SUPPLEMENTAL MATERIAL

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Supplemental Methods

Materials and Methods

Subjects

Previously published GWAS data (European descent KD n=405, Control n=6252) were imputed (see below) and used for pathway analysis followed by gene stability selection[1]. Since the GWAS cohort did not have detailed demographic and clinical information, we used an independent cohort of 161 well-phenotyped, multi-ethnic KD patients from a single institution for the genotype-phenotype association study. Further, 146 of 161 KD pts. had gene expression data from whole blood collected before treatment[2]. We performed eQTL analysis using these data. For the analysis of the characteristics of the subjects by genotype, we collected demographic, clinical, and laboratory data before intravenous immunoglobulin (IVIG) treatment from 161 KD subjects with illness day ≤10 days from the onset of fever who were previously genotyped (Human1M-Duo v3.0, Illumina). Analysis of transcript abundance patterns were available in a subset (n=146) of the 161 subjects as described previously[2].

Coronary artery status of the subjects was assessed by echocardiography during the acute, subacute, and convalescent (illness day ≤65) phases. Measurements of the internal diameters of the proximal right coronary artery (RCA) and left anterior descending (LAD) were normalized for body surface area and expressed as standard deviation units from the mean (Z-scores)[3]. CAA was defined as a Z-score ≥4.0. Dilated was defined as Z-score ≥ 2.5. The worst-ever Z-score (Z-worst) for either the RCA or LAD within the first 3 months after illness onset or the Z score of the largest aneurysm was used for the continuous variable analysis. IVIG resistance was defined as previously described[4].

ECG analysis

Of the 88 subjects homozygous for the risk or wild type alleles (Table 3. rs13017968 AA n=25 and CC n=63), 58 ECGs were available during acute phase (illness day ≤16) (AA n=16 and CC n=42 from Table 3). Measurements were made using a hand caliper for five ECG variables on each tracing: PR interval, QRS duration, corrected QT interval using Bazett's method (QTc), QT dispersion, and T wave peak-to-end (Tp-e). ECG variables were analyzed by genotype. Comments were also provided for qualitative morphology observations not lending themselves to quantitative measurement, such as T wave inversion, flat T waves, intraventricular conduction delays and bundle branch blocks, terminal QRS slurring, hypertrophy, infarction, ST segment changes and early repolarization patterns.

Imputation and meta-analysis using imputed GWAS data

QC was conducted at both the SNP-level and individual-level using PLINK v1.07[5] and R 3.1.1[6]. Pre-phasing was carried out using SHAPEIT2[7] and reference panels of 1000 Genomes and HapMap3 phase 3 (human genome build hg18). Next, imputation of genotypes was conducted with IMPUTE2 v2.3.1[8]. LiftOver was used for position conversion to hg19 from hg18. Meta-analysis to combine the results from two GWA studies, IKDGC and RIKEN, were conducted. After getting meta-analysis z-scores weighted by the per-study sample size, these were converted to p-values based on Chi-square distribution[9].

Immunohistochemical (IHC) staining of tissue

Coronary artery tissue for IHC was obtained from autopsies of a 3 month-old infant who died on illness day 12 and a 3 year 7 month-old child who died on illness day 7[10, 11]. Control tissue was obtained from a 9 month-old patient who died from acute pneumonia with no cardiovascular pathology. IHC was performed as previously described[10]. Anti-human NCX1 mouse-monoclonal antibody (1:100 dilution, ab2869, Abcam) or rabbit IgG (negative control) was used to stain the tissues[10].

Calcium analysis by Fluorescence Activated Cell Sorting (FACS)

EBV infected B-cells (5-8x10^6 cells) were loaded with Fluo-4/AM and Fura Red (Life Technologies) loading dyes in Ca^{2+} free complete DMEM media and incubated at 37^{o}C for 35 min. The cells were rested at room temperature for 20 min before diluting the loaded cells to 3x10^6 cells/ml in Ca^{2+} free DMEM media

supplemented with 10% FBS, 1mM Sodium pyruvate, 0.1mM non-essential amino acids, 50 μM 2-ME, 2mM L-glutamine and 10mM HEPES. Intracellular calcium $[Ca^{2+}]_i$ mobilization was acquired for a continuous 10 minutes using BD™ LSR II Analyzer (BD Biosciences, Mississauga, ON, Canada). To induce Ca^{2+} flux, Ionomycin (1μM) was added at 1 min during the acquisition. Peak mean fluorescence intensity **(**MFI) of Fluo-4AM per minute is represented over time. Data were analyzed using FlowJo v9 (Tree star, OR, USA) software.

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Supplemental Table S1. 100 significantly associated pathways

Pathway	Source	-log p-value
Acetylcholine pathway*	KEGG 2006	11.02
Endothelial release factors*	KEGG/IPA modified in house	9.80
NO pathway*	KEGG/IPA modified in house	9.63
ACH 3 - Acetylcholine Mode of Action*	KEGG/IPA modified in house	9.44
NO pathway*	KEGG/IPA modified in house	9.21
Synaptic transmission	Pathway commons	8.70
Glypican 1 network	Pathway commons	8.68
Metabolism of amino acids and derivatives	Pathway commons	8.09
Catecholamine pathway*	KEGG/IPA modified in houses	7.92
Catecholamine - action*	KEGG/IPA modified in houses	7.85
Signaling events mediated by hepatocyte growth factor receptor (c-Met)	Pathway commons	7.79
Class I PI3K signaling events mediated by Akt	Pathway commons	7.79
Signaling events mediated by focal adhesion kinase	Pathway commons	7.50
TRAIL signaling pathway	Pathway commons	6.92
EGF receptor (ErbB1) signaling pathway	Pathway commons	6.90
WNT signaling pathway	KEGG	6.80
Type I diabetes Mellitus	KEGG	6.62
Bradykinin pathway	KEGG/IPA modified in house	6.54
ErbB1 downstream signaling	Pathway commons	6.47
Tight junction	KEGG/IPA modified in houses	6.46
Hormone biosynthesis	Pathway commons	6.37
Rheumatoid arthritis related genes 1	KEGG/IPA modified in houses	6.23
Formation of a pool of free 40S subunits	Pathway commons	5.96
Vasopressin pathway*	KEGG/IPA modified in house	5.83
CAT pathway*	KEGG/IPA modified in house	5.82
Nat Pep 4 - whole pathway*	KEGG/IPA modified in house	5.50
Rheumatoid arthritis related genes 2	KEGG/IPA modified in houses	5.40
Long term depression	KEGG	5.39
MAPK signaling pathway	KEGG	5.36
RAA-aldosterone-vasopressin pathways1*	KEGG/IPA modified in house	5.34
Type I diabetes mellitus	KEGG 2006	5.29
RAA - aldosterone - vasopressin pathways2*	KEGG/IPA modified in house	5.28
Calcium signaling pathway*	**KEGG**	**5.28**
3' -UTR-mediated translational regulation	Pathway commons	5.15
L13a-mediated translational silencing of ceruloplasmin expression	Pathway commons	5.08
Tight junction	KEGG	5.04
Eukaryotic translation initiation	Pathway commons	4.97
Cell cycle mitotic	Pathway commons	4.95
NO pathway	KEGG/IPA modified in house	4.94
Endothelins	Pathway commons	4.93
Antigen processing and presentation	KEGG/IPA modified in house	4.87
Plasma membrane estrogen receptor signaling	Pathway commons	4.82
Calcium signaling pathway*	**KEGG 2006**	**4.69**
Arf6 signaling events	Pathway commons	4.67
aldosterone	KEGG/IPA modified in house	4.50
Cell adhesion molecules	KEGG/IPA modified in house	4.50
Toll pathway	KEGG/IPA modified in house	4.46
Long-term depression	KEGG/IPA modified in house	4.46
Diabetes pathways	Pathway commons	4.42
Gene Expression	Pathway commons	4.41
Nat Pep 3 - Action + degradation*	KEGG/IPA modified in house	4.39
Calcium regulation in cardiac cells*	**Genmapp**	**4.34**
Nucleotide sugars metabolism	KEGG modified in house	4.31
IGF1 pathway	Pathway commons	4.31
MAPK signaling pathway	KEGG/IPA modified in house	4.27
TGF-beta receptor signaling	Pathway commons	4.25

HIV Infection	Pathway commons	4.24
RAA-Aldosterone-Vasopressin pathways Combined 3*	KEGG/IPA modified in house	4.16
Membrane Trafficking	Pathway commons	4.14
Formation of the ternary complex_ and subsequently_ the 43S complex	Pathway commons	4.12
Wnt signaling pathway	KEGG/IPA modified in house	4.11
NrCAM interactions	Pathway commons	4.11
Eukaryotic translation termination	Pathway commons	4.10
Regulation of cytoplasmic and nuclear SMAD2/3 signaling	Pathway commons	4.06
Nucleotide sugars metabolism	KEGG	4.06
ABC transporters - general	KEGG/IPA modified in house	4.06
Insulin synthesis and processing	Pathway commons	4.04
ALK1 pathway	Pathway commons	4.01
Antigen processing and presentation	KEGG	4.00
MAPK	KEGG/IPA modified in house	3.99
Nat pep action and degradation	KEGG/IPA modified in house	3.99
Hematopoietic cell lineage bone marrow	KEGG/IPA modified in house	3.99
GTP hydrolysis and joining of the 60S ribosomal subunit	Pathway commons	3.96
Neurofascin interactions	Pathway commons	3.95
Translation	Pathway commons	3.94
Negative regulation of the PI3K AKT network	Pathway commons	3.88
COX reactions	Pathway commons	3.86
Nat pep entire pathway	KEGG/IPA modified in house	3.85
Synthesis secretion and deacylation of ghrelin	Pathway commons	3.81
Peptide chain elongation	Pathway commons	3.79
Interferon alpha beta signaling	Pathway commons	3.78
Cell adhesion molecules	KEGG	3.77
Mitotic M-M G1 phases	Pathway commons	3.76
Regulation of nuclear SMAD2/3 signaling	Pathway commons	3.76
Insulin pathway	Pathway commons	3.74
Arf6 downstream pathway	Pathway commons	3.74
Coagulation pathway	KEGG/IPA modified in house	3.72
Cell communication	KEGG	3.68
Ubiquitin mediated proteolysis	KEGG/IPA modified in house	3.62
Smooth muscle contraction*	Genmapp	3.61
Presenilin action in Notch and Wnt signaling	Pathway commons	3.60
Metabolism of lipids and lipoproteins	Pathway commons	3.56
Incretin synthesis secretion and inactivation	Pathway commons	3.53
Activation of the mRNA upon binding of the cap-binding complex and eIFs_ and	Pathway commons	3.52
Regulation of PAK-2p34 activity by PS-GAP RHG10	Pathway commons	3.41
Metabolism of RNA	Pathway commons	3.40
Cap-dependent translation initiation	Pathway commons	3.38
Regulation of APC C activators between G1 S and early anaphase	Pathway commons	3.37
Nef mediated downregulation of MHC class I complex cell surface expression	Pathway commons	3.37
Canonical Wnt signaling pathway	Pathway commons	3.35
*: 18 pathways that include SLC8A1		

Supplemental Table S2. 26 genes with 116 SNPs that were selected by gene stability analysis

Gene symbol	Gene Name	Chr.	SNP	Position (hg19)	Allele	OR	p
RYR2	ryanodine receptor 2 (cardiac)	1	rs7547032	237338293	A	0.80	0.004
			rs2490353	237342647	G	0.81	0.007
			rs187910	237359988	A	0.80	0.004
			rs12401834	237364582	A	0.81	0.006
			rs618083	237375157	A	1.34	0.000
NRXN1	neurexin 1	2	rs1517827	50377588	A	0.69	0.004
			rs1452769	50396135	G	0.68	0.001
			rs1377238	50398902	G	0.68	0.001
			rs17040117	50409803	A	0.65	0.0003
			rs11897191	50443908	A	0.67	0.009
			rs1104979	50524783	A	0.79	0.008
PLB1	phospholipase B1	2	rs10205008	28765309	G	0.82	0.010
			rs1881254	28768251	A	1.24	0.004
			rs11127168	28774245	A	0.81	0.007
			rs1534476	28833479	A	0.81	0.009
			rs4666111	28838795	A	0.69	0.009
SLC8A1	solute carrier family 8 (sodium/calcium exchanger), member 1	2	rs3922283	40331135	A	0.81	0.009
			rs417591	40400312	G	0.76	0.004
			rs380590	40473347	A	1.31	0.008
			rs17025772	40522774	C	1.52	0.005
			rs10490051	40571426	G	1.25	0.005
			rs7561383	40574207	A	0.80	0.005
			rs13017968	40574672	A	1.24	0.008
			rs12712691	40575809	A	1.26	0.002
			rs12988856	40577723	A	1.24	0.005
			rs12989852	40578036	A	1.29	0.001
			rs12995004	40578116	A	1.30	0.001
			rs12712692	40580065	C	1.31	0.0003
			rs6544323	40582014	A	1.29	0.001
			rs990270	40582349	A	1.23	0.006
			rs6544324	40583058	A	1.24	0.004
			rs1558655	40586022	A	1.27	0.001
			rs2301343	40680149	C	0.76	0.004
			rs11679585	40691468	A	1.36	0.001
			rs2042016	40699189	G	0.78	0.002
CACNA2D3	calcium channel, voltage-dependent, alpha 2/delta subunit 3	3	rs4485754	54234722	G	0.74	0.002
			rs9839121	54240680	G	0.73	0.0004
			rs9825455	54242041	A	0.73	0.001
MAGI1	membrane associated guanylate kinase, WW and PDZ domain containing 1	3	rs4407359	65597953	C	1.23	0.007
LPHN3	adhesion G protein-coupled receptor L3	4	rs1505679	62198201	G	1.35	0.002
			rs335306	62381539	A	1.25	0.006
			rs335317	62387140	A	1.24	0.008
			rs186750	62393646	A	1.30	0.002
			rs17239136	62646231	G	0.72	0.009
PDE4D	phosphodiesterase 4D, cAMP-specific	5	rs6867591	58508712	A	0.65	0.008
			rs10514865	58675538	C	0.76	0.010
FARS2	phenylalanyl-tRNA synthetase 2, mitochondrial	6	rs9502305	5484829	G	0.77	0.004
			rs12204218	5513550	G	0.80	0.006
HLA-B	major histocompatibility complex, class I, B	6	rs2844623	31232543	A	0.74	0.005
			rs2524099	31236051	A	0.81	0.005

			rs2524070	31244520	A	0.75	0.007
			rs6906846	31245736	A	1.26	0.003
			rs7382297	31247067	A	1.29	0.009
			rs2596551	31332239	C	0.73	0.003
			rs2844575	31334945	G	0.82	0.009
			rs2523535	31336250	G	0.80	0.004
			rs2254556	31342631	A	1.29	0.005
CNTNAP2	contactin associated protein-like 2	7	rs10487921	146430441	A	1.33	0.006
			rs11972861	146500532	G	1.26	0.007
			rs4367451	146559474	A	1.36	0.0003
			rs9640485	146570960	G	1.30	0.001
			rs12703845	146571183	A	0.79	0.006
			rs1024528	147225881	G	0.81	0.008
			rs2707559	147754924	G	0.81	0.007
			rs10441210	147779648	A	0.81	0.006
			rs10464461	147967593	A	1.22	0.008
			rs6973491	147968791	G	1.24	0.005
			rs12111911	147971938	G	1.23	0.007
MAGI2	membrane associated guanylate kinase, WW and PDZ domain containing 2	7	rs727200	78170588	A	0.76	0.002
			rs10230681	78193436	G	1.41	0.002
PTPRN2	protein tyrosine phosphatase, receptor type, N polypeptide 2	7	rs1263560	157415516	G	1.25	0.009
			rs1268391	157418904	G	1.24	0.007
			rs10250971	157480939	A	1.23	0.008
			rs6962998	157487013	C	1.23	0.006
			rs1796236	157493836	A	1.41	0.002
			rs1242778	157560763	A	1.36	0.001
			rs999407	157566417	G	1.33	0.001
			rs1630862	158268596	G	0.79	0.002
ANK1	ankyrin 1, erythrocytic	8	rs2111807	41685166	C	1.32	0.001
NRG1	neuregulin 1	8	rs989465	32105334	C	0.81	0.009
PPP2R2A	protein phosphatase 2, regulatory subunit B, alpha	8	rs6557837	25221000	A	1.28	0.009
			rs17054249	25599783	A	0.78	0.003
			rs1559725	25600615	G	0.79	0.005
			rs2467680	25601529	A	1.40	0.001
			rs12543714	25615706	A	0.79	0.007
			rs13279614	25616023	A	1.27	0.007
			rs12542834	25625754	C	0.80	0.005
			rs1365007	25644016	G	0.79	0.006
			rs11989071	25797627	C	1.54	0.00001
			rs7006936	25804508	G	0.77	0.009
CACNB2	calcium channel, voltage-dependent, beta 2 subunit	10	rs2489198	18636568	G	0.78	0.001
CTNNA3	catenin (cadherin-associated protein), alpha 3	10	rs1925580	68684249	G	1.54	0.0003
DOCK1	dedicator of cytokinesis 1	10	rs11016935	129048503	A	0.77	0.001
			rs11016936	129048746	G	1.23	0.008
			rs11017012	129060759	A	0.78	0.002
			rs11017023	129063539	C	0.77	0.001
			rs7916371	129072439	A	0.80	0.004
			rs10829711	129089317	G	0.80	0.004
			rs2720972	129118884	A	1.23	0.006
			rs2720971	129119793	C	0.81	0.007
			rs2766056	129123388	G	0.78	0.001
			rs2766059	129127446	A	1.22	0.008

KCNMA1	potassium channel, calcium activated large conductance subfamily M alpha, member 1	10	rs250710	79123321	G	0.78	0.008
LHPP	phospholysine phosphohistidine inorganic pyrophosphate phosphatase	10	rs4962386	126266756	A	1.26	0.002
			rs17152064	126267759	A	0.58	0.005
			rs12773846	126275914	A	0.74	0.001
			rs4962664	126280593	A	1.27	0.002
PRKG1	protein kinase, cGMP-dependent, type I	10	*				
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	12	rs2238077	2466084	A	1.31	0.005
PRICKLE1	prickle homolog 1	12	rs11832772	42859588	A	1.34	0.0001
			rs3213989	42863801	A	1.29	0.001
			rs4768412	42869140	A	1.28	0.001
			rs6582398	42870444	G	0.80	0.004
			rs11181569	42980489	G	1.23	0.007
IGF1R	insulin-like growth factor 1 receptor	15	rs7169544	99457752	A	1.28	0.001
			rs9920651	99462640	A	1.30	0.003
			rs1829652	99524865	G	1.47	0.003
RILP	Rab interacting lysosomal protein	17	*				

*: no SNPs associated with $p<0.01$
Yellow highlighted genes: calcium channel genes

Supplemental Table S3. Gene ontology analysis for 26 genes selected by gene stability analysis

Gene ontology classification	Term	# of genes included	P-value	Genes
Biological process	GO:0006816~calcium ion transport	5	1.05×10^{-4}	*SLC8A1, RYR2, CACNB2, CACNA2D3, CACNA1C*
	GO:0006936~muscle contraction	5	1.40×10^{-4}	*KCNMA1, SLC8A1, RYR2, PDE4D, CACNA1C*
	GO:0003012~muscle system process	5	2.01×10^{-4}	*KCNMA1, SLC8A1, RYR2, PDE4D, CACNA1C*
	GO:0015674~di-, tri-valent inorganic cation transport	5	2.40×10^{-4}	*SLC8A1, RYR2, CACNB2, CACNA2D3, CACNA1C*
Molecular function	GO:0046873~metal ion transmembrane transporter activity	6	2.86×10^{-4}	*KCNMA1, SLC8A1, RYR2, CACNB2, CACNA2D3, CACNA1C*
	GO:0005262~calcium channel activity	4	4.00×10^{-4}	*RYR2, CACNB2, CACNA2D3, CACNA1C*

SLC8A1: Solute Carrier Family 8, Member 1, RYR2: ryanodine receptor 2, CACNB2: calcium channel, voltage-dependent, beta 2 subunit, CACNA2D3: calcium channel, voltage-dependent, alpha 2/delta subunit 3, CACNA1C: calcium channel, voltage-dependent, L type, alpha 1C subunit, *KCNMA1*: potassium channel, calcium activated large conductance subfamily M alpha, member 1, *PDE4D:* phosphodiesterase 4D

Supplemental Table S4. Ethnicity of subjects genotyped only for *SLC8A1* rs13017968

	Normal n=92	Aneurysms n=91	P-value*
Asian, n (%)	12 (13)	16 (18)	NS
African American, n (%)	3 (3)	0 (0)	
Caucasian, n (%)	35 (38)	38 (42)	
Hispanic, n (%)	24 (26)	12 (13)	
More than 2 races, n (%)	18 (20)	16 (18)	
unknown, n (%)	4 (4)	9 (10)	

*: one-way anova

Supplemental Table S5. Association between *SLC8A1* rs13017968 and coronary artery abnormalities

CA status	AA n=55	AC + CC n=289	P-value*
CAA + dilated, n (%)	31 (56)	114 (39)	0.029
Normal, n(%)	24 (44)	175 (61)	

*: Fisher's exact T-test.

Supplemental Table S6. Allele and genotype frequencies of SNPs in calcium channel genes

Gene	SNPs	genotype or allele	1000 Genomes frequencies			
			EAS	EUR	HIS	AFR
SLC8A1	rs10490051	GG	40.9	7	11.5	2.3
		GA	45.2	44.9	47.3	23.8
		AA	13.9	48.1	41.2	74
		G	63	29	35	14
	rs13017968	AA	40.3	6.6	10.4	0
		AG	44	42.7	42.7	0.9
		GG	15.7	50.7	47	0.991
		A	62	28	32	0
	rs12989852	AA	47.2	15.3	19.3	43
		AG	41.3	49.3	50.7	43
		GG	11.5	35.4	30	14.1
		A	68	40	45	64
RYR2	rs7547032	A	63	50	45	67
	rs2490353	G	76	52	50	95
	rs187910	A	49	44	40	73
	rs12401834	A	35	41	32	25
	rs618083	A	39	45	52	17
CACNA2D3	rs4485754	G	38	18	18	33
	rs9839121	G	76	25	43	78
	rs9825455	A	58	20	25	66
CACNB2	rs2489198	G	7	42	46	50
CACNA1C	rs2238077	A	27	17	10	1

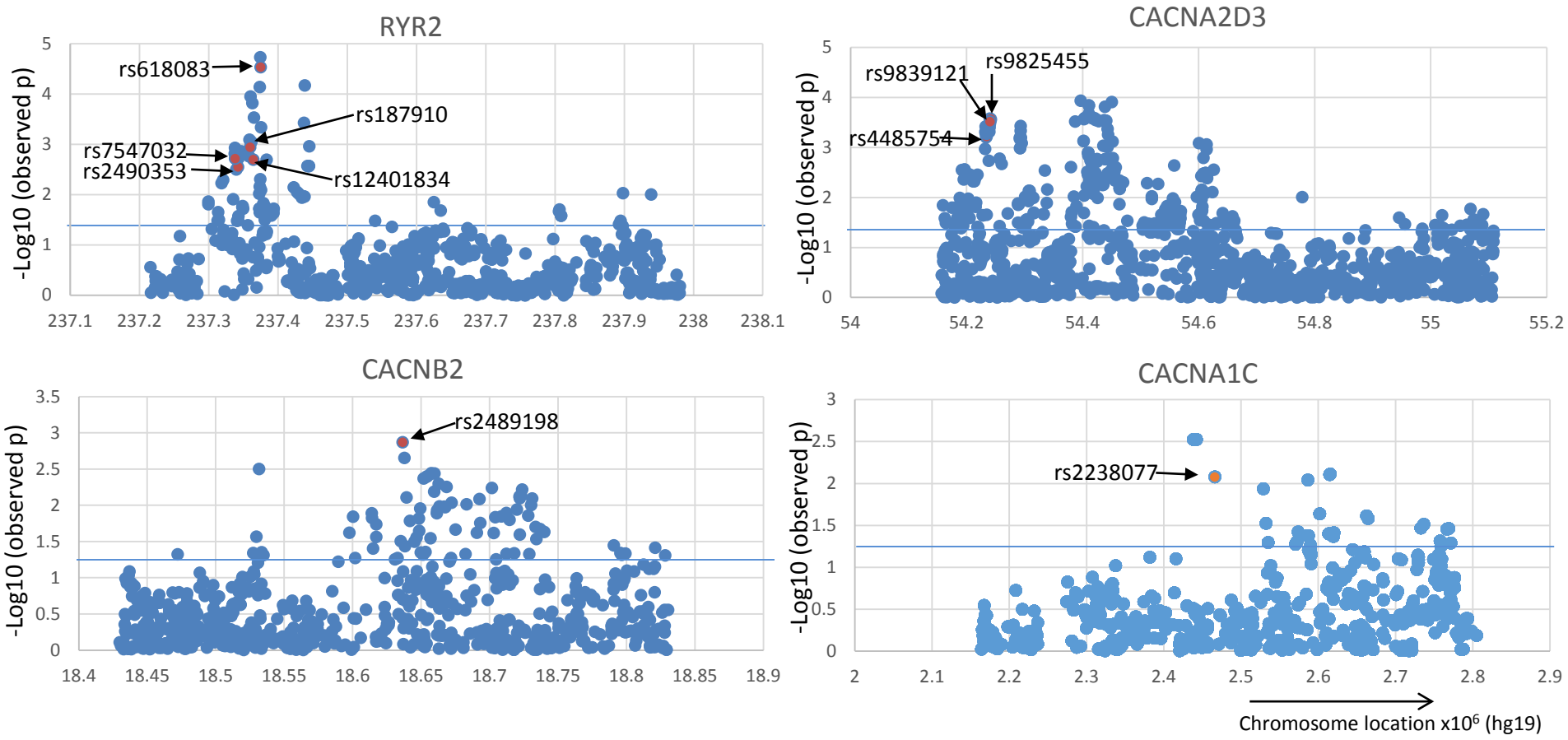
EAS: east Asian, EUR: European decent, HIS: Hispanic, AFR: African

Supplemental Table S7. Cell- and tissue-specific chromatin state in validated SNPs

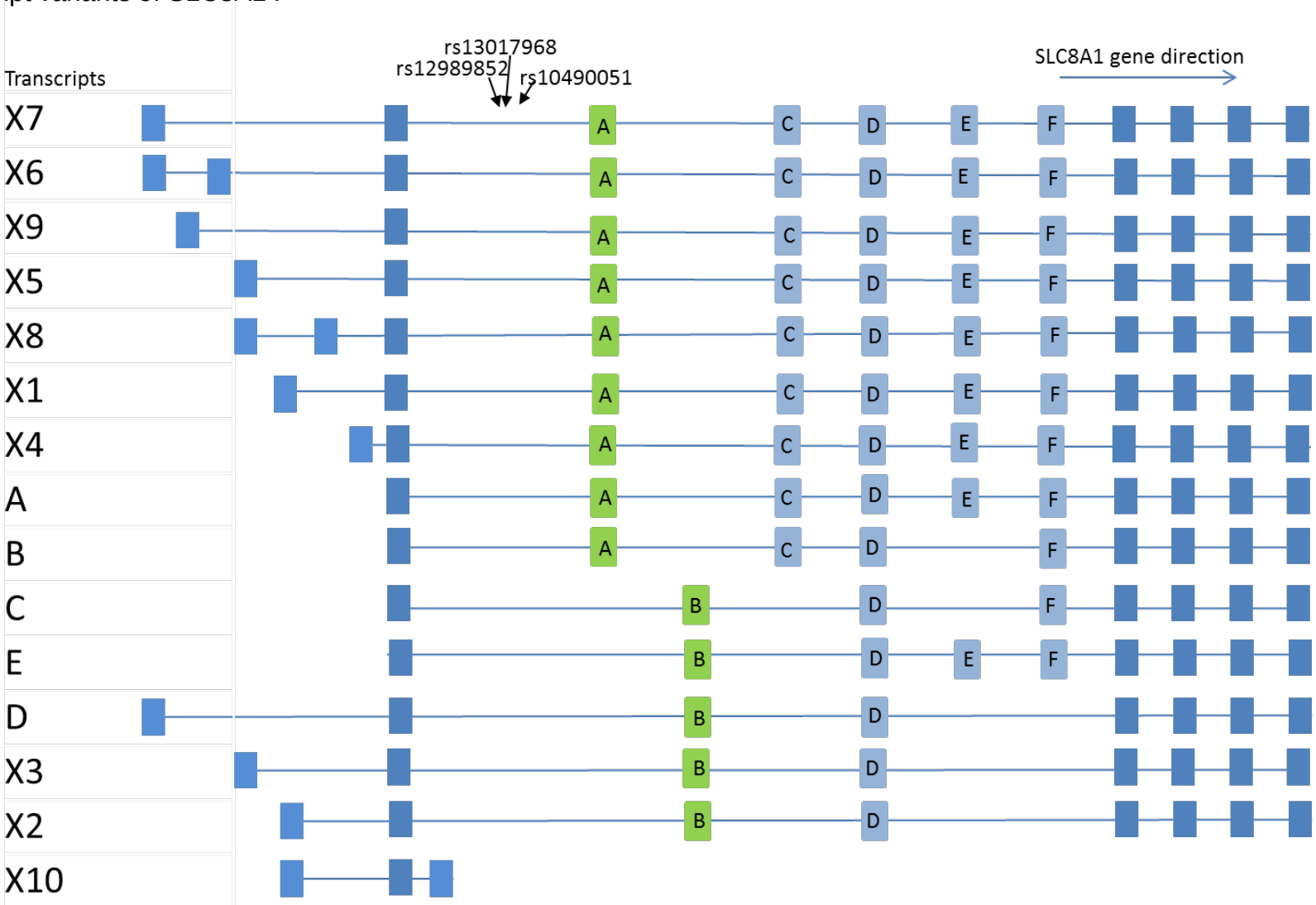
Cell category	Cell ID	Cell description	Source	Chromatin state*		
				rs10490051	rs13017968	rs12989852
Mesenchymal stem cell	MSC.ADIPC	Mesenchymal Stem Cell Derived Adipocyte Cultured Cells	RoadMap	Weakly active enhancer	Flanking to transcription start site	Active enhancer
	BM.MSC	Bone Marrow Derived Mesenchymal Stem Cell Cultured Cells	RoadMap	Active enhancer	Active enhancer	
	CHON.BMMSC	Chondrocytes from Bone Marrow Derived Mesenchymal Stem Cell Cultured Cells	RoadMap	Weakly active enhancer	Active enhancer	
Heart	LV	Left Ventricle	RoadMap	Active enhancer	Active enhancer	Active enhancer
	HRT.FE	Fetal Heart	RoadMap	Weakly active enhancer	Weakly active enhancer	
Muscle cell	MUS.SC	Muscle Satellite Cultured Cells	RoadMap	Active enhancer	Active enhancer	Active enhancer
	ST.SMUS28	Stomach Smooth Muscle.Donor 28	RoadMap	Active enhancer	Active enhancer	
	HSMM	skeletal muscle myoblasts	Encode	Active enhancer	Active enhancer	
Fibroblast	IMR90	IMR90 Cell Line	RoadMap	Weakly active enhancer	Active enhancer	
	PFF.2	Penis Foreskin Fibroblast Primary Cells.Donor skin02	RoadMap	Active enhancer	Weakly active enhancer	
	PFF.1	Penis Foreskin Fibroblast Primary Cells.Donor skin01	RoadMap	Weakly active enhancer	Active enhancer	
	NHLF	lung fibroblasts	Encode	Weakly active enhancer	Weakly active enhancer	

*: Active enhancer and transcription start site of chromatin state are associate with expressed genes. Active enhander includes chromatin state of 13_EnhA: Enhancer_active, 14_Enh: Enhancer_active_with_weakK4me1_strong_K27ac in RoadMap and 5_strong enhancer in Encode. Weakly active enhancer is chromatin state of 11_EnhWk1: Enhancer_weak in RoadMap. Flanking to transcription start site is chromatin state of 2_TssF: Transcription start sites (TSS)_flanking_more_upstream in RoadMap.

Supplemental Figure S1. log scale p-values for association with KD susceptibility and location of SNPs for four genes (*RYR2, CACNA2D3, CACNB2, CACNA1C*) in the calcium signaling pathway found by gene stability test. Red dod show gene stability selected SNPs. Blue holizontal lines show p=0.05.



Supplemental Figure S2. 15 transcripts of human *SLC8A1* and location of validated SNPs. NCX1 has 11 transmembrane segments with a large intracellular loop whose gene structure contains a cluster of six exons, designated A, B, C, D, E, and F, for alternative splicing. Exons A and B are mutually exclusive, whereas exons C, D, E, and F are cassette exons that may be spliced out of the primary transcript or retained [19]. In humans, combinations of these exons creates 15 transcript variants (NCBI Homo sapience annotation release 106, NCBI Reference Sequence: NC_000002.12) [19]. Exon A is retained in transcripts from excitable cells such as heart and skeletal muscle while Exon B is retained in non-excitable cells. Three polymorphisms in *SLC8A1* are located 172Kb 5' upstream of Exon A, the first of six exons (A-F) that make up the 15 transcript variants of SLC8A1 .



Supplemental Figure S3. LD block difference between EUR and JPT for CACNA1C (A), CACNB2 (B), CACNA2D3 (C), and RYR2 (D). Locations of SNPs used in pathway and gene stability selection were shown with arrows. EUR: European descent, JPT: Japanese