

SUPPLEMENTARY MATERIAL

Lipoprotein Proteomics and Aortic Valve Transcriptomics Identify Biological Pathways Linking Lipoprotein(a) levels to Aortic Stenosis

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Figure S1. Molecular Complex Detection (MCODE) algorithm network performed for the top genes influenced by Lp(a) levels. MCODE algorithm detects densely connected regions in large protein-protein interaction networks that may represent molecular complexes. MCODE details are represented in supplementary Table 3.

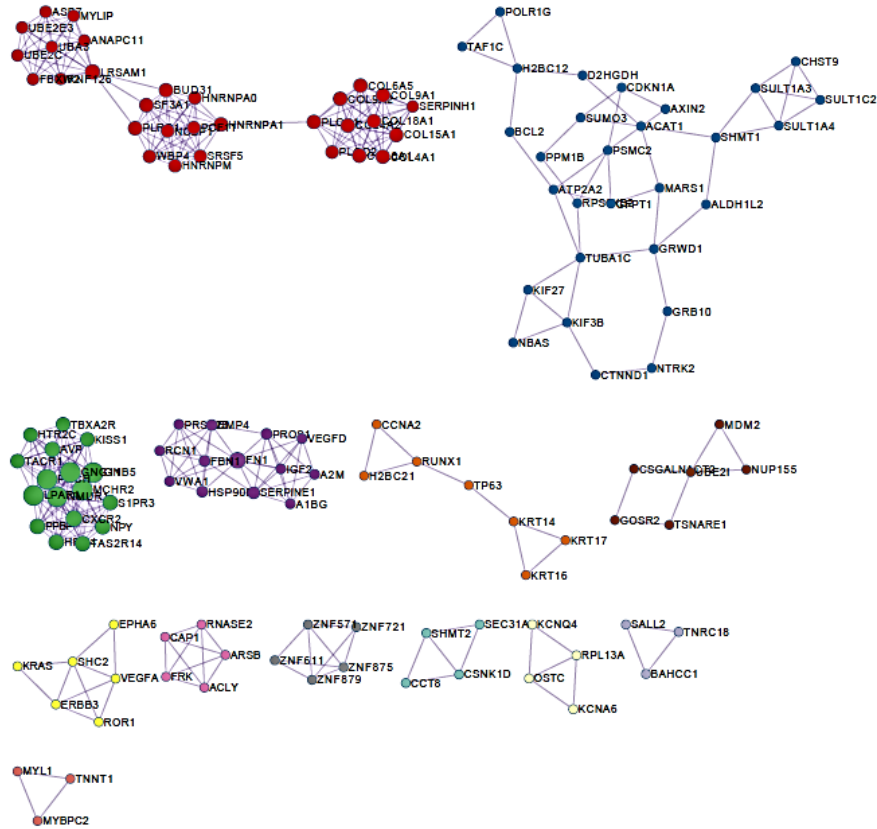


Table S1: Characterisation of the proteins found on Lp(a) particles regardless of CAVS status according to their relative abundance

Gene	Protein	Mean signal
APOB	Apolipoprotein B-100;Apolipoprotein B-48	3,76E+11
LPA	Apolipoprotein(a)	6,85E+10
APOA1	Apolipoprotein A-I	1,40E+10
SERPING1	Plasma protease C1 inhibitor	1,04E+10
APOE	Apolipoprotein E	7,40E+09
APOC3	Apolipoprotein C-III	4,99E+09
A0A0U1RR20		4,53E+09
CLU	Clusterin	2,90E+09
APOA4	Apolipoprotein A-IV	2,16E+09
HP	Haptoglobin	1,93E+09
SERPINA1	Alpha-1-antitrypsin	1,82E+09
PON1	Serum paraoxonase/arylesterase 1	1,54E+09
HBB	Hemoglobin subunit beta	1,22E+09
IGHA1	Ig alpha-1 chain C region	1,15E+09
APOA2	Apolipoprotein A-II	8,66E+08
TTR	Transthyretin	8,58E+08
APOD	Apolipoprotein D	7,62E+08
SERPINA3	Alpha-1-antichymotrypsin	7,14E+08
C3	Complement C3	6,46E+08
KNG1	Kininogen-1	5,64E+08
APOC1	Apolipoprotein C-I	5,16E+08
IGKC	Ig kappa chain C region	5,15E+08
F2	Prothrombin	5,00E+08
HBA1;HBA2	Hemoglobin subunit alpha	4,80E+08
APOC4-APOC2;APOC2	Apolipoprotein C-II	4,69E+08
C4A	Complement C4-A	4,52E+08
VTN	Vitronectin	4,18E+08
APOF	Apolipoprotein F	4,15E+08
ITIH2	Inter-alpha-trypsin inhibitor heavy chain H2	4,01E+08
AMBP	Protein AMBP	3,98E+08
ORM1	Alpha-1-acid glycoprotein 1	3,50E+08
IGHM	Ig mu chain C region	3,49E+08
ITIH3	Inter-alpha-trypsin inhibitor heavy chain H3	3,42E+08
SERPINC1	Antithrombin-III	3,37E+08
ITIH1	Inter-alpha-trypsin inhibitor heavy chain H1	3,16E+08
IGHG1	Ig gamma-1 chain C region	2,97E+08
GP1BA	Platelet glycoprotein Ib alpha chain	2,96E+08
F5	Coagulation factor V	2,81E+08
PCYOX1	Prenylcysteine oxidase 1	2,58E+08

FLNA	Filamin-A	2,45E+08
ACTB;ACTG1	Actin, cytoplasmic 1;Actin, cytoplasmic 1, N-terminally processed	2,26E+08
A2M	Alpha-2-macroglobulin	2,25E+08
PLTP	Phospholipid transfer protein	2,23E+08
IGLL5;IGLC1	Immunoglobulin lambda-like polypeptide 5;Ig lambda-1 chain C regions	2,21E+08
HEG1	Protein HEG homolog 1	2,16E+08
PODXL	Podocalyxin	2,16E+08
GOLM1	Golgi membrane protein 1	2,11E+08
APOM	Apolipoprotein M	2,09E+08
PI16	Peptidase inhibitor 16	1,99E+08
SPARCL1	SPARC-like protein 1	1,97E+08
A0A2R8Y4Z1		1,74E+08
CFH	Complement factor H	1,54E+08
SSC5D	Soluble scavenger receptor cysteine-rich domain-containing protein SSC5D	1,46E+08
FN1	Fibronectin	1,32E+08
PTPRG	Receptor-type tyrosine-protein phosphatase gamma	1,31E+08
CD44	CD44 antigen	1,30E+08
SAA2-SAA4;SAA4	Serum amyloid A-4 protein	1,29E+08
LBP	Lipopolysaccharide-binding protein	1,28E+08
ORM2	Alpha-1-acid glycoprotein 2	1,22E+08
ABI3BP	Target of Nesh-SH3	1,17E+08
AGT	Angiotensinogen	1,07E+08
CENPF	Centromere protein F	1,03E+08
A1BG	Alpha-1B-glycoprotein	9,80E+07
ITGA2B	Integrin alpha-Iib	9,31E+07
HPR	Haptoglobin-related protein	8,92E+07
TF	Serotransferrin	8,80E+07
IGHG2	Ig gamma-2 chain C region	8,68E+07
AHSG	Alpha-2-HS-glycoprotein	7,90E+07
TLN1	Talin-1	7,59E+07
MENT	Protein MENT	7,15E+07
APOC4	Apolipoprotein C-IV	6,87E+07
PLA2G7	Platelet-activating factor acetylhydrolase	6,53E+07
HSPA5	78 kDa glucose-regulated protein	6,30E+07
COL18A1	Collagen alpha-1(XVIII) chain	6,24E+07
PTPRJ	Receptor-type tyrosine-protein phosphatase	5,63E+07
AKAP12	A-kinase anchor protein 12	5,41E+07
C9	Complement component C9	5,35E+07
SERPINF2	Alpha-2-antiplasmin	5,12E+07
YWHAZ	14-3-3 protein zeta/delta	5,09E+07

TNC	Tenascin	4,81E+07
SERPIND1	Heparin cofactor 2	4,53E+07
VCAM1	Vascular cell adhesion protein 1	4,42E+07
ITIH4	Inter-alpha-trypsin inhibitor heavy chain H4	4,35E+07
APOL1	Apolipoprotein L1	4,28E+07
SELL	L-selectin	3,89E+07
CPN2	Carboxypeptidase N subunit 2	3,61E+07
C4BPA	C4b-binding protein alpha chain	3,54E+07
ITGB3	Integrin beta-3	3,45E+07
JCHAIN;IGJ	Immunoglobulin J chain	3,43E+07
C1S	Complement C1s subcomponent	3,34E+07
TNXB	Tenascin-X	3,29E+07
SERPINA1	Alpha-I-antitrypsin	3,21E+07
PTPRZ1	Receptor-type tyrosine-protein phosphatase zeta	3,18E+07
GC	Vitamin D-binding protein	3,15E+07
DCD	Dermcidin	3,13E+07
TTN	Titin	2,99E+07
MUC1	Mucin-1	2,98E+07
C1R	Complement C1r subcomponent	2,93E+07
S100A9	Protein S100-A9	2,87E+07
HRG	Histidine-rich glycoprotein	2,73E+07
VCAN	Versican core protein	2,71E+07
A0A140TA44		2,71E+07
NCAM1	Neural cell adhesion molecule 1	2,70E+07
CP	Ceruloplasmin	2,51E+07
P01619	Ig kappa chain V-III region B6	2,50E+07
CHL1	Neural cell adhesion molecule L1-like protein	2,42E+07
PON3	Serum paraoxonase/lactonase 3	2,31E+07
LCAT	Phosphatidylcholine-sterol acyltransferase	2,30E+07
HPX	Hemopexin	2,26E+07
A0A2Q2TTZ9	Ig kappa chain V-I region	2,18E+07
GPR126	G-protein coupled receptor 126	2,08E+07
PROS1	Vitamin K-dependent protein S	1,95E+07
AFM	Afamin	1,88E+07
NUCB1	Nucleobindin-1	1,88E+07
ITGB1	Integrin beta-1	1,86E+07
S100A8	Protein S100-A8	1,86E+07
CD9	CD9 antigen	1,85E+07
STOM	Erythrocyte band 7 integral membrane protein	1,84E+07
ACTN1	Alpha-actinin-1	1,82E+07
ITGA6	Integrin alpha-6	1,80E+07
GPR116	Probable G-protein coupled receptor 116	1,80E+07
SELP	P-selectin	1,76E+07








LYVE1	Lymphatic vessel endothelial hyaluronic acid receptor 1	1,75E+07
PIP	Prolactin-inducible protein	1,74E+07
VASN	Vasorin	1,71E+07
IGHA2	Ig alpha-2 chain C region	1,71E+07
F10	Coagulation factor X	1,69E+07
VCL	Vinculin	1,68E+07
IGFALS	Insulin-like growth factor-binding protein complex acid labile subunit	1,68E+07
CD34	Hematopoietic progenitor cell antigen CD34	1,59E+07
MADCAM1	Mucosal addressin cell adhesion molecule 1	1,57E+07
MCAM	Cell surface glycoprotein MUC18	1,52E+07
PTPRC	Receptor-type tyrosine-protein phosphatase C	1,47E+07
MUC20	Mucin-20	1,43E+07
IGHG3	Ig gamma-3 chain C region	1,39E+07
TFPI	Tissue factor pathway inhibitor	1,35E+07
LAMP2	Lysosome-associated membrane glycoprotein 2	1,30E+07
SYNE1	Nesprin-1	1,29E+07
CPN1	Carboxypeptidase N catalytic chain	1,29E+07
SEPP1	Selenoprotein P	1,27E+07
CD248	Endosialin	1,25E+07
HLA-A	HLA class I histocompatibility antigen, A-24 alpha chain	1,23E+07
F13A1	Coagulation factor XIII A chain	1,20E+07
SPN	Leukosialin	1,17E+07
PGLYRP2	N-acetylmuramoyl-L-alanine amidase	1,12E+07
C5	Complement C5	1,12E+07
FERMT3	Fermitin family homolog 3	1,10E+07
SERPINA10	Protein Z-dependent protease inhibitor	1,08E+07
UBC;UBB;RPS27A;UBA52	Ubiquitin; Polyubiquitin-C; Ubiquitin-40S ribosomal protein S27a; Ubiquitin-60S ribosomal protein L40	9,51E+06
APCS	Serum amyloid P-component	9,16E+06
CD36	Platelet glycoprotein 4	9,14E+06
P4HB	Protein disulfide-isomerase	9,14E+06
IGLV3-9	Ig lambda chain V-III region LOI	8,79E+06
GPLD1	Phosphatidylinositol-glycan-specific phospholipase D	8,77E+06
FBLN1	Fibulin-1	8,40E+06
AZGP1	Zinc-alpha-2-glycoprotein	8,12E+06
C1RL	Complement C1r subcomponent-like protein	7,80E+06
IGKV2D-30	Ig kappa chain V-II region RPMI 6410	7,34E+06
BASP1	Brain acid soluble protein 1	7,28E+06
SERPINA6	Corticosteroid-binding globulin	6,88E+06




CETP	Cholesteryl ester transfer protein	6,79E+06
APOH	Beta-2-glycoprotein 1	6,66E+06
ANPEP	Aminopeptidase N	6,57E+06
B2M	Beta-2-microglobulin	6,50E+06
MXRA5	Matrix-remodeling-associated protein 5	5,56E+06
LGALS3BP	Galectin-3-binding protein	3,78E+06
MEGF9	Multiple epidermal growth factor-like domains protein 9	3,61E+06
PARVB	Beta-parvin	3,36E+06
CAMP	Cathelicidin antimicrobial peptide	3,34E+06
MANSC1	MANSC domain-containing protein 1	2,96E+06
SUSD5	Sushi domain-containing protein 5	2,65E+06
CRTAC1	Cartilage acidic protein 1	2,46E+06

Table S2: Top 10 genes influenced by Lp(a) levels

LogFC high minus low Lp(a)	Average Expression	T	p-value	p-value FDR	B	Gene	Chromosome
-0,1081	6,5926	-4,9045	2,943E-06	0,0696	4,342	SERPINB9	chr6
-0,1390	7,0563	-4,3916	2,423E-05	0,2594	2,442	ADAMTSL5	chr19
-0,1614	7,0877	-4,3112	3,327E-05	0,2594	2,157	SGTB	chr5
0,1756	6,6305	4,2696	3,914E-05	0,2594	2,011	NANOS1	chr10
-0,1233	8,1592	-4,2251	4,652E-05	0,2594	1,856	PVR	chr19
0,0988	6,0877	4,1890	5,347E-05	0,2594	1,732	PNMT	chr17
-0,0834	6,1023	-4,1477	6,262E-05	0,2594	1,590	VWDE	chr7
-0,1233	10,6033	-4,1241	6,854E-05	0,2594	1,509	EHD1	chr11
0,0929	6,3793	4,0159	1,031E-04	0,3142	1,145	ZFP62	chr5
-0,1371	6,9186	-3,9799	1,179E-04	0,3142	1,025	RASD2	chr22

Table S3: Pathways description and log10(p) from the MCODE algorithm analysis of the top genes identified in the transcriptomic stud.

Color	MCODE	GO	Description	Log10(P)
	MCODE_1	R-HSA-1650814	Collagen biosynthesis and modifying enzymes	-21.5
	MCODE_1	R-HSA-1474290	Collagen formation	-20.0
	MCODE_1	R-HSA-8948216	Collagen chain trimerization	-16.0
	MCODE_2	R-HSA-156584	Cytosolic sulfonation of small molecules	-5.7
	MCODE_2	GO:0051923	sulfation	-5.7
	MCODE_2	GO:0034035	purine ribonucleoside bisphosphate metabolic process	-5.7
	MCODE_3	R-HSA-500792	GPCR ligand binding	-30.4
	MCODE_3	R-HSA-373076	Class A/1 (Rhodopsin-like receptors)	-24.2
	MCODE_3	R-HSA-416476	G alpha (q) signalling events	-19.3
	MCODE_4	R-HSA-381426	Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	-15.8
	MCODE_4	R-HSA-8957275	Post-translational protein phosphorylation	-13.8
	MCODE_4	GO:0002576	platelet degranulation	-13.2
	MCODE_5	GO:0030216	keratinocyte differentiation	-8.5
	MCODE_5	GO:0042303	molting cycle	-8.2
	MCODE_5	GO:0042633	hair cycle	-8.2
	MCODE_6	GO:0033674	positive regulation of kinase activity	-10.0
	MCODE_6	GO:0051347	positive regulation of transferase activity	-9.7
	MCODE_6	ko01521	EGFR tyrosine kinase inhibitor resistance	-9.1
	MCODE_7	R-HSA-3232142	SUMOylation of ubiquitinylation proteins	-7.3
	MCODE_7	GO:0016925	protein sumoylation	-6.3
	MCODE_7	R-HSA-3108232	SUMO E3 ligases SUMOylate target proteins	-5.3

	MCODE_8	R-HSA-6798695	Neutrophil degranulation	-8.8
	MCODE_8	GO:0043312	neutrophil degranulation	-8.8
	MCODE_8	GO:0002283	neutrophil activation involved in immune response	-8.8
	MCODE_9	hsa05168	Herpes simplex virus 1 infection	-8.5
	MCODE_13	R-HSA-390522	Striated Muscle Contraction	-8.7
	MCODE_13	WP383	Striated Muscle Contraction Pathway	-8.6
	MCODE_13	GO:0033275	actin-myosin filament sliding	-8.6
