized LOC440910)	2q21.1	no data on RNA expression	
WTH3DI (= RAB6D, member ras oncogene family)	2q21.1	no data on mRNA expression	
MZT2A (mitotic spindle organizing protein 2A)	2q21.1	mRNA widely expressed	

gene	chromosome	expression pattern, potential cardiac relevance	reference(s)
NOC2LP2 (NOC2 like nucleolar associated transcriptional repressor pseudogene 2)	2q21.1	pseudogene	
LINC01120 (long intergenic non-protein coding RNA 1120)	2q21.1	ncRNA widely exprressed	
TUBA3D (tubulin alpha 3d)	2q21.1	mRNA widely expressed, cardiac arrrhthmia	Friedman et al., NPJ Genom. Med., 3;9 (2018)
MIR4784 (micro RNA 4784)	2q21.1	RNA weakly expressed in different tissues	
LOC150776 (sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3))	2q21.1	pseudogene	
Supplemental Figure 3B	**rs114503684**	**left heart lesions**	
LOC646730 (LINC02618)	3q23	no data on mRNA expression	
RNF7 (ring finger protein 7)	3q23	mRNA widely expressed	
GRK7 (G protein coupled receptor kinase 7)	3q23	mRNA widely expressed	
ATP1B3 (ATPase Na+/K+ transporting subunit beta 3)	3q23	mRNA widely expressed	
***LOC646730* (LINC02618)**	3q23	no data on mRNA expression	
TFDP2 (transcription factor Dp-2)	3q23	mRNA widely expressed	
GK5 (glycerol kinase 5)	3q23	mRNA widely expressed	
Supplemental Figure 3C	**rs2046060**	**left heart lesions**	
LPP-AS2 (LPP antsense RNA 2)	3q27.3	RNA widely expressed	
FLJ42393 (uncharacterized LOC401105)	3q27.3	ncRNA widely exprressed	
LPP (LIM domain containing preferred translocation partner in lipoma)	3q27.3-q28	mRNA widely expressed	
Supplemental Figure 4A	**rs185531658**	**septal defects**	
see above (Figure 1)			
Supplemental Figure 4B	**rs138741144**	**septal defects**	
ASIC2 (acid sensing ion channel subunit 2)	17q11.2-q12	mRNA widely expressed, protein in heart	
AA06 (uncharacterized LOC100506677)	17q12	pseudogene	
Supplemental Figure 5	**rs870142**	**ASD**	
STX18-AS1 (STX18 anti-sense RNA 1 (head to head))	4p16.2	ncRNA widely exprressed	
SNORD162 (small nucleolar RNA, C/D box 162)	4p16.2	no data on RNA expression	
Supplemental Figure 6A	**rs72917381**	**ASDII**	
TXNL1 (thioredoxin like 1)	18q21.31	mRNA widely expressed, lower expression in RV	Su et al., Pulm. Circ., 5;481-497 (2015)
WDR7 (WD repeat domain 7)	18q21.31	mRNA widely expressed	
Supplemental Figure 6B	**rs187369228**	**ASDII**	
TP63 (tumor protein 63)	3q28	mRNA widely expressed, arrhthmogenic cardiomyopathy	Poloni et al., Heart Rhythm, 16;773-780 (2019)
MIR944 (micro RNA 944)	3q28	RNA weakly expressed in skeletal muscle, esophagus and skin	
LEPREL1 (=*P3H2*, proloy 3 hydroxylase 2)	3q28	protein expressed in heart	
Supplemental Figure 7	**rs117527287**	**thoracic arteries and veins**	
TBX18-AS1 (TBX18 antisense RNA 1)	6q14.3	no data on RNA expression	
TBX18 (T-box 18)	6q14.3	mRNA widely expressed, protein in heart and lung, cardiac development	Kapoor et al., Nat. Biotechnol., 31;54-62 (2013)
LOC101928820 (long intergenic non-protein coding	6q14.3	no data on RNA expression	

gene	chromosome	expression pattern, potential cardiac relevance	reference(s)
RNA 2535)			
NT5E (5' nucleotidase ecto)	6q14.3	mRNA widely expressed, calcification of arteries	Hellman et al., Medicine (Baltimore), 98;e15065 (2019)
SNX14 (sorting nexin 14)	6q14.3	mRNA widely expressed	

Supplemental Table 5. Gene list for GSEA analysis

CHD population	gene
all	*GRM4*
ASD	*IGSF21*
	LEPREL1
	MAML3
	ADAMTSL1
	RHBDF2
ASDII	*LEPREL1*
	TMTC2
	WDR7
left heart lesions	*ARHGEF4*
	TRAF3IP1
	TFDP2
	LPP
	ZFC3H1
	THAP2
	RP11-293I14.2
	SMCHD1
right heart lesions	*FBN2*
	SLC27A6
	ISOC1
	FLT4
septal defects	*CACNA2D1*
	AKR1C1
thoracic arteries and veins	*INHBA*
	GATA4
	C8orf49
	NEIL2
	FDFT1
	RP11-297N6.4
	CTSB
	WNT9B
	GOSR2
	RP11-156P1.2
	RPRML
	CDC27
	MYL4
TGA	*HS6ST1*
	GABRA6
	GABRA1
	ZNF704
	TMEM74
	GATA3
	DLG2
	MACROD2

red: genes with genome-wide significance. Cutoff value for all genes $p < 0.0005$

Supplemental Table 6. GSEA analysis

Gene set name	# genes	*p* value	FDR *q* value
cell-cell signaling	8	3.41×10^{-7}	2.02×10^{-3}
embryonic organ development	6	1.59×10^{-6}	2.64×10^{-3}
anatomical structure formation involved in morphogenesis	8	1.79×10^{-6}	2.64×10^{-3}
embryonic morphogenesis	6	8.03×10^{-6}	7.83×10^{-3}

Supplemental Table 7. Patients for candidate gene expression analyses

ID	sex	age [1]	genotype [2]	genotyped by	tissue	diagnosis	STS code	gene expression
604	m	5 d	wt	GWAS	aorta	TGA, IVS	83	
687	m	6 d	wt	GWAS	aorta	TGA, IVS	83	
690	f	9 d	wt	GWAS	aorta	TGA, IVS	83	
707	m	9 d	wt	GWAS	aorta	TGA, IVS	83	
726	m	6 d	wt	GWAS	aorta	TGA, IVS	83	
745	m	4 d	wt	GWAS	aorta	TGA, IVS	83	
841	m	7 d	wt	GWAS	aorta	TGA, IVS	83	
937	m	6 d	wt	GWAS	aorta	TGA, IVS	83	
1048	m	6 d	wt	GWAS	aorta	TGA, IVS	83	
1638	m	7 d	wt	GWAS	aorta	TGA, IVS	83	
2594	m	6 d	wt	GWAS	aorta	TGA, VSD	85	
2771	f	8 d	wt	GWAS	aorta	TGA, IVS	83	
2773	m	9 d	wt	GWAS	aorta	TGA, IVS	83	
3234	m	10 d	wt	GWAS	aorta	TGA, VSD	85	
3755	f	9 d	wt	GWAS	aorta	TGA, IVS	83	
3883	m	8 d	wt	GWAS	aorta	TGA, IVS	83	
703	m	7 d	het	GWAS	aorta	TGA, IVS	83	
859	m	9 d	het	GWAS	aorta	TGA, IVS	83	*MACROD2*
1755	m	5 d	het	GWAS	aorta	TGA, IVS	83	
2812	m	6 d	het	GWAS	aorta	TGA, IVS	83	
3898	m	8 d	het [3]	GWAS	aorta	TGA, VSD	85	
605	m	10 d	wt	PCR	aorta	TGA, IVS	83	
1026	f	6 d	wt	PCR	aorta	TGA, IVS	83	
1663	f	18 d	wt	PCR	aorta	TGA, IVS	83	
1665	f	13 d	wt	PCR	aorta	TGA, VSD	85	
1789	m	12 d	wt	PCR	aorta	TGA, IVS	83	
2855	f	9 d	wt	PCR	aorta	TGA, IVS	83	
2982	m	10 d	wt	PCR	aorta	TGA, IVS	83	
3156	m	14 d	wt	PCR	aorta	TGA, IVS	83	
3589	m	6 d	wt	PCR	aorta	TGA, IVS	83	
3624	m	13 d	het	PCR	aorta	TGA, IVS	83	
3789	m	8 d	wt	PCR	aorta	ccTGA	82	
4063	m	30 d	wt	PCR	aorta	TGA, IVS	83	
4114	m	7 d	wt	PCR	aorta	TGA, VSD	85	
4639	m	6 d	wt	PCR	aorta	TGA, VSD	85	
	28m/7f	8 (4-30)						
300	m	12378 d	wt	GWAS	aorta	aortic aneurysm (including pseudoaneurysm)	102	
801	m	78 d	wt	GWAS	aorta	coronary artery anomaly, anomalous pulmonary origin (includes ALCAPA)	159	
821	m	3 d	wt	GWAS	ductus	coarctation of aorta	95	
1949	m	6 d	wt	GWAS	ductus	VSD + aortic arch hypoplasia	168	
2061	f	8 d	wt	GWAS	ductus	interrupted aortic arch	98	*GOSR2, WNT3*
2330	f	32 d	wt	GWAS	ductus	VSD + aortic arch hypoplasia	168	
2405	f	87 d	wt	GWAS	ductus	VSD + aortic arch hypoplasia	168	
2529	f	9673 d	wt	GWAS	aorta	coarctation of aorta	95	
3466	m	7 d	wt	GWAS	ductus	coarctation of aorta	95	
3815	f	8 d	wt	GWAS	ductus	coarctation of aorta	95	
3992	m	120 d	wt	GWAS	ductus	coarctation of aorta	95	
771	m	3 d	het	GWAS	ductus	aortic arch hypoplasia	96	
1308	m	5455 d	het	GWAS	aorta	aortic aneurysm (including pseudoaneurysm)	102	
1461	m	4 d	het	GWAS	ductus	coarctation of aorta	95	

ID	sex	age [1]	genotype [2]	genotyped by	tissue	diagnosis	STS code	gene expression
2329	m	5 d	het	GWAS	ductus	aortic arch hypoplasia	96	
3961	f	4 d	het	GWAS	ductus	coarctation of aorta	95	
867	m	11 d	het	PCR	aorta	coarctation of aorta	95	
2754	m	8 d	wt	PCR	ductus	aortic arch hypoplasia	96	
2993	f	3 d	hom [4]	PCR	ductus	coarctation of aorta	95	*GOSR2, WNT3*
3754	f	7 d	het	PCR	ductus	interrupted aortic arch	98	
4038	f	6 d	het [5]	PCR	aorta	aortic arch hypoplasia	96	
4038	f	6 d	het [5]	PCR	ductus	aortic arch hypoplasia	96	
4180	m	60 d	hom	PCR	aorta	coarctation of aorta	95	
	13m/10f	8 (3-12378)						
27	f	1465 d			right atrium	HLHS	69	
266	f	9 d			right atrium	HLHS	69	
474	f	540 d			right atrium	HLHS	69	
2677	m	19 d			right atrium	HLHS	69	
2684	m	8 d			right atrium	HLHS	69	
3007	f	5 d			right atrium	HLHS	69	
3582	f	10 d			right atrium	HLHS	69	
5347	f	6 d			right atrium	HLHS	69	*ARHGEF4, TFDP2*
	2m/6f	9.5 (5-1465)						
1531	m	6 d			aorta	HLHS	69	
3258	f	6 d			aorta	HLHS	69	
4221	m	7 d			aorta	HLHS	69	
5942	m	8 d			aorta	HLHS	69	
6179	m	7 d			aorta	HLHS	69	
	4m/1f	7 (6-8)						
3526	m	140 d			right atrium	TOF	28	
3951	f	1004 d			right atrium	TOF	28	
4499	f	342 d			right atrium	TOF	28	
4618	m	106 d			right atrium	TOF	28	*SLC27A6*
4758	m	113 d			right atrium	TOF	28	
6122	m	130 d			right atrium	TOF	28	
	4m/2f	135 (106–1004)						
28	f	2272 d			right atrium	ASDII	2	
92	f	4262 d			right atrium	ASDII	2	
98	f	824 d			right atrium	ASDII	2	
332	m	2980 d			right atrium	ASDII	2	
614	f	5183 d			right atrium	ASDII	2	
739	f	1887 d			right atrium	ASDII	2	
2930	f	2600 d			right atrium	ASDII	2	*ASIC2, STX18-AS1, STX18, MSC1, P3H2, WDR7*
3586	f	1069 d			right atrium	ASDII	2	
5321	m	692 d			right atrium	ASDII	2	
6166	f	6 d			right atrium	ASDII	2	
	2m/8f	2079.5 (6–5183)						
5352	m	11 d			aorta	ASDII	2	
5387	f	9 d			aorta	ASDII	2	
5632	m	8 d			aorta	ASDII	2	
5817	m	7 d			aorta	ASDII	2	
5920	m	4 d			aorta	ASDII	2	
5973	m	7 d			aorta	ASDII	2	
	5m/1f	7.5 (4–11)						

[1] at the time of operation, [2] *MACROD2* locus for all four SNPs wt: wild-type, het: heterozygous, [3] only rs149890280 and rs150246290 are heterozygous, [2] *GOSR2* locus for all three SNPs wt: wild-type, het: heterozygous, hom: homozygous, [4]only rs76774446 is homozygous, [5] only rs17677363 is heterozygous. HLHS: hypoplastic left heart syndrome

Supplemental Table 8. Adult control patients for candidate gene expression analyses

ID	sex	age [1]	tissue	type of OP	diagnosis	tested for expression of
A463	m	77 y	aorta	CABG	atherosclerotic heart disease	
A3677	m	76 y	aorta	CABG	atherosclerotic heart disease	
A4613	m	57 y	aorta	CABG	atherosclerotic heart disease	
A4861	f	79 y	aorta	AVR + aorta	aortic insufficiency	
A4872	f	82 y	aorta	AVR + aorta	aortic insufficiency	*GOSR2, MACROD2, WNT3*
A4877	f	67 y	aorta	aorta	aortic aneurysm with dissection	
A4902	m	78 y	aorta	CABG	atherosclerotic heart disease	
A5199	m	71 y	aorta	CABG	atherosclerotic heart disease	
A5356	m	57 y	aorta	CABG	atherosclerotic heart disease	
A5644	m	53 y	aorta	CABG	atherosclerotic heart disease	
	7m/3f	73.5 (53 – 82)				
A3100	m	59	aorta	AVR + aorta	aortic insufficiency	
A3111	m	41	aorta	Aorta	aortic aneurysm	
A345	m	58	aorta	Aorta	aortic insufficiency	
A3562	m	48	aorta	Aorta	aortic insufficiency	
A4472	m	53	aorta	Aorta	aortic insufficiency	
A4989	m	42	aorta	AVR + aorta	aortic insufficiency	
A5072	m	60	aorta	AVR + aorta	aortic insufficiency	
A5283	f	57	aorta	AVR + aorta	aortic insufficiency	
A5851	f	38	aorta	AVR + aorta	combined aortic vitium	
A5892	m	51	aorta	AVR + aorta	aortic stenosis	*ARHGEF4, TFDP2, ASIC2, STX18-AS1, STX18, MSX1, LEPREL1 (=P3H2), WDR7*
A6382	m	52	aorta	AVR + aorta	aortic insufficiency	
A6478	m	64	aorta	AVR + aorta	aortic insufficiency	
A6641	m	49	aorta	AVR + aorta	combined aortic vitium	
A7338	m	53	aorta	AVR + aorta	aortic insufficiency	
A7711	f	64	aorta	AVR + aorta	coronary heart disease (unspecified)	
A7741	f	66	aorta	AVR + aorta	aortic insufficiency	
A7857	m	55	aorta	AVR + aorta	aortic insufficiency	
A8307	m	58	aorta	AVR + aorta	aortic stenosis	
A8454	m	68	aorta	AVR + aorta	aortic insufficiency	
A8684	m	56	aorta	AVR + aorta	aortic insufficiency	
	16m/4f	55.5 (38 – 68)				
A4419	m	51	right atrium	AVR	aortic stenosis	
A4438	f	64	right atrium	AVR	aortic stenosis	
A4885	m	54	right atrium	AVR	aortic stenosis	
A4968	f	55	right atrium	AVR	aortic insufficiency	
A4990	f	54	right atrium	AVR	aortic stenosis	*ARHGEF4, TFDP2, ASIC2, STX18-AS1, STX18, MSX1, LEPREL1 (=P3H2), WDR7*
A5569	f	52	right atrium	AVR	aortic stenosis	
A5629	m	71	right atrium	AVR	aortic stenosis	
A5666	f	59	right atrium	AVR	aortic stenosis	
A5945	m	52	right atrium	AVR	combined aortic vitium	
A6115	m	58	right atrium	AVR	aortic stenosis	
A6587	m	25	right atrium	AVR	aortic insufficiency	
A6603	m	55	right atrium	AVR	aortic stenosis	
	7m/5f	54.5 (25 – 71)				

[1] at the time of operation, CABG: coronary artery bypass graft, AVR: aortic valve replacement

Supplemental Table 9. Candidate gene knockout mouse models

gene	phenotype	reference
Macrod2	increase in intestinal tumorigenicity, no cardiac phenotype	Sakthianandeswaren et al., Cancer Disc., 8:988-1005 (2018); Lo Re et al., Front. Genet., 9:654 (2018)
Slc27a6	--	
Arhgef4	atypical peripheral blood lymphocyte parameters (B cells ↓, granulocytes ↑)	Gerdin. Acta. Ophthalm., 88:925-927 (2010)
Gosr2	homozygous: (male/female) preweaning lethality, complete penetrance, heterozygous (male) abnormal gait	International Mouse Phenotyping Consortium
***Asic2* (*LOC107985038*)**	abnormal blood vessel physiology, decreased vasoconstriction, hypertension	Gannon et al., Am. J. Physiol. Heart Circ. Physiol., 294:H1793-1803 (2008); Lu et al., Neuron, 64:885-897 (2009)
Stx18-AS1	--	
***P3h2* (= *Leprel1*)**	abnormal thrombosis, embryonic lethality during organogenesis (complete penetrance), embryonic lethality (incomplete penetrance)	Pokidysheva et al., Proc. Natl. Acad. Sci. USA, 111:161-166 (2014)
Wdr7	--	

Supplemental Table 10. Cross ethnical validation

rsid	Lin et. al (2015)				EU allele (+)		EU all			EU septal defects			gene	cytoband
	ea	oa	or	*p*	ea	oa	beta	se	*p*	beta	se	*p*		
rs1400558	A	G	1.15	$1.63x10^{-9}$	t	c	0.0096	0.0306	0.7547	0.0042	0.0515	0.9346	EDNRA	4q31.22
rs7863990	T	C	1.34	$3.71x10^{-14}$	t	c	0.0315	0.0333	0.3437	0.0028	0.0564	0.9608	SMARCA2	9p24.2
rs2433752	G	A	0.83	1.04x10-^{10}	a	g	-0.0146	0.0448	0.7452	0.0188	0.0763	0.8055	TBX3–TBX5	12q24.13
rs490514	G	A	1.19	$1.20x10^{-13}$	t	c	-0.0909	0.0422	0.03117	-0.1478	0.0691	0.03248	PTPRT	20q12

EU: DHM+UK meta-analysis, ea: effective allele, oa: other allele, or: odds ratio, *p*: *p* value, EU allele(+): eu allele in positive strand, beta: effective size, se: standard error

Supplemental Table 11. Imputation score for all lead SNPs

rsid	chr	pos_hg19	A1	A2	DHM	UK
rs35437121	2	131769448	T	C	0.854281	0.871797
rs114503684	3	141834969	G	C	0.816128	0.859228
rs2046060	3	187852486	G	A	0.938114	0.979392
rs187369228	3	189802439	G	A	0.761438	0.789581
rs870142	4	4648047	T	C	0.990797	genotyped
rs185531658	5	113136521	C	T	0.826139	0.806271
rs185531658	5	113136521	C	T	0.826139	0.806271
rs146300195	5	128326845	A	G	0.794733	0.880439
rs117527287	6	85729959	A	G	0.737518	0.824389
rs148563140	8	81475406	T	C	0.862684	0.911681
rs11065987	12	112072424	G	A	genotyped	genotyped
rs7982677	13	92988323	A	C	0.989636	genotyped
rs138741144	17	32286564	A	G	0.785646	0.812021
rs11874	17	45017193	A	G	0.990608	0.992829
rs72917381	18	54546223	T	C	0.936111	0.949522
rs150246290	20	15112880	C	G	0.823259	0.873741

Supplemental Table 12. Genomic inflation

	cases before imputation	controls after imputation	genomic inflation λ	
			before imputation	after imputation
all CHD	1,495	3,554	1.032	1.041
septal defects	445	3,554	1.023	1.036
ASD	232	3,554	1.014	1.039
right heart lesions	270	3,554	1.017	1.034
left heart lesions	138	3,554	1.011	1.022
transposition of the great arteries	146	3,554	1.024	1.032
anomalies of thoracic arteries and veins	205	3,554	1.007	1.028

Supplemental Table 13. Power analysis

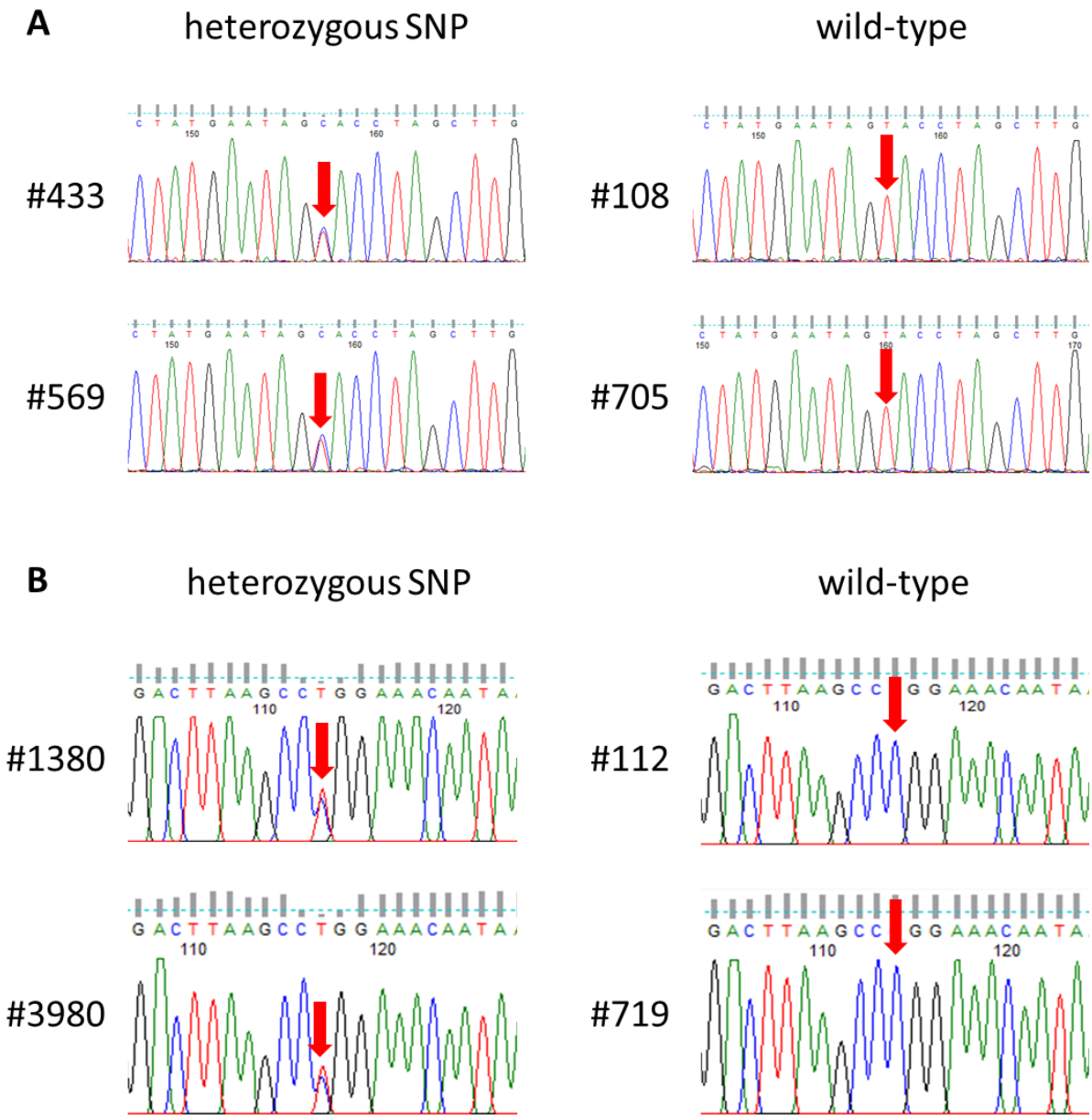
			Power with n cases and 8486 controls, MAF=0.05, prevalance=9/1000, genotyping error=0.001													
	OR	alpha	n=100	n=200	n=300	n=326	n=399	n=453	n=486	n=500	n=1074	n=1296	n=1500	n=3000	n=4034	n=5000
suggestive significance	1.2	$1x10^{-6}$	$2.39x10^{-5}$	$2.07x10^{-4}$	$4.43x10^{-4}$	$7.53x10^{-4}$	0.001243	0.001012	0.001751	0.001714	0.019214	0.031534	0.051429	0.265726	0.428973	0.553271
	1.5	$1x10^{-6}$	$3.70x10^{-3}$	$2.67x10^{-2}$	$1.09x10^{-1}$	$1.55x10^{-1}$	0.231282	0.309943	0.376382	0.399426	0.957304	0.986148	0.996780	1	1	1
	2.0	$1x10^{-6}$	$1.59x10^{-1}$	$7.95x10^{-1}$	$9.69x10^{-1}$	$9.86x10^{-1}$	0.997805	0.999608	0.999859	0.999934	1	1	1	1	1	1
	2.5	$1x10^{-6}$	$8.03x10^{-1}$	$9.98x10^{-1}$	$9.99x10^{0}$	$9.99x10^{0}$	1	1	1	1	1	1	1	1	1	1
	3.0	$1x10^{-6}$	$9.90x10^{-1}$	$9.99x10^{0}$	$9.99x10^{0}$	$9.99x10^{0}$	1	1	1	1	1	1	1	1	1	1
genome-wide significance	1.2	$5x10^{-8}$	$1.86x10^{-6}$	$2.15x10^{-5}$	$5.14x10^{-5}$	$9.46x10^{-5}$	0.000169	0.000133	0.000251	0.000245	0.004270	0.007795	0.014232	0.117917	0.230057	0.335148
	1.5	$5x10^{-8}$	$6.02x10^{-4}$	$6.37x10^{-3}$	$3.68x10^{-2}$	$5.78x10^{-2}$	0.097780	0.145557	0.190877	0.207678	0.877087	0.949684	0.984798	0.999996	1	1
	2.0	$5x10^{-8}$	$5.96x10^{-2}$	$6.04x10^{-1}$	$9.05x10^{-1}$	$9.50x10^{-1}$	0.988961	0.997435	0.998934	0.999451	1	1	1	1	1	1
	2.5	$5x10^{-8}$	$6.15x10^{-1}$	$9.91x10^{-1}$	$9.99x10^{0}$	$9.99x10^{0}$	1	1	1	1	1	1	1	1	1	1
	3.0	$5x10^{-8}$	$9.60x10^{-1}$	$9.99x10^{0}$	$9.99x10^{0}$	$9.99x10^{0}$	1	1	1	1	1	1	1	1	1	1

Supplemental Table 14. Primers used for qRT-PCR analyses and genotyping

primer	sequence	length of amplicon
hu MACROD2_F1100	5' CAG ATG GTG TCA ACA CTG TCA CT 3'	
hu MACROD2_R1190	5' TTT TCA TCC TTT GCA AAA TCT TC 3'	91 bp
hu GOSR2_F71	5' GGC GAC ATG GAT CCC CTG T 3'	
hu GOSR2_R171	5' ATG TGC ACA GAC TGC TTG TCT 3'	101 bp
hu WNT3_F1221	5' CCT GCA AGT AGG GCA CCA 3'	
hu WNT3_R1333	5' TCT GAC GCT GAG GGC TGT 3'	108 bp
hu ARHGEF4_F4853	5' CTG TAA GAA GGA CCT GCT CCG 3'	
hu ARHGEF4_R4936	5' GTC TCT GTC CTT CCC GTC CT 3'	84 bp
hu ASIC2_F1032	5' AGC CAC CTT TCA TCC AAG AG 3'	
hu ASIC2_R1126	5' TGG GGG CAG GTA TGT GAG 3'	95 bp
hu MSX1_F661	5´ GAC CCC GTG GAT GCA GAG 3´	
hu MSX1_R752	5´ GGT TCG TCT TGT GTT TGC GG 3´	92 bp
hu P3H2_F1278	5' GCC TCT CTC CCA TCG AGA AT 3'	
hu P3H2_R1366	5' CAG GGC TTT CAC ATA CTC ACC 3'	89 bp
hu SLC27A6_F1446	5' TTA CAT TTT TAC CTC TGG AAC AAC A 3'	
hu SLC27A6_R1555	5' CAT GAG CAG TAC AAC CAA AAG C 3'	110 bp
hu STX18_F986	5' TCA AGG AAG GCA ACG AAG AC 3'	
hu STX18_R1080	5' GGA GAA GGA GCA CAT CAC G 3'	94 bp
hu STX18-AS1_F455	5' GCC ATC CCT AAG ACA GCA AG 3'	
hu STX18-AS1_R540	5' GCT TAG ACT CTC TGA ATC TCT GCA T 3'	86 bp
hu TFDP2_F960	5' GCT GGT GTC AGA GTT CAC CA 3'	
hu TFDP2_R1041	5' TCT TCG CCT AAT GTT CTT CTG A 3'	82 bp
hu WDR7_F1913	5' TGG AGG CCT TCT GAT GAT TAC 3'	
hu WDR7_R2006	5' TCA CAC AAC GAT CCA ATG C 3'	94 bp
hu OCT4_F268	5' GGG ATG GCG TAC TGT GGG 3'	
hu OCT4_R416	5' GCA CCA GGG GTG ACG GTG 3'	149 bp
hu KLF4_F1441	5' TCT TCG TGC ACC CAC TTG GG 3'	
hu KLF4_R1574	5' CTG CTC AGC ACT TCC TCA AG 3'	134 bp
hu SOX2_F840	5' ACA GCT ACG CGC ACA TGA 3'	
hu SOX2_R908	5' GGT AGC CCA GCT GCT CCT 3'	69 bp
hu CMYC_F1311	5' CAC CAG CAG CGA CTC TGA 3'	
hu CMYC_R1412	5' GAT CCA GAC TCT GAC CTT TTG C 3'	102 bp
hu NANOG_F253	5' TGC TTT GAA GCA TCC GAC TGT 3'	
hu NANOG_R446	5' GGT TGT TTG CCT TTG GGA CTG 3'	194 bp
hu REX1_F292	5' AGT AGT GCT CAC AGT CCA GCA G 3'	
hu REX1_R397	5' TGT GCC CTT CTT GAA GGT TT 3'	106 bp
mu Gosr2_F217	5' TGG AGA TTT TGT CAA GCA AGG A	
mu Gosr2_R306	5' GCA AGT GCT GGA CAT CAT ACT	90 bp
mu Macrod2_F264	5' AAA AGG TGT GGA GAG AGG AGA A	
mu Macrod2_R371	5' TCC ATG ATA GAA TGG TGC TCA	108 bp
mu Msx1_F659	5' GCC CCG AGA AAC TAG ATC G 3'	
mu Msx1_R767	5' TTG GTC TTG TGC TTG CGT AG 3'	109 bp
mu Wnt3_F107	5' CTG CTC GGG CTG CTA CTC	
mu Wnt3_R211	5' GGC CAG AGA TGT GTA CTG CTG	105 bp
SeV_F	5' GGA TCA CTA GGT GAT ATC GAG C 3'	
SeV_R	5' ACC AGA CAA GAG TTT AAG AGA TAT GTA TC 3'	181 bp
hu β-actin_F382	5' CCA ACC GCG AGA AGA TGA 3'	
hu β-actin_R478	5' CCA GAG GCG TAC AGG GAT AG 3'	97 bp
MACROD2_SNP280_F	5' ACA AGG AAC CAC TAA ACA GCT T 3'	
MACROD2_SNP280_R2	5' GAG CTA TTT CAA TTA TGT TAC TC 3'	340 bp
MACROD2_SNP290_F	5' AGT GAA CAA TAA GGT AAA CAG TTA 3'	
MACROD2-SNP290_R2	5' ATC CAT CCA ACC AAC TGG CTA 3'	409 bp
MACROD2_SNP721_F	5' TGT GTG GTT ATG ACA TTT GTC C 3'	
MACROD2_SNP721_R	5' CTG TTC AAT TTG CCC CTG CTA 3'	500 bp
MACROD2_SNP733_F	5' TGA GTG AGT CTC CTG TAA GCA 3'	
MACROD2_SNP733_R	5' CAA CAA TAT GAC TTG CAG GTG T 3'	393 bp
GOSR2_SNP363_F	5' GGT GTC TCA CAG CCT GAC TA 3'	
GOSR2_SNP363_R	5' ATG CTA TTC ACT CAG CCT TGT A 3'	467 bp

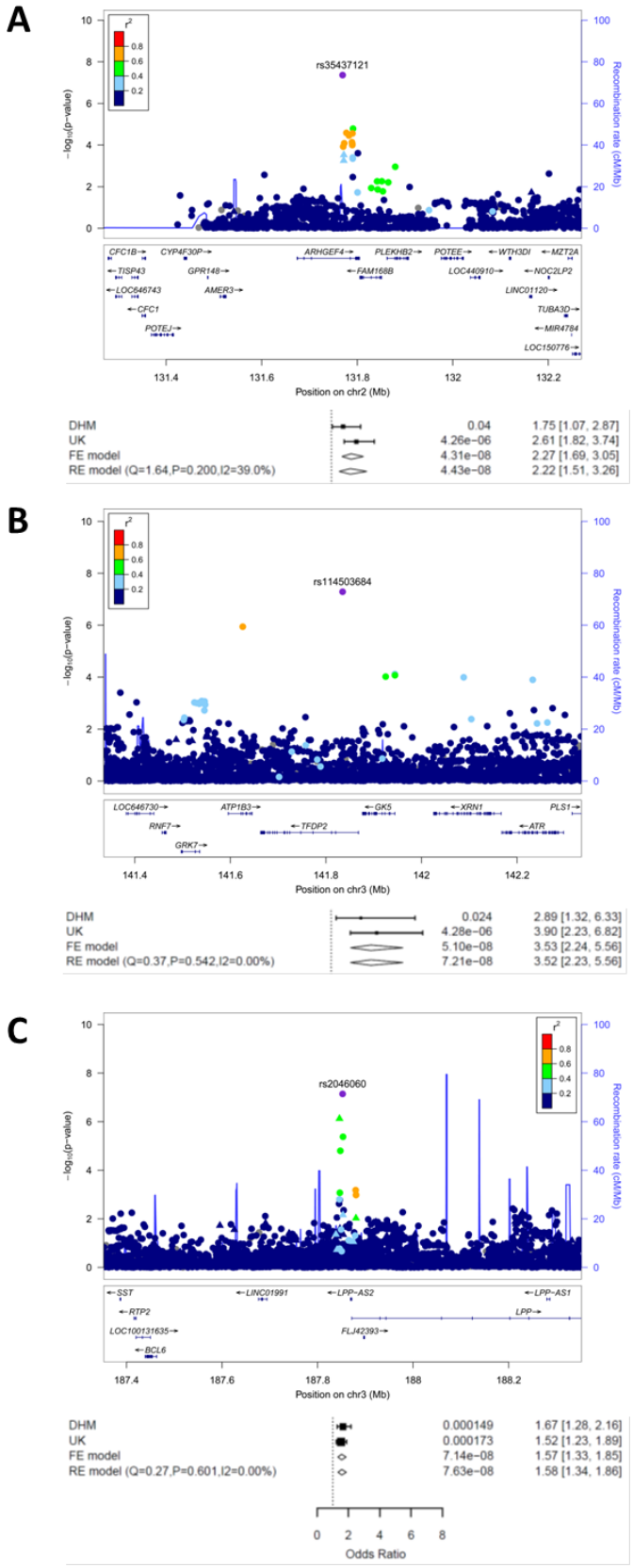
primer	sequence	length of amplicon
GOSR2_SNP446_F	5’ CTA CCT GAG ACT GGA ACA TCA 3’	
GOSR2_SNP446_R	5’ CGA GAT CGG CTT CCG CTT C 3’	365 bp
GOSR2_SNP874_F	5’ CCA GTG TGG GCA GAT CCC A 3’	
GOSR2_SNP874_R	5’ ACA AGA AAC TAA CAG AGC AGG 3’	371 bp
rs185531658_GT_F	5’ TTG TCG GTG GCA CCA TGT TAA 3’	
rs185531658_GT_R	5’ AAA CGA GGA GAG TTG TAG CAC 3’	307 bp
rs117527287_GT_F	5’ ATA TAT GCT GCC AAA CAA GTG G 3’	
rs117527287_GT_R	5’ TCA CCA CAG GCA ACC TAG GT 3’	335 bp

Supplemental Figure 1. Validation of rs185531658 and rs117527287 by Sanger sequencing



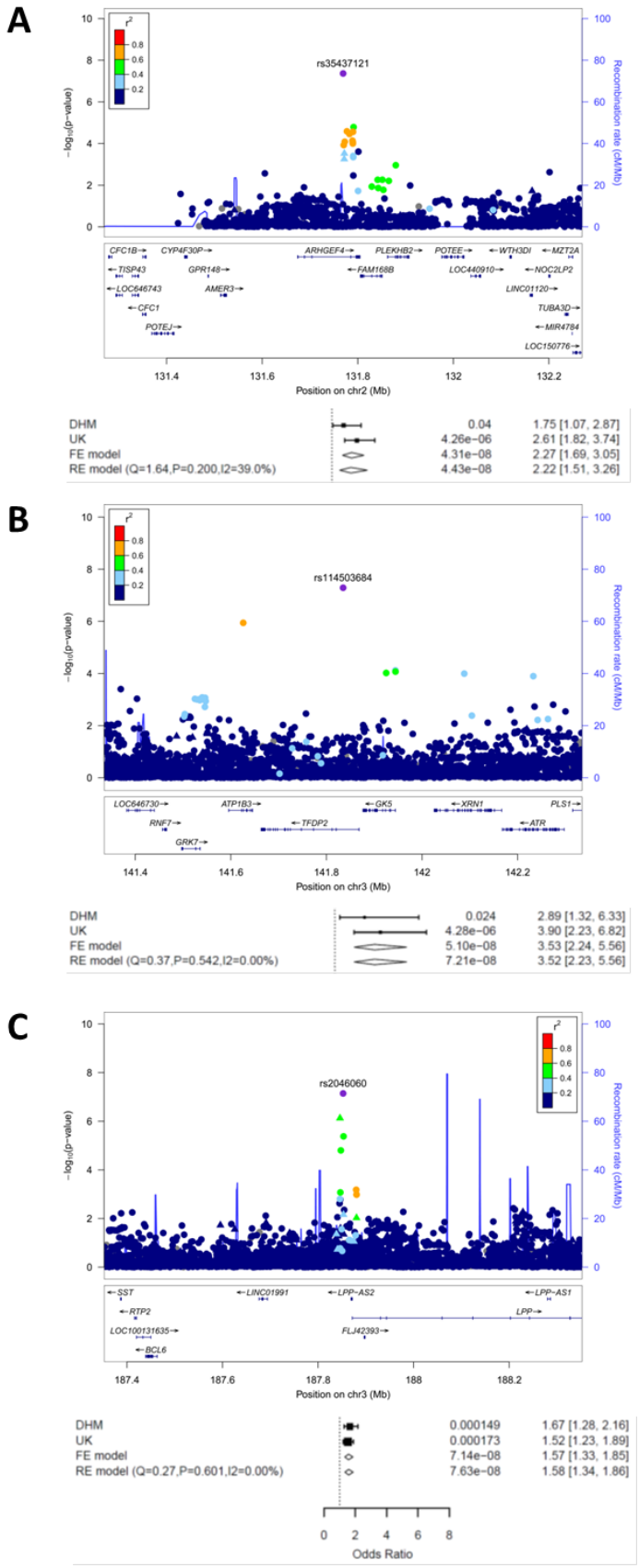
Representative chromatograms of two patients heterozygous for rs185531658 (**A**) or rs117527287 (**B**) and appropriate control patients with wild-type sequence are shown.

Supplemental Figure 2. SNPs associated with right heart lesions



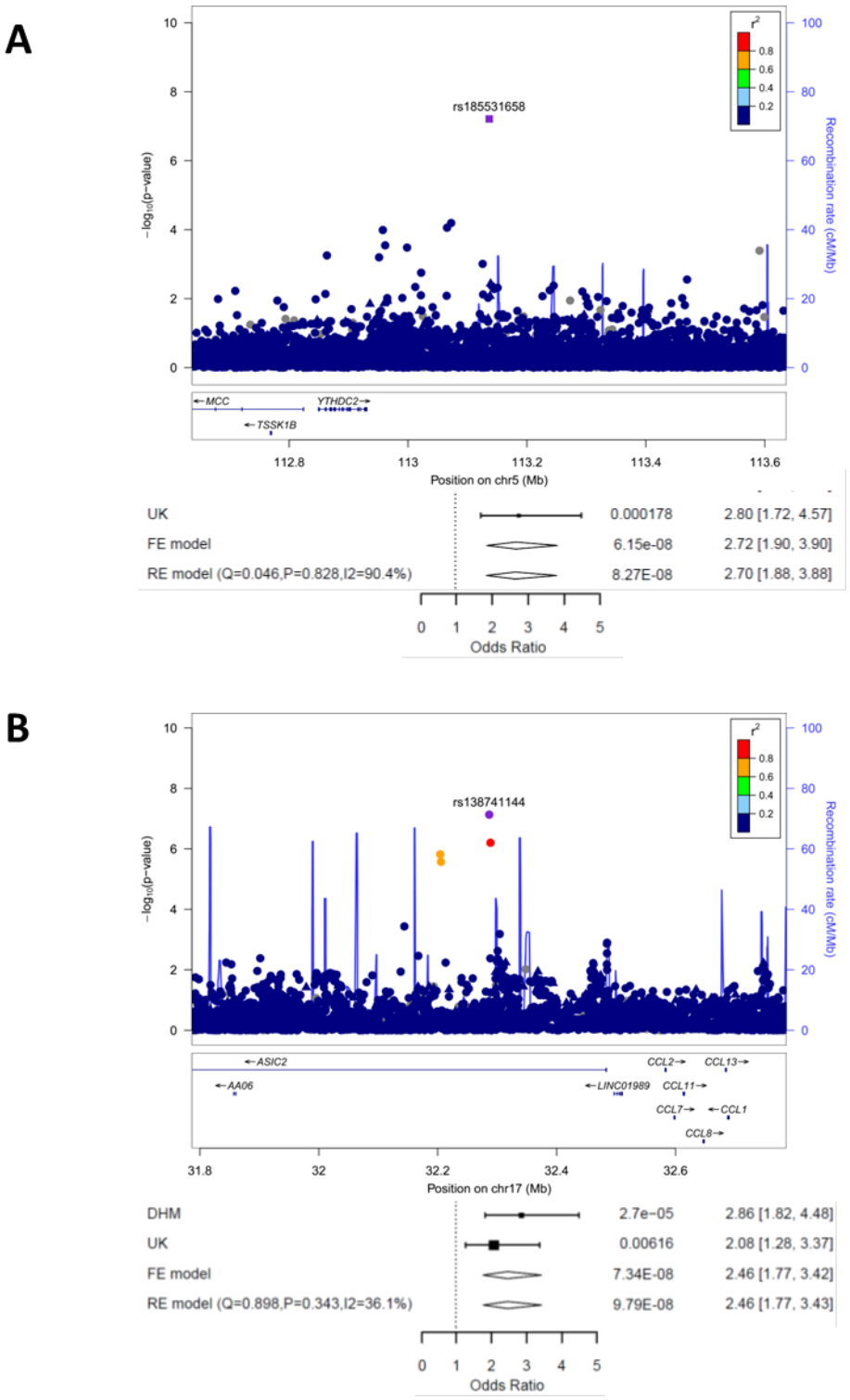
A: LocusZoom plot of the genomic region of rs11065987 on chromosome 12. **B:** LocusZoom plot of the genomic region of rs7982677 on chromosome 13. **C:** LocusZoom plot of the *SLC27A6* region on chromosome 5. The index SNP is indicated as purple diamonds and the other SNPs are color coded depending on their degree of correlation (r^2). Circles represent imputed SNPs, triangles genotyped SNPs. FE: fixed effects, RE: random effects. Patients with right heart lesions, *n*=1,296. -log10 *p* values were determined by association statistics from the GWAS (logistic regression).

Supplemental Figure 3. SNPs associated with left heart lesions



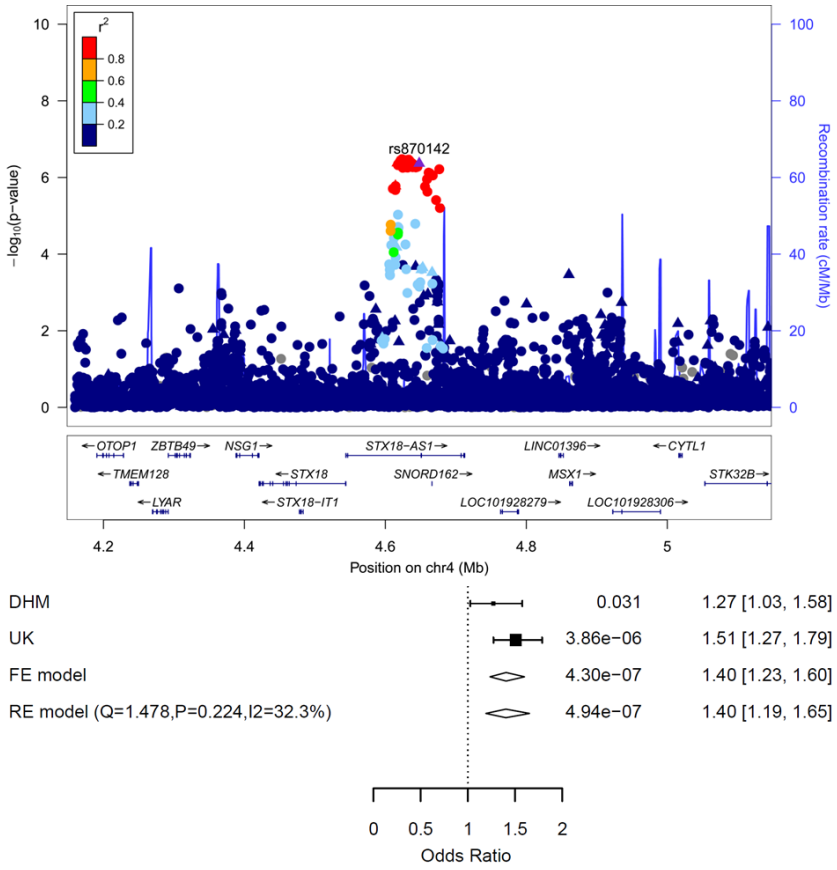
A: LocusZoom plot of the *ARHGEF4* region on chromosome 2. **B:** LocusZoom plot of the *TFDP2* region on chromosome 3. **C:** LocusZoom plot of the *FLJ42993* region on chromosome 3.The index SNPs are indicated as purple diamonds and the other SNPs are color coded depending on their degree of correlation (r^2). Circles represent imputed SNPs, triangles genotyped SNPs. FE: fixed effects, RE: random effects. Patients with left heart lesions, *n*=326. -log10 *p* values were determined by association statistics from the GWAS (logistic regression).

Supplemental Figure 4. SNPs associated with septal defects



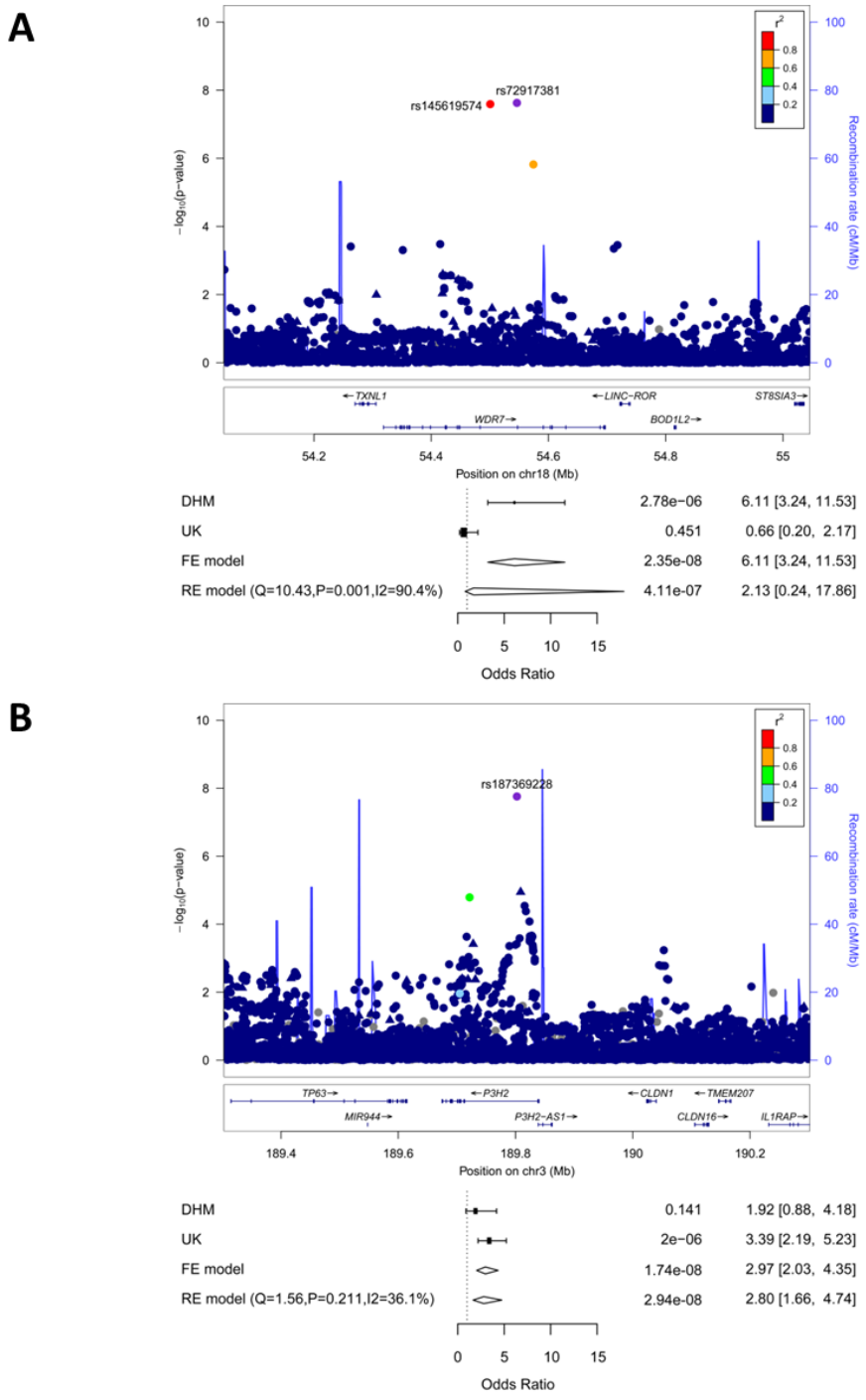
A: LocusZoom plot of the region on chromosome 5. **B:** LocusZoom plot of the region on chromosome 17. The index SNP is indicated as purple diamonds and the other SNPs are color coded depending on their degree of correlation (r^2). Circles represent imputed SNPs, triangles genotyped SNPs. FE: fixed effects, RE: random effects. Patients with septal defects, *n*=1,074. -log10 *p* values were determined by association statistics from the GWAS (logistic regression).

Supplemental Figure 5. SNPs associated with ASD



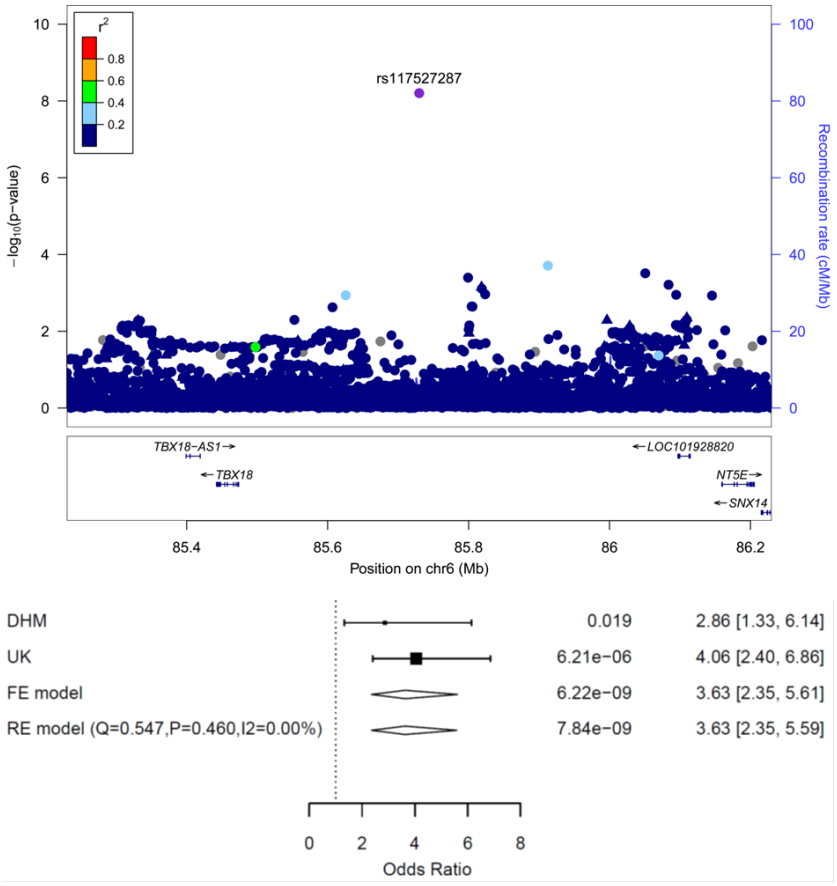
LocusZoom plot of the *SNORD162* region on chromosome 4. The index SNP is indicated as purple diamonds and the other SNPs are color coded depending on their degree of correlation (r^2). Circles represent imputed SNPs, triangles genotyped SNPs. FE: fixed effects, RE: random effects. ASD patients, *n*=572. -log10 *p* values were determined by association statistics from the GWAS (logistic regression).

Supplemental Figure 6. SNPs associated with ASDII



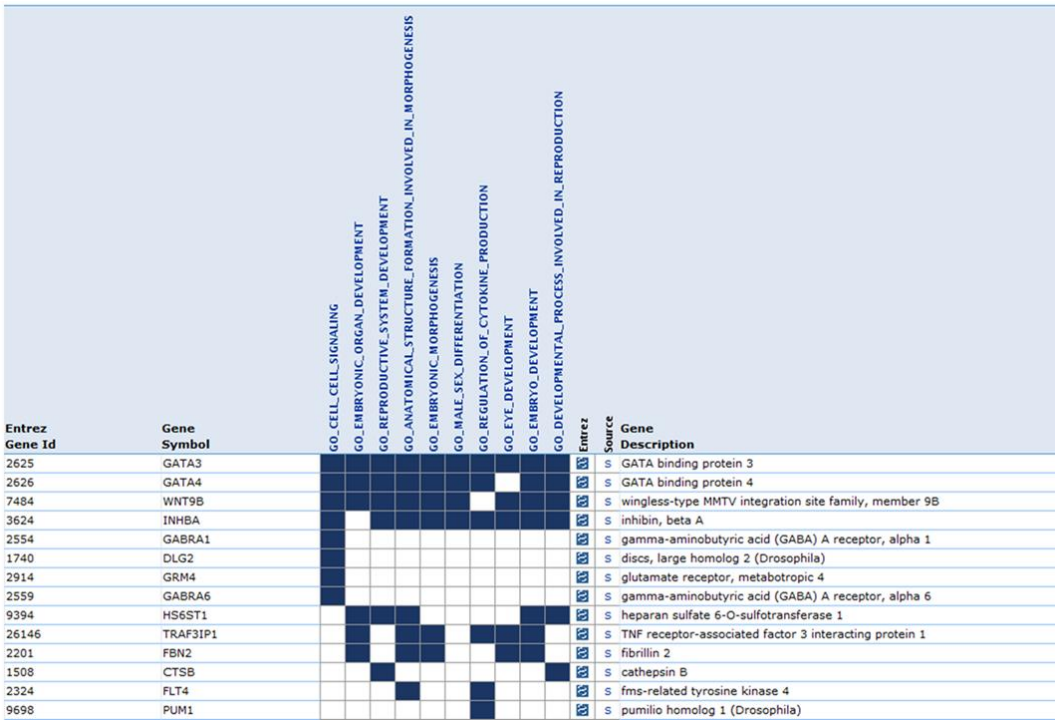
A: LocusZoom plot of the *WDR7* region on chromosome 18. **B:** LocusZoom plot of the *P3H2* (= *LEPREL1*) region on chromosome 3.The index SNPs are indicated as purple diamonds and the other SNPs are color coded depending on their degree of correlation (r^2). Circles represent imputed SNPs, triangles genotyped SNPs. FE: fixed effects, RE: random effects. ASDII patients, *n*=489. -log10 *p* values were determined by association statistics from the GWAS (logistic regression).

Supplemental Figure 7. SNPs associated with anomalies of thoracic arteries and veins



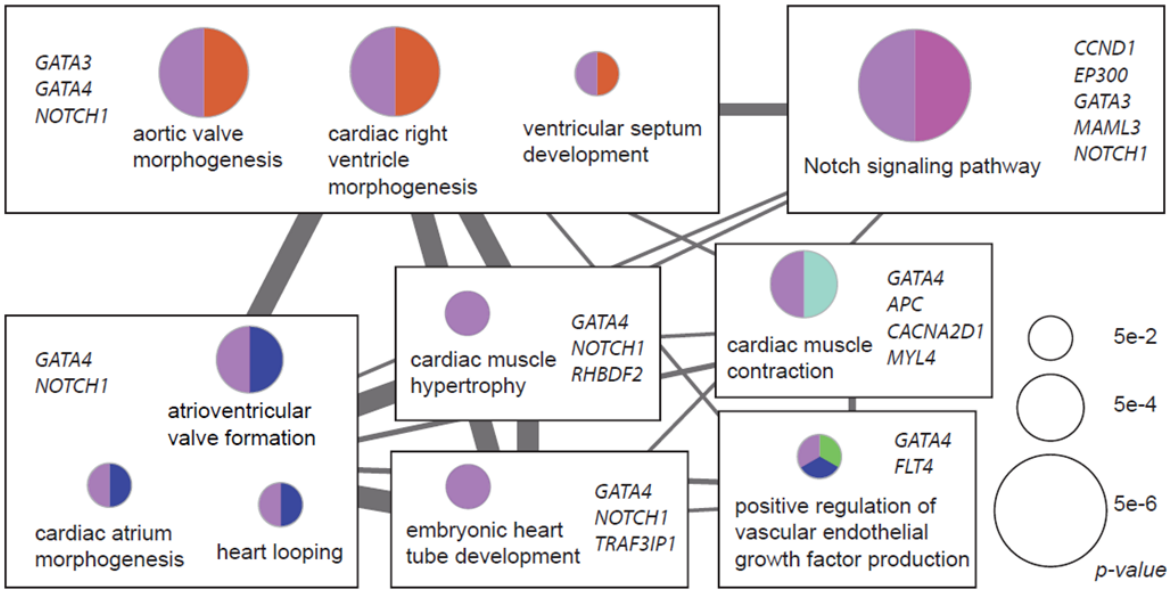
LocusZoom plot of the region on chromosome 6. The index SNP is indicated as purple diamonds and the other SNPs are color coded depending on their degree of correlation (r^2). Circles represent imputed SNPs, triangles genotyped SNPs. FE: fixed effects, RE: random effects. ATAV patients, *n*=486. -log10 *p* values were determined by association statistics from the GWAS (logistic regression).

Supplemental Figure 8. Participation of CHD-associated SNP-carrying genes in signaling cascades



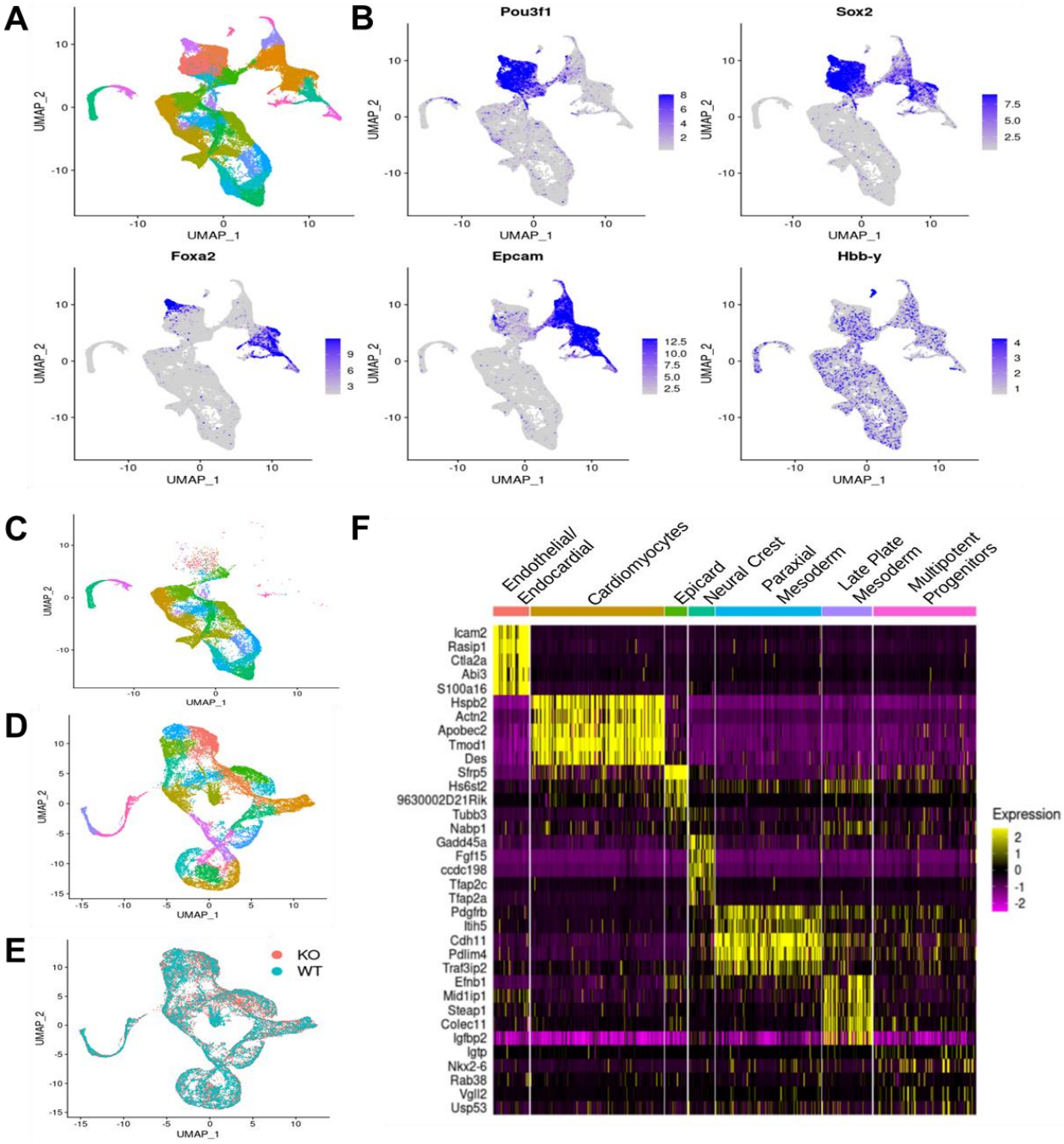
Entrez Gene Id	Gene Symbol	GO_CELL_CELL_SIGNALING	GO_EMBRYONIC_ORGAN_DEVELOPMENT	GO_REPRODUCTIVE_SYSTEM_DEVELOPMENT	GO_ANATOMICAL_STRUCTURE_FORMATION_INVOLVED_IN_MORPHOGENESIS	GO_EMBRYONIC_MORPHOGENESIS	GO_MALE_SEX_DIFFERENTIATION	GO_REGULATION_OF_CYTOKINE_PRODUCTION	GO_EYE_DEVELOPMENT	GO_EMBRYO_DEVELOPMENT	GO_DEVELOPMENTAL_PROCESS_INVOLVED_IN_REPRODUCTION	Entrez	Source	Gene Description
2625	GATA3	■	■	■	■	■	■	■	■	■	■		S	GATA binding protein 3
2626	GATA4	■	■	■	■	■	■	■		■	■		S	GATA binding protein 4
7484	WNT9B	■	■	■	■	■	■		■	■	■		S	wingless-type MMTV integration site family, member 9B
3624	INHBA	■		■	■	■	■	■	■	■	■		S	inhibin, beta A
2554	GABRA1	■											S	gamma-aminobutyric acid (GABA) A receptor, alpha 1
1740	DLG2	■											S	discs, large homolog 2 (Drosophila)
2914	GRM4	■											S	glutamate receptor, metabotropic 4
2559	GABRA6	■											S	gamma-aminobutyric acid (GABA) A receptor, alpha 6
9394	HS6ST1		■	■	■					■	■		S	heparan sulfate 6-O-sulfotransferase 1
26146	TRAF3IP1		■		■	■		■	■	■			S	TNF receptor-associated factor 3 interacting protein 1
2201	FBN2		■		■	■			■	■			S	fibrillin 2
1508	CTSB			■							■		S	cathepsin B
2324	FLT4				■			■					S	fms-related tyrosine kinase 4
9698	PUM1							■					S	pumilio homolog 1 (Drosophila)

Supplemental Figure 9. Network-based functional enrichment analysis of pathways involved in cardiac development



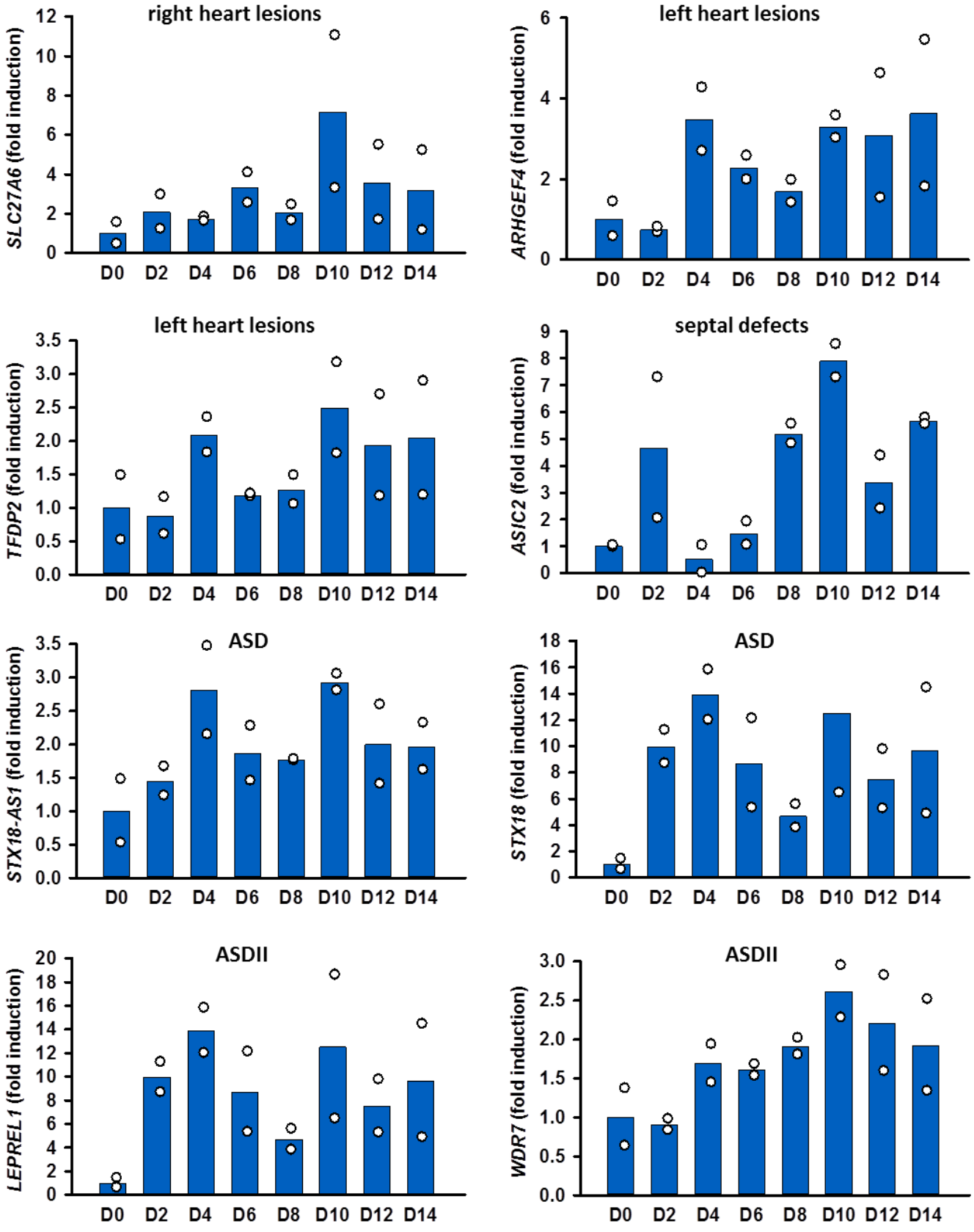
Significantly enriched gene sets by ClueGO (Bonferroni-corrected *p* values < 0.1). Each circle represents a pathway/GO-term with each type of pie chart (identified by color and pattern) represents a functional group. The size of the circles represents raw *p* values of enrichment tests for GO terms. The width of the edges represents the degree of similarity between GO terms. Rectangles encompass the GO terms that share the same significant genes. *p* values were calculated with the unpaired two-tailed Student's *t* test or the Mann-Whitney Rank Sum test.

Supplemental Figure 10. Identification and reclustering of mesodermal and neural crest cells of the murine cardiogenic region



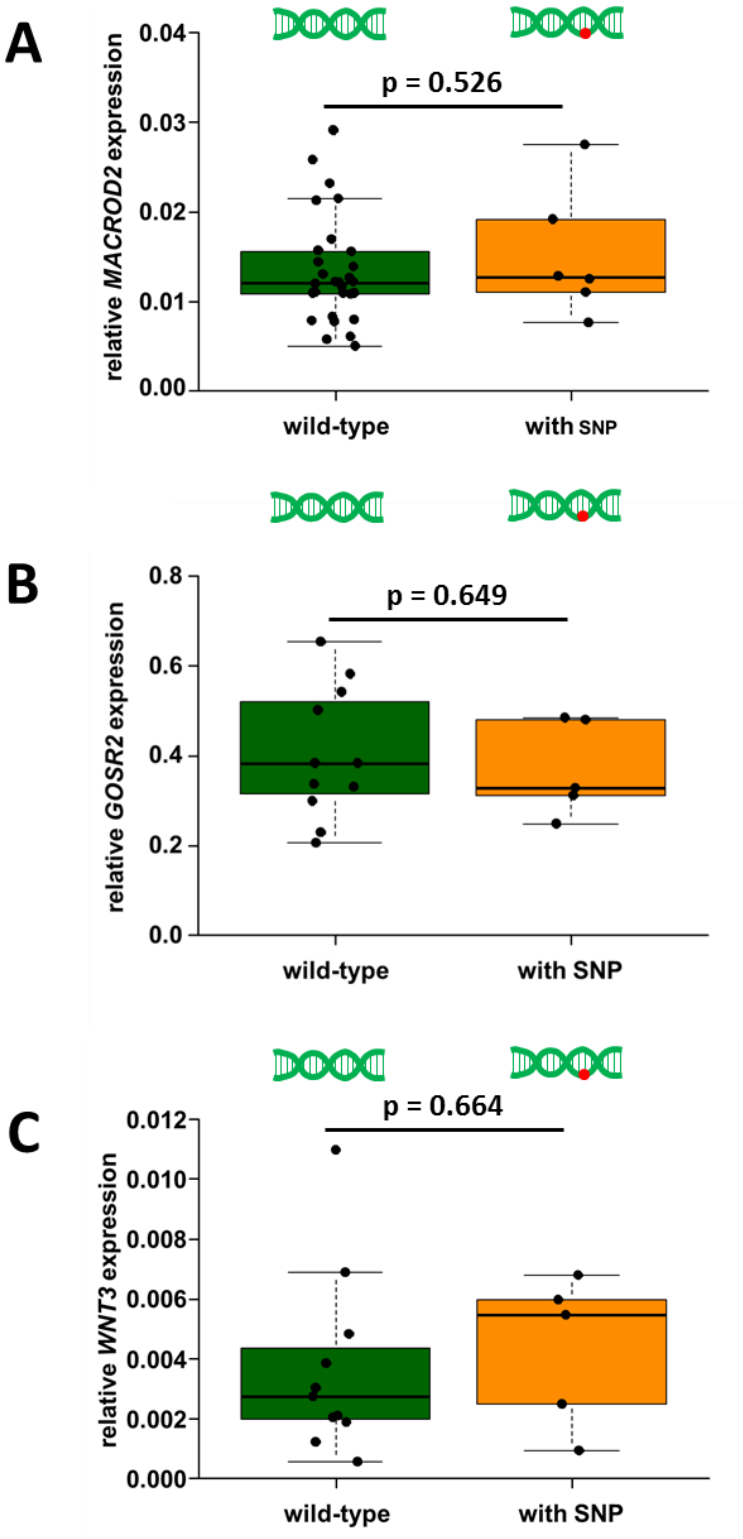
A: UMAP plot showing clusters of all captured cell populations (*n*=56,743). **B:** Expression of *Pou3f1*, *Sox2* (ectodermal marker genes), *Foxa2*, *Epcam* (endodermal marker genes) and *Hbb-y* (blood cells). **C:** UMAP plot of all mesodermal cells after exclusion of ecto- and endodermal cells (*n*=21,745). **D:** UMAP plot of reclustered mesodermal cells. **E:** Comparison of clustering of mesodermal cells from wild-type and *Hand2*-null embryos. **F:** Gene expression heatmap of the identified populations in Figure 5A.

Supplemental Figure 11. Expression of candidate genes during cardiac differentiation of human iPS cells



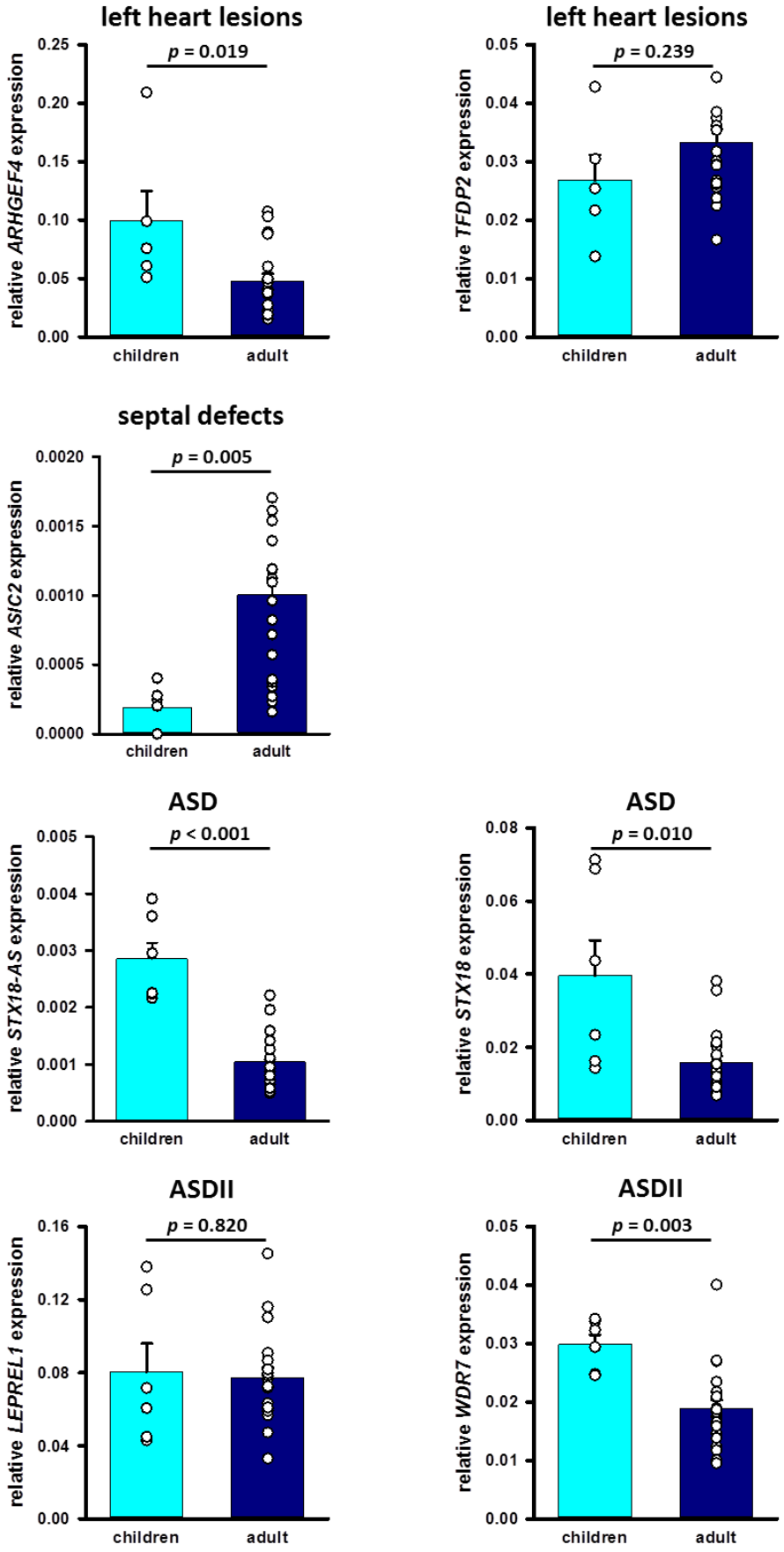
Expression of candidate genes during directed cardiac differentiation of human iPS cells.

Supplemental Figure 12. Expression of *MACROD2*, *GOSR2* and *WNT3* in patient tissue with or without risk variant



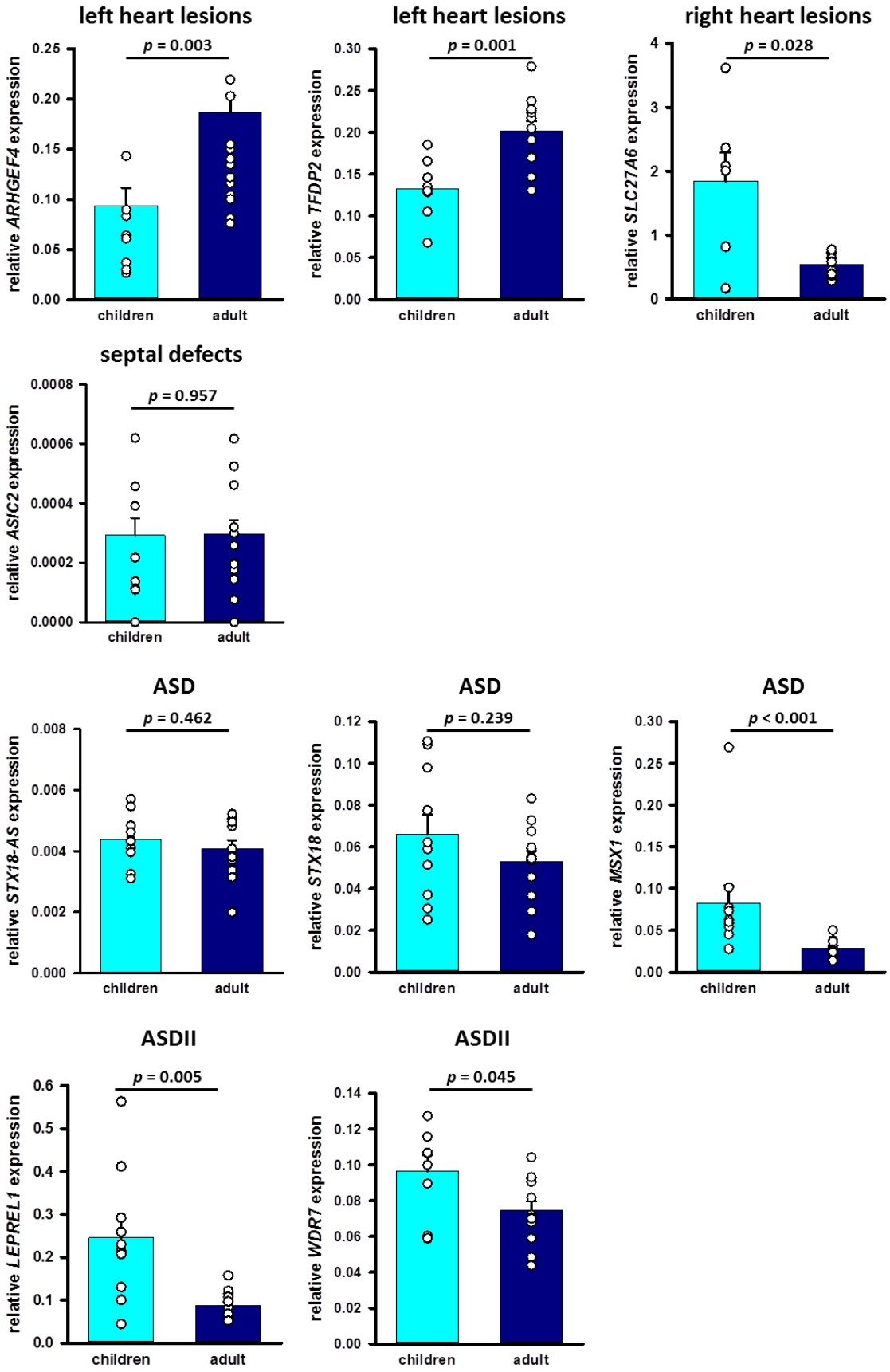
A: Expression of *MACROD2* in aortic tissue of pediatric TGA patients with wild-type (*n*=29) or heterozygous SNP genotype (*n*=6). **B:** Expression of *GOSR2* in tissue of pediatric patients with anomalies of thoracic arteries and veins with wild-type (*n*=11) or heterozygous SNP genotype (*n*=5). **C:** Expression of *WNT3* in tissue of pediatric patients with anomalies of thoracic arteries and veins with wild-type (*n*=11) or heterozygous SNP genotype (*n*=5). *p* values were calculated with the unpaired two-tailed Student's *t* test or the Mann-Whitney Rank Sum test.

Supplemental Figure 13. Expression of candidate genes in pediatric and adult aortic tissue



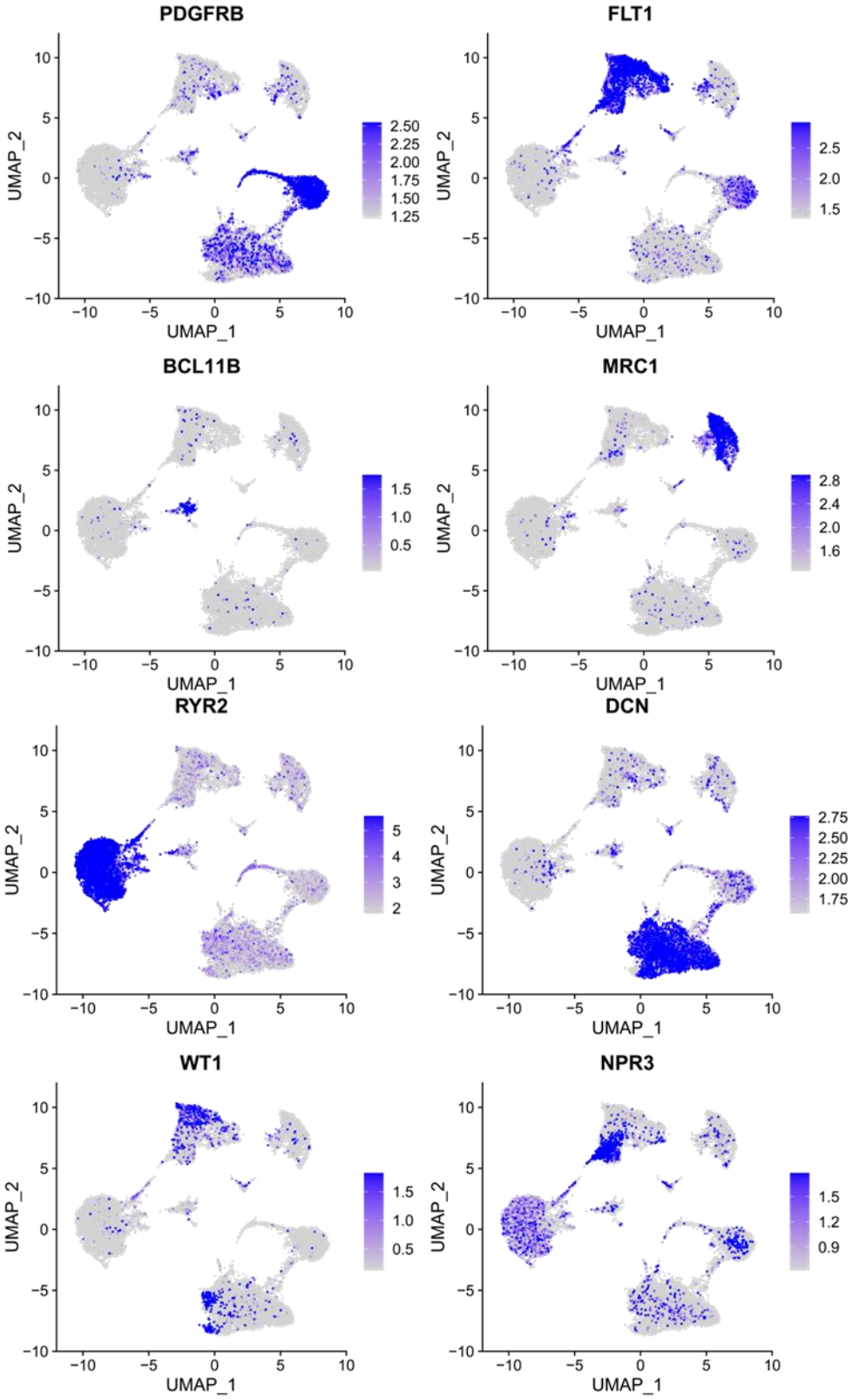
Expression of candidate genes in aortic tissue of CHD patients with left heart lesions (*n*=5), septal defects (*n*=6), ASD (*n*=6), ASDII (*n*=6) and adult surgical patients (*n*=20). *p* values were calculated with the unpaired two-tailed Student's *t* test or the Mann-Whitney Rank Sum test.

Supplemental Figure 14. Expression of candidate genes in pediatric and adult atrial tissue



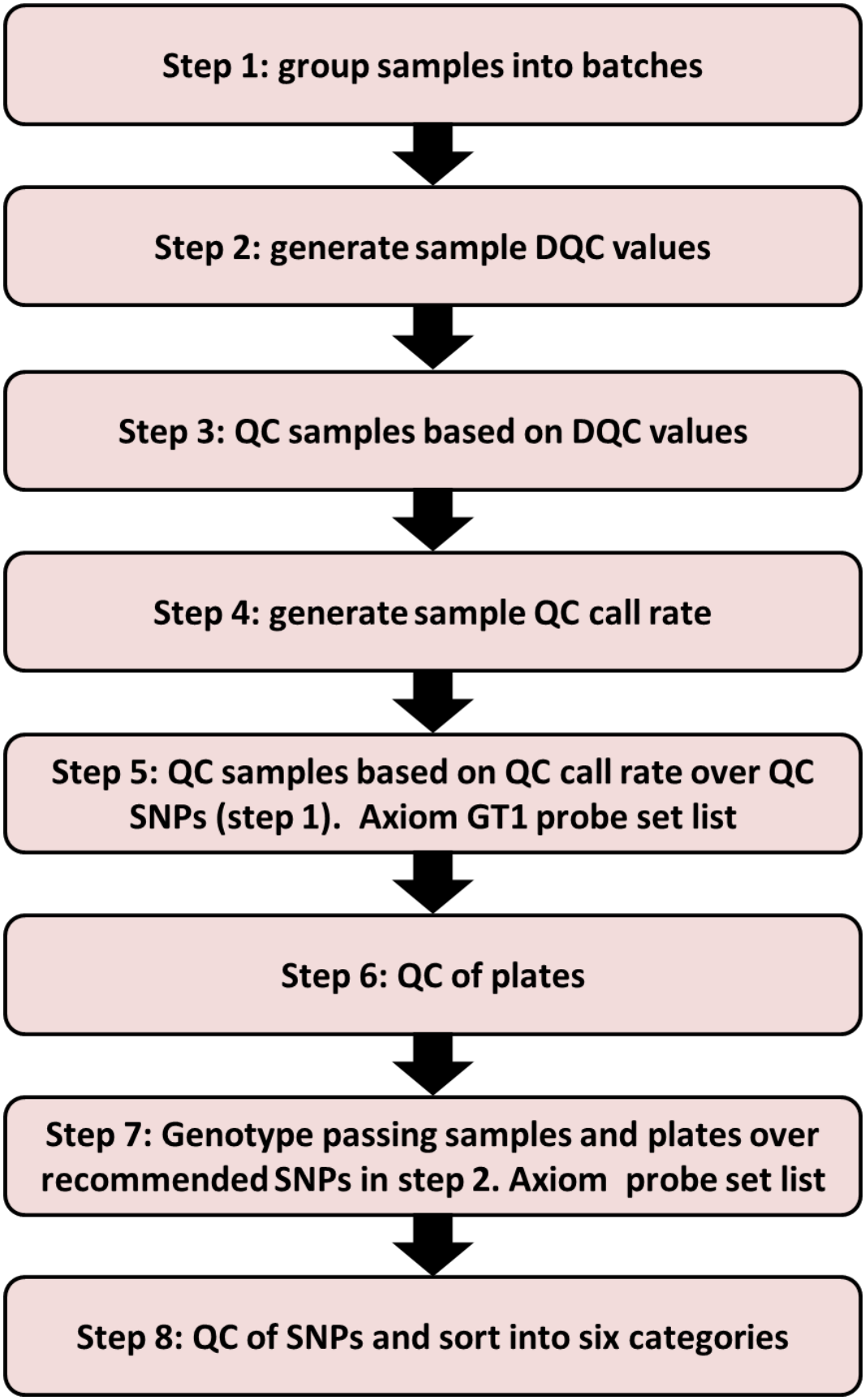
Expression of candidate genes in atrial tissue of CHD patients with left heart lesions (*n*=8), right heart lesions (*n*=6), septal defects (*n*=10), ASD (*n*=10), ASDII (*n*=10) and adult surgical patients (*n*=12). *p* values were calculated with the unpaired two tailed Student's *t* test or the Mann-Whitney Rank Sum test.

Supplemental Figure 15. Identification of different cell types after single-cell RNAseq by expression of defined marker genes



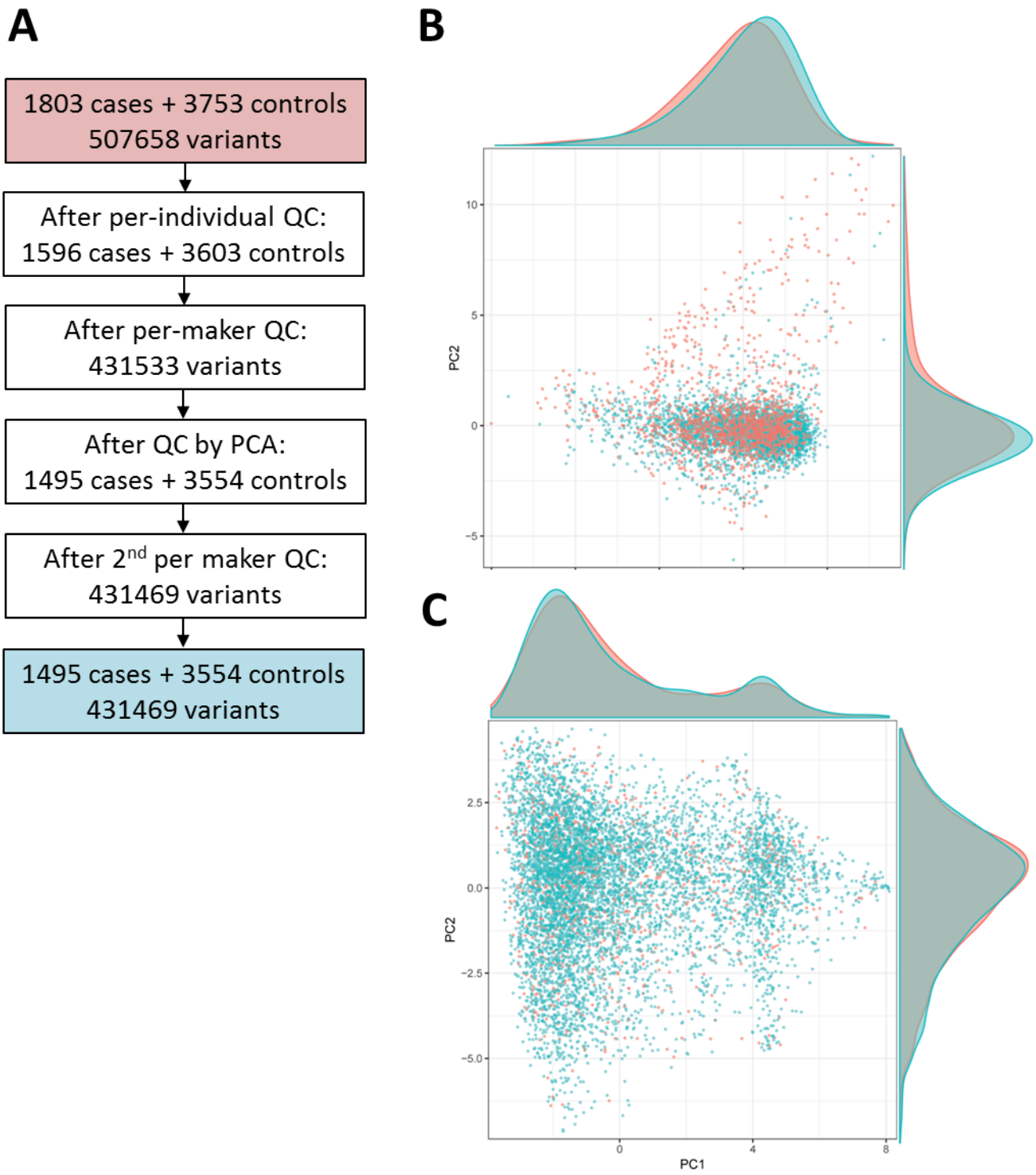
PDGFRB (platelet-derived growth factor receptor β), *FLT1* (fms related receptor kinase 1), *BCL11B* (BAF chromatin remodeling complex subunit BCL11B), *MRC1* (mannose receptor C-type 1), *RYR2* (ryanodine receptor 2), *DCN* (decorin), *WT1* (WT1 transcription factor), *NPR3* (natriuretic peptide receptor 3).

Supplemental Figure 16. Workflow for general GWAS quality control



Application of these filters resulted in 1,495 cases, 3,554 controls and 432,097 variants. The genomic inflation λ is 1.03.

Supplemental Figure 17. Quality control steps and PCA plots to analyze population stratification



A: Quality control steps. **B, C:** Scatter plots with density plots in the margins for PC1 and PC2. The red dots are cases and the blue ones are the controls. **B:** DHM cohort. **C:** British cohort.