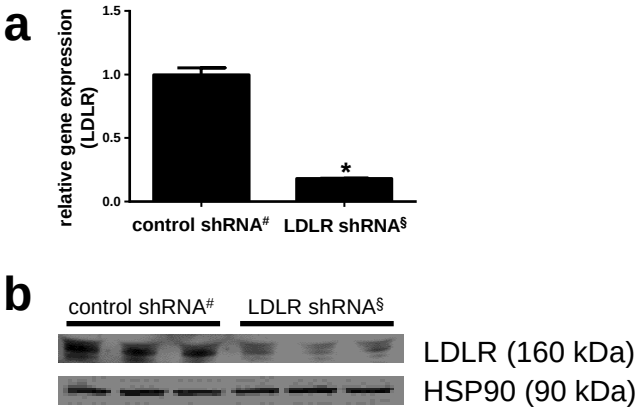
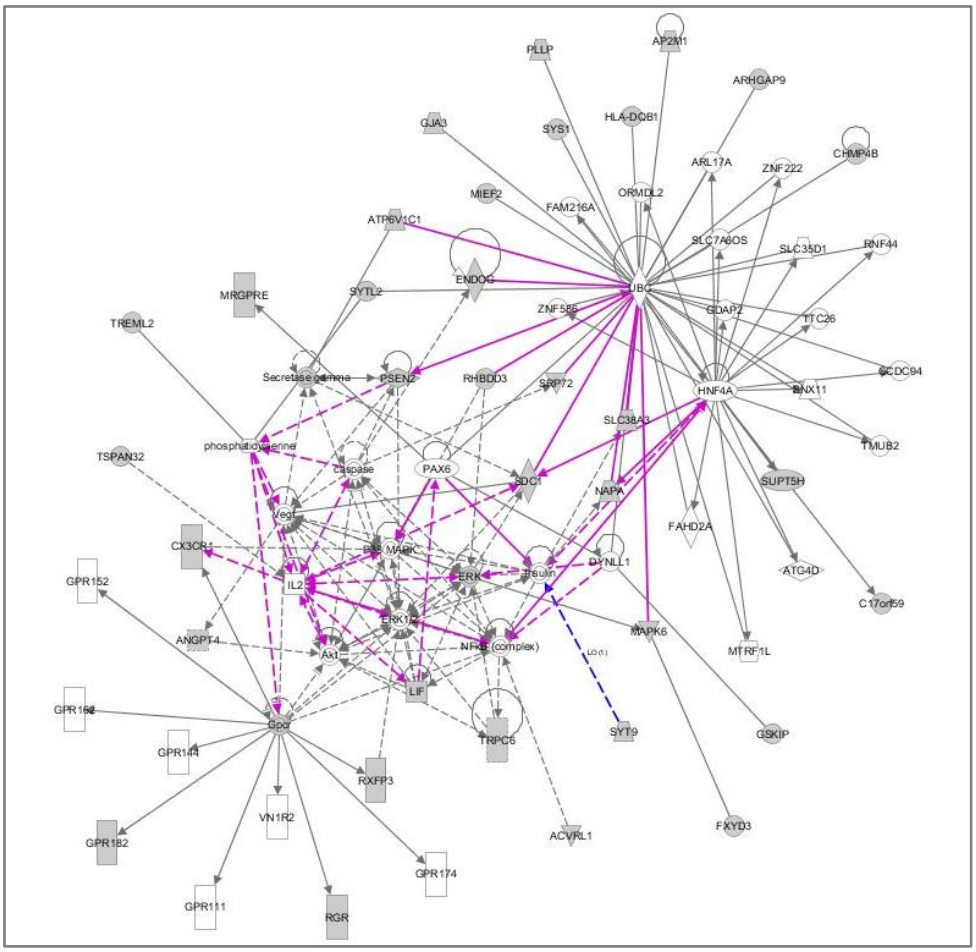
Supplementary Figure 1



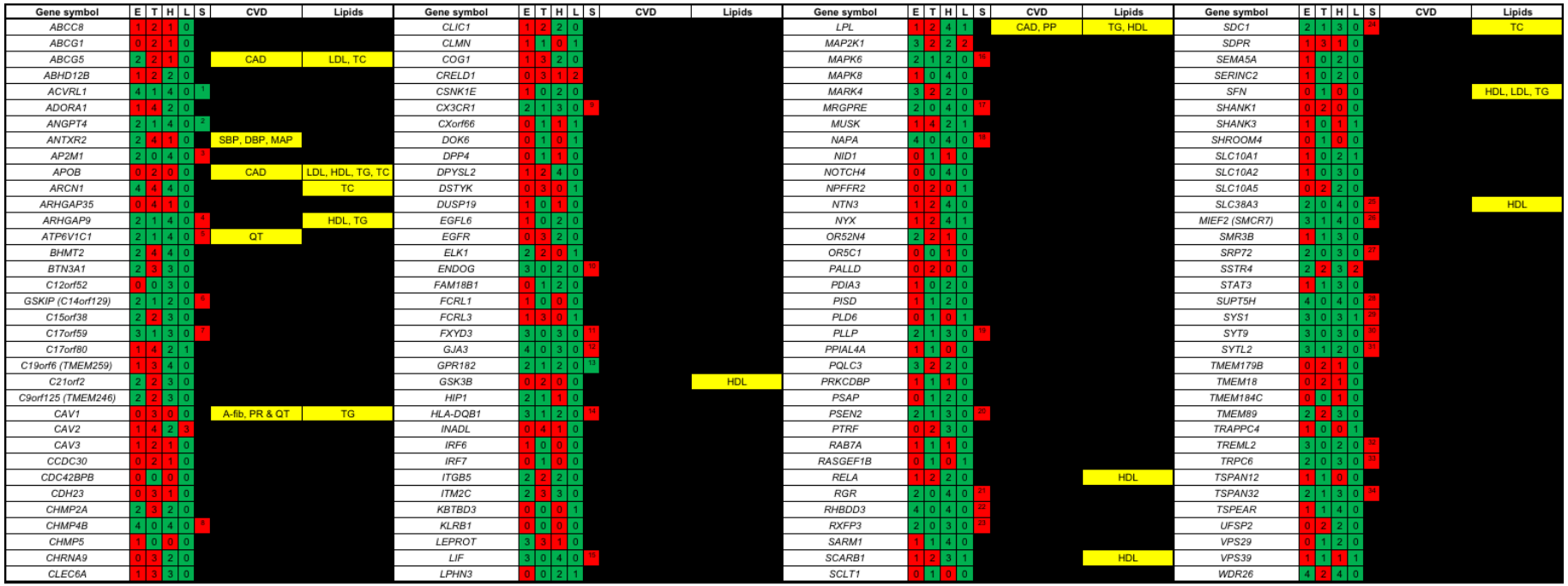
Supplementary Fig. 1. EA.hy926 cell line with LDLR knockdown.
a) qPCR result for EA.hy926 transduced with either scramble shRNA lentivirus or the 5 shRNA lentiviruses targeting the ORF of LDLR. #, cells cultured in LPDS. §, cells cultured in LDL supplemented media (25 µg/ml). Data represent the mean ± SEM and are representative of 3 experiments in duplicate. *$p < 0.05$, Student's t-test. b) Western blot analysis for EA.hy926 transduced with either scramble shRNA lentivirus or the 5 shRNA lentiviruses targeting the ORF of LDLR. #, cells cultured in LPDS. §, cells cultured in LDL-supplemented media (25 µg/ml) A non-cropped western blot for this experiment can be found in Supplementary Figure 11b.

Supplementary Figure 2



Supplementary Fig. 2. Qiagen's Ingenuity Pathway Analysis.
Analysis of the 34 gene hits revealed 3 distinct networks. Representation in a gene cluster format.

Supplementary Figure 3



Gene symbol	E	T	H	L	S	CVD	Lipids
ABCC8	1	2	1	0			
ABCG1	0	2	1	0			
ABCG5	2	2	1	0		CAD	LDL, TC
ABHD12B	1	2	2	0			
ACVRL1	4	1	4	0	1		
ADORA1	1	4	2	0			
ANGPT4	2	1	4	0	2		
ANTXR2	2	4	1	0		SBP, DBP, MAP	
AP2M1	2	0	4	0	3		
APOB	0	2	0	0		CAD	LDL, HDL, TG, TC
ARCN1	4	4	4	0			TC
ARHGAP35	0	4	1	0			
ARHGAP9	2	1	4	0	4		HDL, TG
ATP6V1C1	2	1	4	0	5	QT	
BHMT2	2	4	4	0			
BTN3A1	2	3	3	0			
C12orf52	0	0	3	0			
GSKIP (C14orf129)	2	1	2	0	6		
C15orf38	2	2	3	0			
C17orf59	3	1	3	0	7		
C17orf80	1	4	2	1			
C19orf6 (TMEM259)	1	3	4	0			
C21orf2	2	2	3	0			
C9orf125 (TMEM246)	2	2	3	0			
CAV1	0	3	0	0		A-fib, PR & QT	TG
CAV2	1	4	2	3			
CAV3	1	2	1	0			
CCDC30	0	2	1	0			
CDC42BPB	0	0	0	0			
CDH23	0	3	1	0			
CHMP2A	2	3	2	0			
CHMP4B	4	0	4	0	8		
CHMP5	1	0	0	0			
CHRNA9	0	3	2	0			
CLEC6A	1	3	3	0			
CLIC1	1	2	2	0			
CLMN	1	1	0	1			
COG1	1	3	2	0			
CRELD1	0	3	1	2			
CSNK1E	1	0	2	0			
CX3CR1	2	1	3	0	9		
CXorf66	0	1	1	1			
DOK6	0	1	0	1			
DPP4	0	1	1	0			
DPYSL2	1	2	4	0			
DSTYK	0	3	0	1			
DUSP19	1	0	1	0			
EGFL6	1	0	2	0			
EGFR	0	3	2	0			
ELK1	2	2	0	1			
ENDOG	3	0	2	0	10		
FAM18B1	0	1	2	0			
FCRL1	1	0	0	0			
FCRL3	1	3	0	1			
FXYD3	3	0	3	0	11		
GJA3	4	0	3	0	12		
GPR182	2	1	2	0	13		
GSK3B	0	2	0	0			HDL
HIP1	2	1	1	0			
HLA-DQB1	3	1	2	0	14		
INADL	0	4	1	0			
IRF6	1	0	0	0			
IRF7	0	1	0	0			
ITGB5	2	2	2	0			
ITM2C	2	3	3	0			
KBTBD3	0	0	0	1			
KLRB1	0	0	0	0			
LEPROT	3	3	1	0			
LIF	3	0	4	0	15		
LPHN3	0	0	2	1			
LPL	1	2	4	1		CAD, PP	TG, HDL
MAP2K1	3	2	2	2			
MAPK6	2	1	2	0	16		
MAPK8	1	0	4	0			
MARK4	3	2	2	0			
MRGPRE	2	0	4	0	17		
MUSK	1	4	2	1			
NAPA	4	0	4	0	18		
NID1	0	1	1	0			
NOTCH4	0	0	4	0			
NPFFR2	0	2	0	1			
NTN3	1	2	4	0			
NYX	1	2	4	1			
OR52N4	2	2	1	0			
OR5C1	0	0	1	0			
PALLD	0	2	0	0			
PDIA3	1	0	2	0			
PISD	1	1	2	0			
PLD6	0	1	0	1			
PLLP	2	1	3	0	19		
PPIAL4A	1	1	0	0			
PQLC3	3	2	2	0			
PRKCDBP	1	1	1	0			
PSAP	0	1	2	0			
PSEN2	2	1	3	0	20		
PTRF	0	2	3	0			
RAB7A	1	1	1	0			
RASGEF1B	0	1	0	1			
RELA	1	2	2	0			HDL
RGR	2	0	4	0	21		
RHBDD3	4	0	4	0	22		
RXFP3	2	0	3	0	23		
SARM1	1	1	4	0			
SCARB1	1	2	3	1			HDL
SCLT1	0	1	0	0			
SDC1	2	1	3	0	24		TC
SDPR	1	3	1	0			
SEMA5A	1	0	2	0			
SERINC2	1	0	2	0			
SFN	0	1	0	0			HDL, LDL, TG
SHANK1	0	2	0	0			
SHANK3	1	0	1	1			
SHROOM4	0	1	0	0			
SLC10A1	1	0	2	1			
SLC10A2	1	0	3	0			
SLC10A5	0	2	2	0			
SLC38A3	2	0	4	0	25		HDL
MIEF2 (SMCR7)	3	1	4	0	26		
SMR3B	1	1	3	0			
SRP72	2	0	3	0	27		
SSTR4	2	2	3	2			
STAT3	1	1	3	0			
SUPT5H	4	0	4	0	28		
SYS1	3	0	3	1	29		
SYT9	3	0	3	0	30		
SYTL2	3	1	2	0	31		
TMEM179B	0	2	1	0			
TMEM18	0	2	1	0			
TMEM184C	0	0	1	0			
TMEM89	2	2	3	0			
TRAPPC4	1	0	0	1			
TREML2	3	0	2	0	32		
TRPC6	2	0	3	0	33		
TSPAN12	1	1	0	0			
TSPAN32	2	1	3	0	34		
TSPEAR	1	1	4	0			
UFSP2	0	2	2	0			
VPS29	0	1	2	0			
VPS39	1	1	1	1			
WDR26	4	2	4	0			

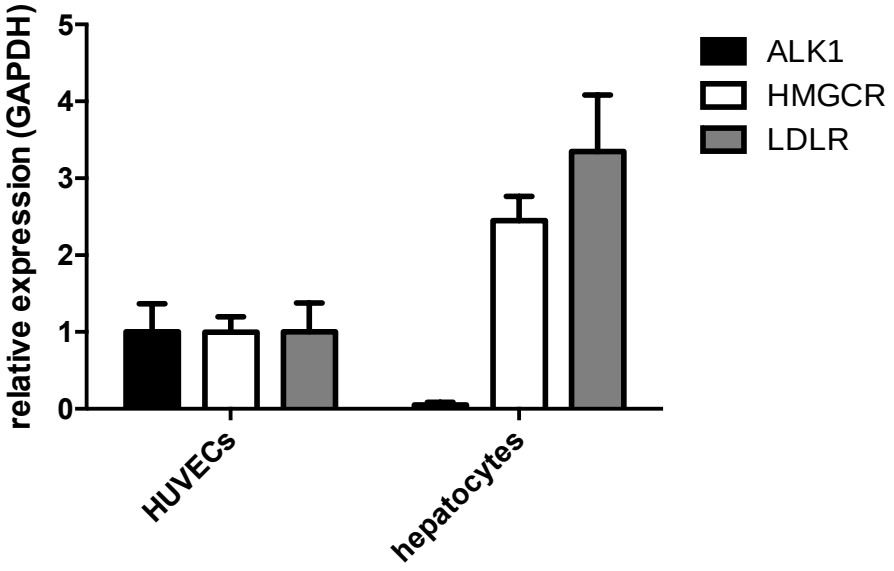
E: DiI-LDL uptake in EA.hy926 cells	
T: Transferrin-FITC uptake in EA.hy926 cells	
H: DiI-LDL uptake in HUVECs	
L: LDLR dependency	
S: endothelial specific	

CVD	cardiovascular traits
Lipids	effect on lipids
A-fib.	atrial fibilliation
CAD	coronary artery disease
DBP	diastoloic blood pressure
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MAP	mean arterial pressure
PP	pulse pressure
PR	PR interval
QT	QT interval
SBP	systolic blood pressure
TC	total cholesterol
TG	triglycerid

Shown are the numbers of individual siRNAs targeting each gene that score positive in each screen. Green, siRNAs fullfil the assay criteria (**E + H**: ≥ 2 positive siRNAs / **T + L**: ≤ 2 positive siRNAs). Red, siRNAs does not fullfil the assay criteria (**E + H**: ≤ 2 positive siRNAs / **T + L**: ≥ 2 positive siRNAs).

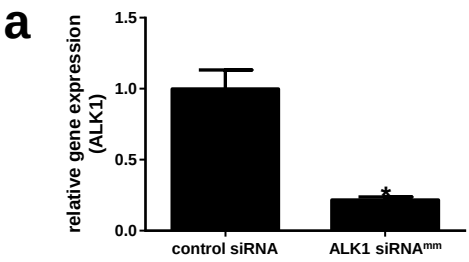
Supplementary Fig. 3. Follow-up screen.
140 genes from the initial GW RNAi screen were further analysed. See Supplementary Datatset 2 for further details. References for the expression pattern are listed under Supplementary References at the end of this document. See Supplementary Dataset 3 for further details on the GWAS data.

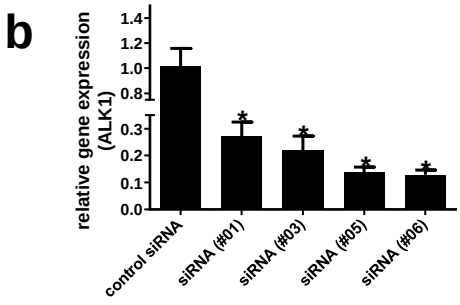
Supplementary Figure 4

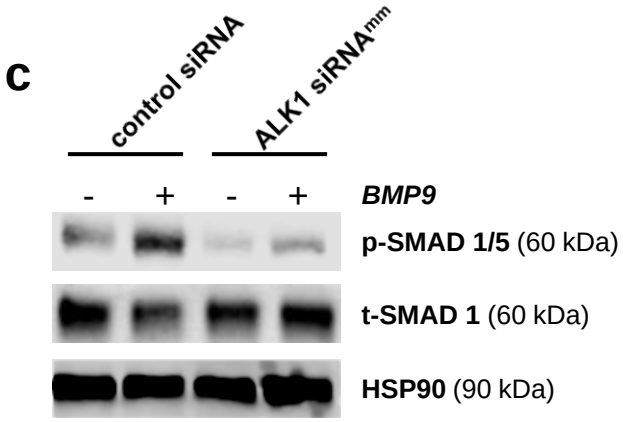


Supplementary Fig. 4. Transcript levels for ALK1 in human primary endothelial cells and hepatocytes
The transcript levels of *ACVRL1*, *HMGCR* and *LDLR* were compared between primary human endothelial cells (HUVEC) and primary human hepatocytes (healthy donors).

Supplementary Figure 5

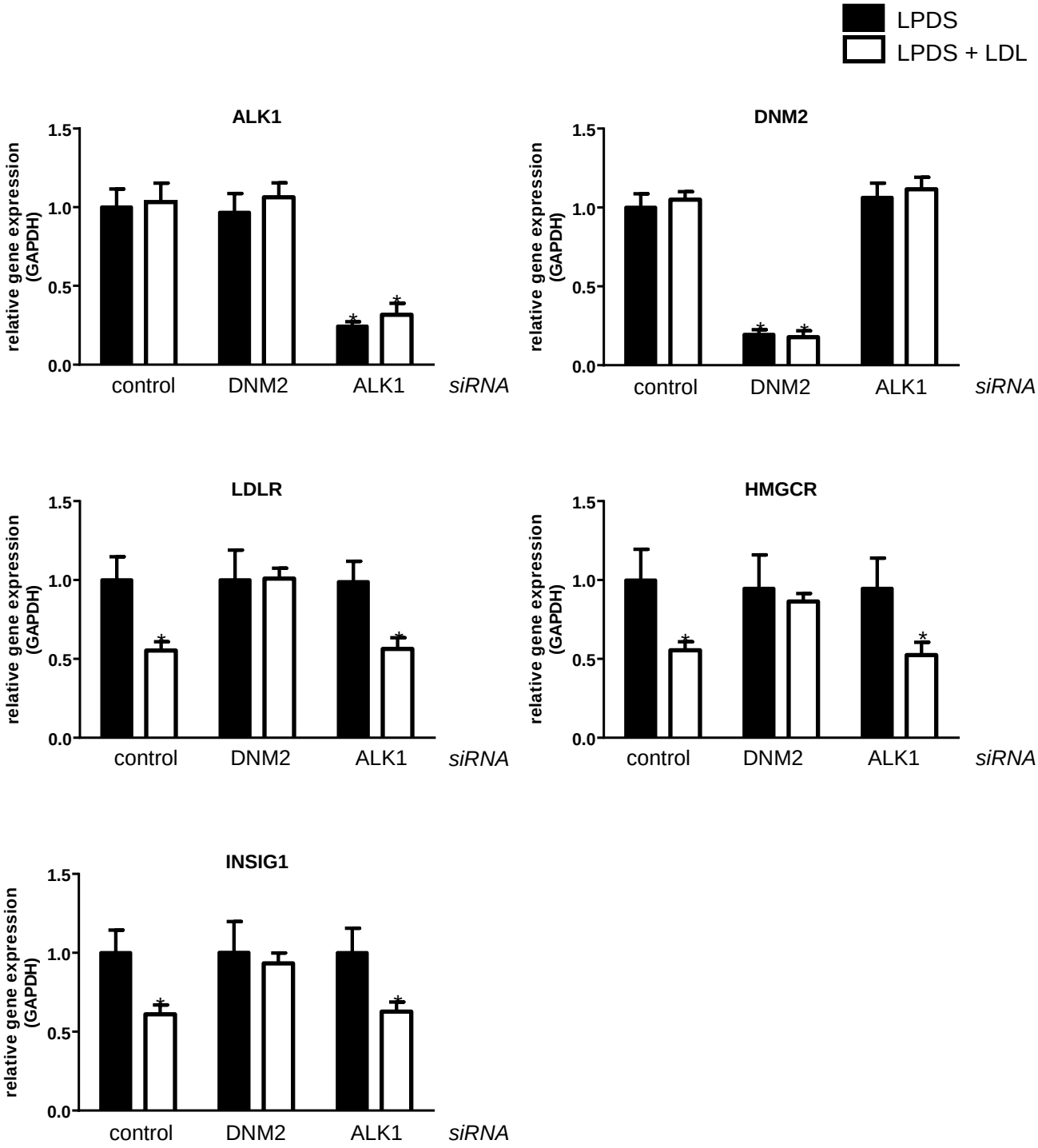






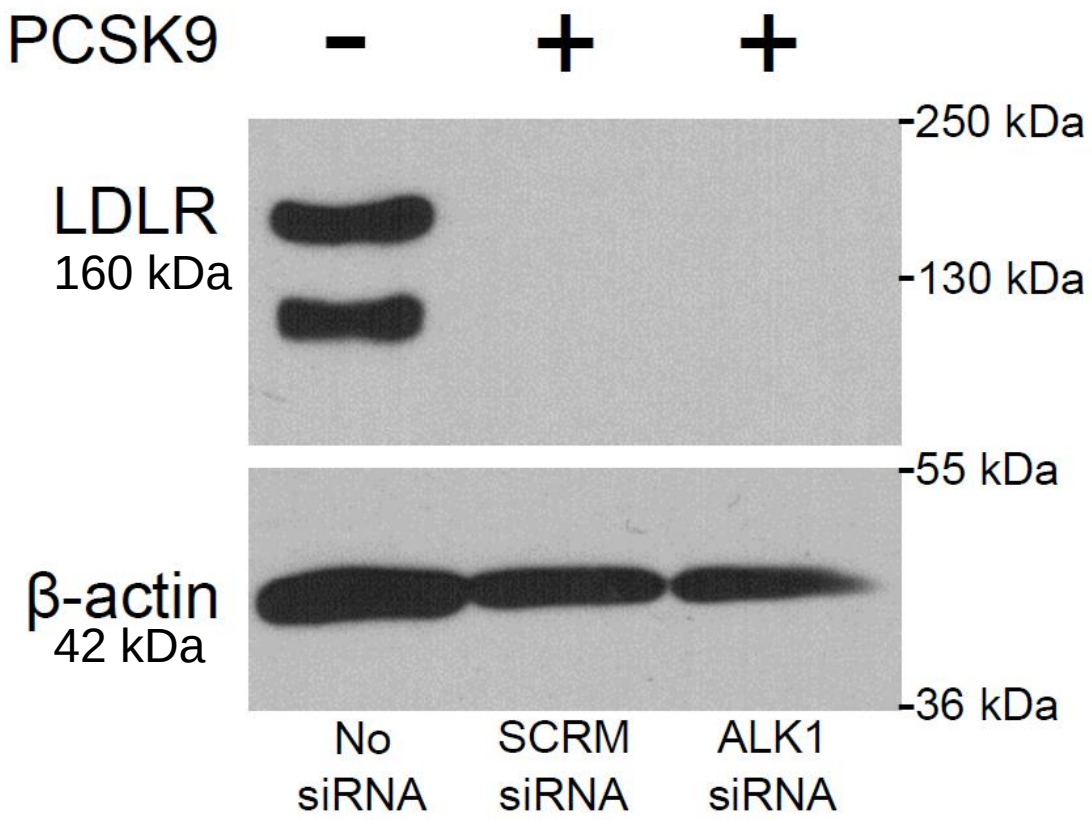
Supplementary Fig. 5. siRNA efficiency analysis
a) qPCR analysis of the knockdown efficiency of siRNA against murine ALK1 (here MLEC). Data represent the mean ± SEM and are representative of 3 experiments in duplicate. *p < 0.05, Student's t-test. b) qPCR analysis of all 4 individual siRNAs against human ALK1 used in the GW RNAi screen. Analysis performed in HUVECs. Data represent the mean ± SEM and are representative of 3 experiments in duplicate. *p < 0.05, Student's t-test. c) Western blot analysis of the knockdown efficiency of siRNA against murine ALK1 (here MLEC) based on the BMP9 (10 ng/ml) induced phosphorylation of SMAD 1/5. A non-cropped western blot for this experiment can be found in Supplementary Figure 12a.

Supplementary Figure 6



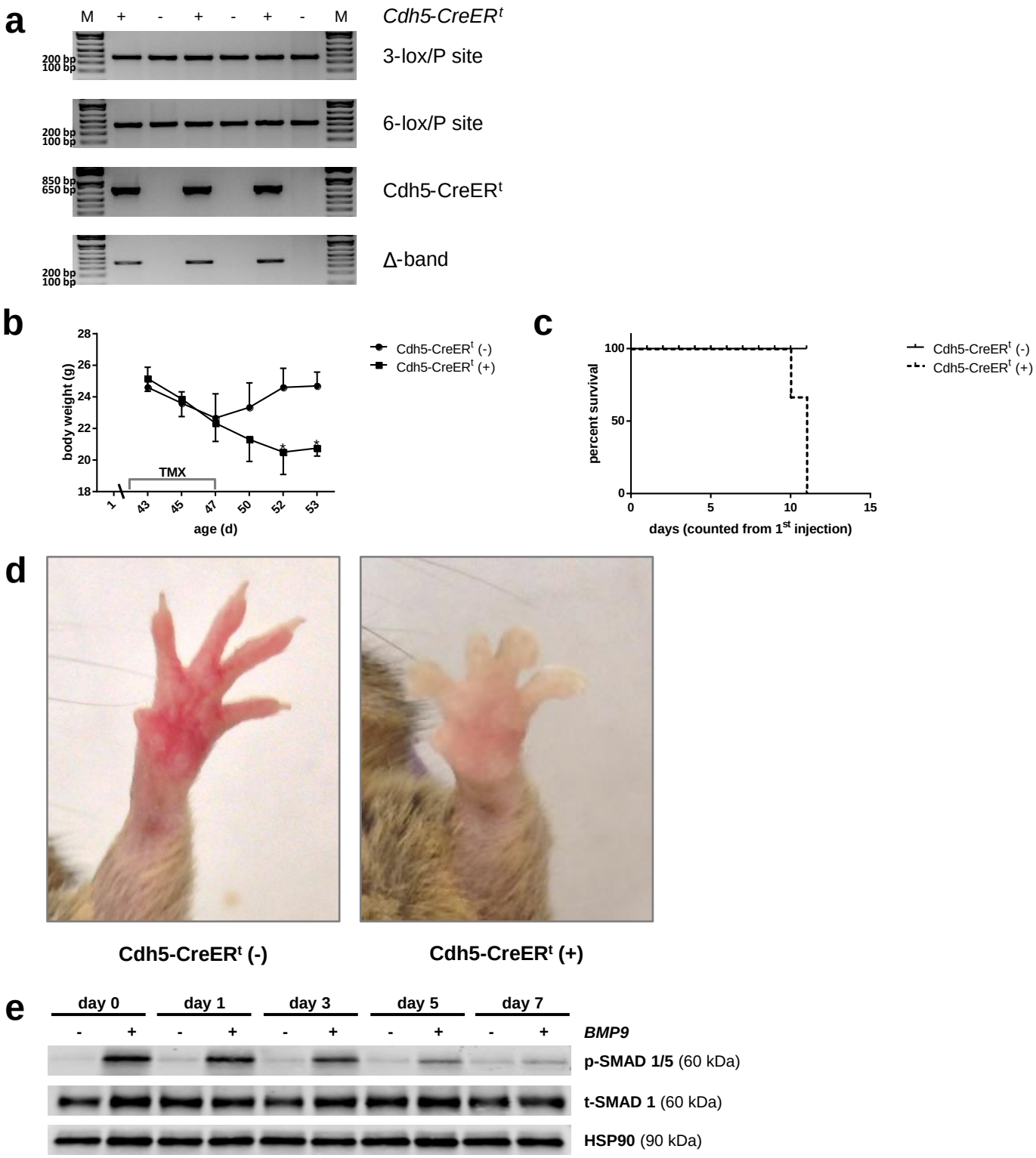
Supplementary Fig. 6. ALK1 knockdown does not affect transcript levels of SREB2-dependent genes
Cells were treated with control siRNA, *ACVRL1* siRNA and *DNM2* siRNA and kept in either low LDL media (LPDS) or high LDL media (LDL pretreated), before transcripts for genes involved in sterol sensing were analysed. Data represent the mean ± SEM and are representative of 3 experiments in duplicate. *p < 0.05, Student's t-test.

Supplementary Figure 7



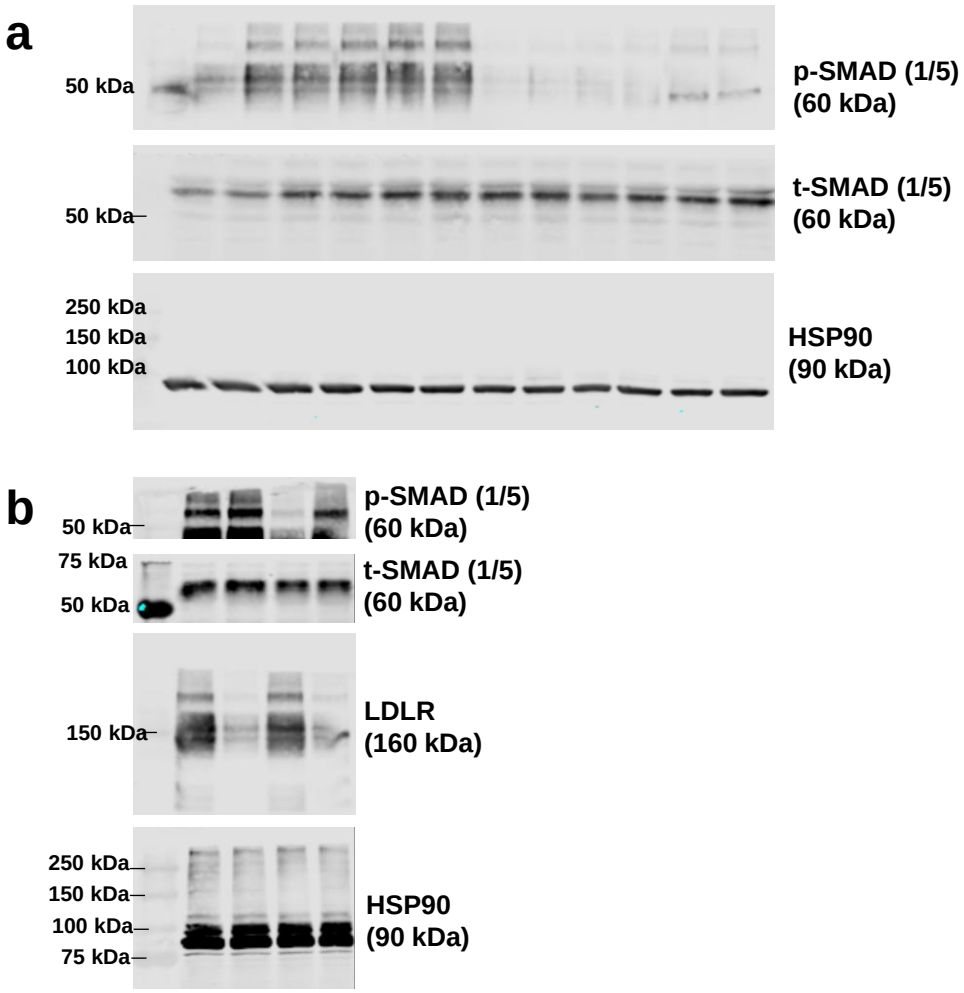
Supplementary Fig. 7. PCSK9 conditioned media leads to degradation of LDLR in HCAECs
Treatment of HCAECs transfected with control siRNA or *ACVRL1* siRNA with PCSK9 conditioned media for at least 6 hrs results in a complete removal of LDLR.

Supplementary Figure 8



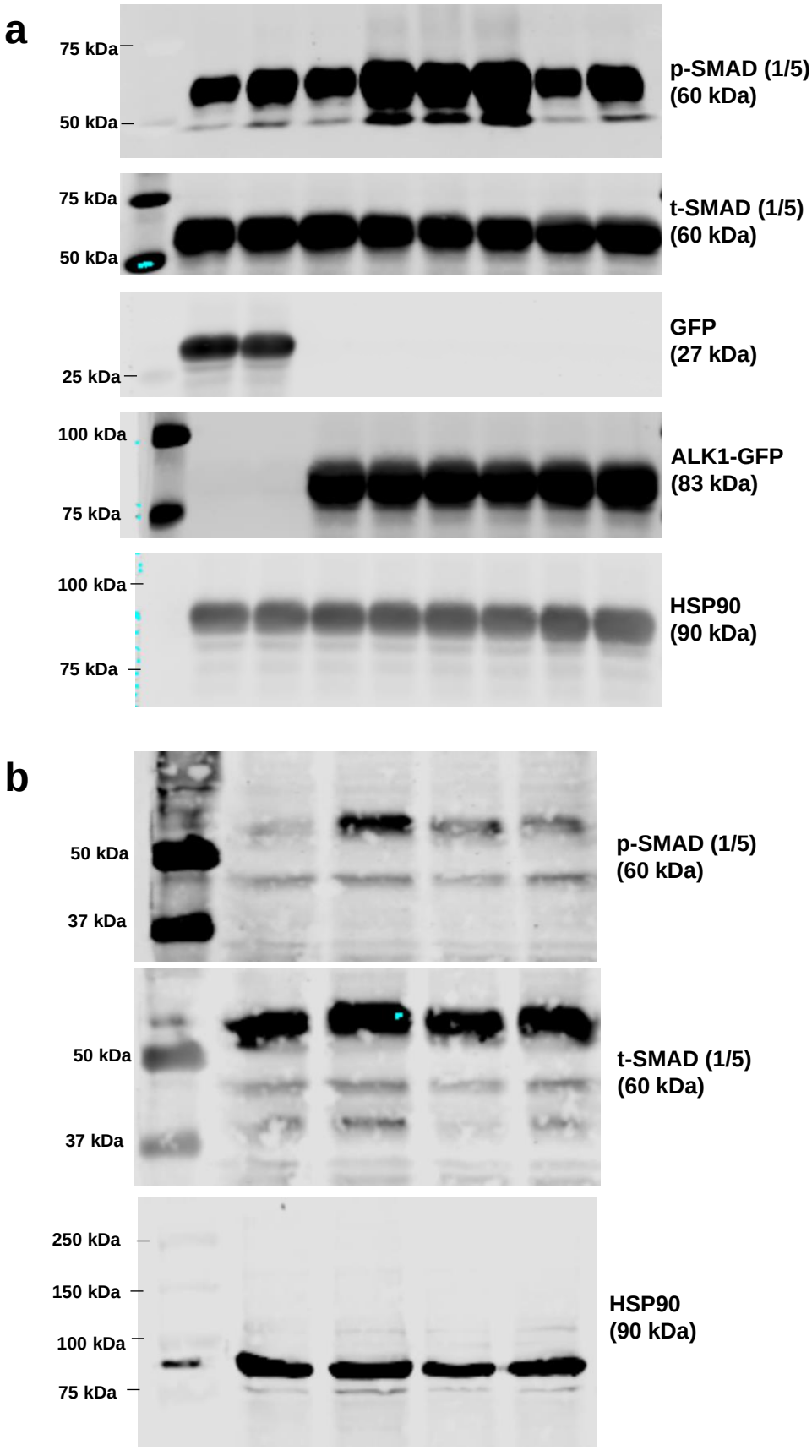
Supplementary Fig. 8. Endothelial specific deletion of ALK1 in adult mice leads to rapid death
a) Genotyping results of *Acvrl1*$^{fl/fl}$ mice with or without the inducible *Cdh5*-CreERT2 transgene 7 days after first TMX injection. b) Weight measurements. Data represent the mean ± SEM and are representative of 3 animals each. *p < 0.05, Student's t-test. c) Kaplan-Meier curve. d) Representative images of paws from Cre-negative and Cre-positive animals 7 days after the first TMX injection. e) Cre-positive animals were injected with TMX for 0, 1, 3, 5 or 7 days and primary MLECs were isolated and treated after 3 hrs of starvation with vehicle or BMP9 (10 ng/ml). A non-cropped western blot for this experiment can be found in Supplementary Figure 12b.

Supplementary Figure 9



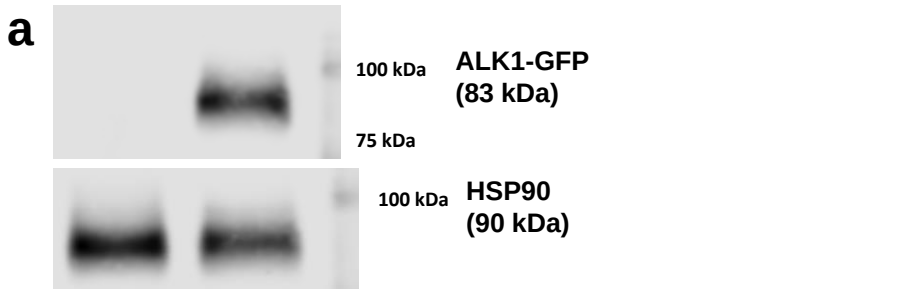
Supplementary Fig. 9. Original Western Blots
a) Original gel scans for Fig. 2b. b) Original gel scans for Fig. 3b.

Supplementary Figure 10



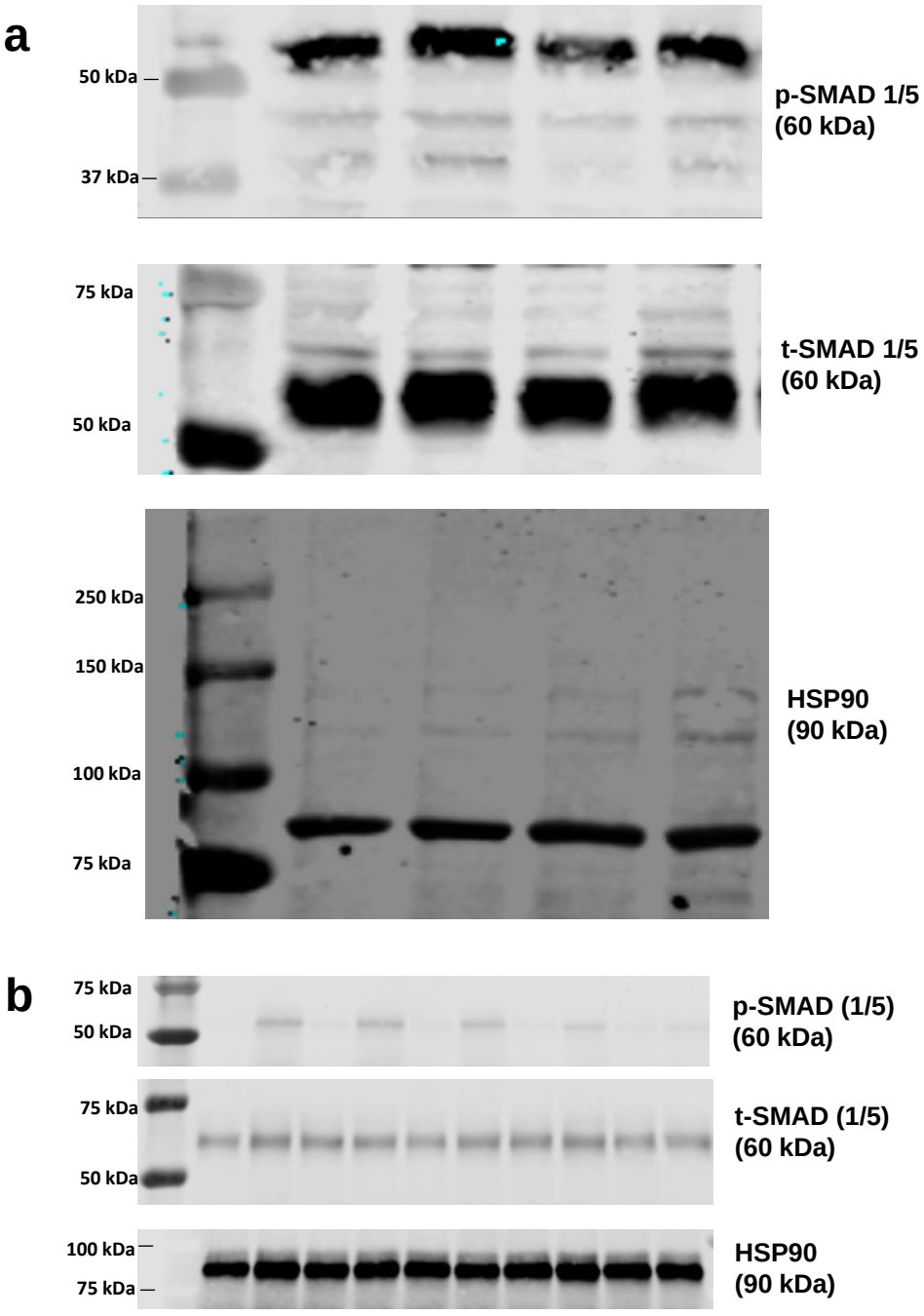
Supplementary Fig. 10. Original Western Blots
a) Original gel scans for Fig. 4c. b) Original gel scans for Fig. 4e.

Supplementary Figure 11



Supplementary Fig. 11. Original Western Blots
a) Original gel scans for Fig. 5a. b) Original gel scans for Sup. Fig. 1b.

Supplementary Figure 12



Supplementary Fig. 12. Original Western Blot
a) Original gel scans for Sup. Fig. 6c. b) Original gel scans for Sup. Fig. 9e.

Supplementary Table 1

Network 1	Network 2	Network 3
Hereditary Disorder, Metabolic Disease, Neurological Disease	Carbohydrate Metabolism, Lipid Metabolism, Small Molecule Biochemistry	Cancer, Carbohydrate Metabolism, Cell Cycle
ACVRL1, Akt, **ANGPT4**, **ATP6V1C1**, caspase, **CX3CR1**, **ENDOG**, ERK, ERK1/2, **FXYD3**, Gpcr, GPR111, GPR144, GPR152, GPR162, GPR174, **GPR182**, Insulin, **LIF**, **MAPK6**, **NAPA**, NFkB (complex), P38 **MAPK6**, **PSEN2**, **RGR**, **RHBDD3**, RXFP3, **SDC1**, Secretase gamma, **SLC38A3**, **SRP72**, **SYT9**, **TRPC6**, Vegf, VN1R2	**AP2M1**, **ARHGAP9**, ARL17A, ATG4D, **C17orf59**, CCDC94, **CHMP4B**, DYNLL1, FAHD2A, FAM216A, GDAP2, **GJA3**, **GSKIP**, **HLA-QB1**, HNF4A, **MIEF2**, **MRGPRE**, MTRF1L, ORMDL2, PAX6, phosphatidylserin, **PLLP**, RNF44, SLC35D1, SLC7A6OS, SNX11, **SUPT5H**, **SYS1**, **SYTL2**, TMUB2, **TREML2**, TTC26, UBC, ZNF222, ZNF586	IL2, **TSPAN32**

Supplementary Table 1. Qiagen's Ingenuity Pathway Analysis.
Analysis of the 34 gene hits revealed 3 distinct networks. Representation in a table format. Genes in bold were found in the screen and genes in red cluster in the vesicular trafficking pathway.

Supplementary Table 2

gene	ordering number	company	concentration
control siRNA	D-001220-01	Dharmacon	20 nM
scamble control siRNA	1027310	Qiagen	20 nM
ALK1 siRNA (human)	D-005302-06	Dharmacon	20 nM
ALK1 siRNA (murine)	M-043004-01	Dharmacon	20 nM
DNM2 siRNA (human)	customized target sequence: 5'-AACATGCCGAGTTTTTGCACT-3'	Qiagen	20 nM
LDLR siRNA (human)	4392420 / ID: s224006	Ambion	20 nM
LDLR shRNAs lentiviral knockdown (human)	TRCN0000056517 5′- CCGGACAGAGGATGAGGTCCACATTCTCGAGAAT GTGGACCTCATCCTCTGTTTTTTG-3′ TRCN0000262146 5′- CCGGGGGCGACAGATGCGAAAGAAACTCGAGTTT CTTTCGCATCTGTCGCCCTTTTTG-3′ TRCN0000262148 5′- CCGGACATCAACAGCATCAACTTTGCTCGAGCAA AGTTGATGCTGTTGATGTTTTTTG-3′ TRCN0000262149 5′- CCGGATGGAAGAACTGGCGGCTTAACTCGAGTTA AGCCGCCAGTTCTTCCATTTTTTG-3′ TRCN0000282124 5′- CCGGGATGAAGTTGGCTGCGTTAATCTCGAGATT AACGCAGCCAACTTCATCTTTTTG-3′	Sigma-Aldrich	n/a
NPC2 siRNA (human)	M-017216-00	Dharmacon	20 nM

Supplementary Tab. 2. siRNA and shRNAs used in the study.

Supplementary Table 3

protein	ordering number	company	working concentration
Western Blot			
β-actin	sc-47778	Santa Cruz	1 : 1,000
HSP90	sc-13119	Santa Cruz	1 : 1,000
GFP	sc-8664	Santa Cruz	1 : 1,000
LDLR	10007665	Cayman	1 : 500
p-SMAD 1/5 (S463/S465)	9516	Cell Signaling	1 : 500
t-SMAD 1	9743	Cell Signaling	1 : 1,000
FACS			
LDLR	sc-18823	Santa Cruz	1.5 µg/tube
mmIgG2b	sc-3879	Santa Cruz	1.5 µg/tube
Goat anti-Mouse IgG (H+L) Secondary Antibody, Alexa Fluor® 488 conjugate	A-11001	Invitrogen	1:500
Immunofluorescence			
EEA1	610456	BD Transduction Laboratories	1:200
MLEC isolation			
M-450 Dynabeads conjugated with sheep anti-rat IgG	110.07	Dynal Biotech	50 µl beads/6 µl antibody
Affinity-purified anti-mouse CD31 (PECAM-1) antibody	553370	Pharmingen	6 µl antibody/3 mice

Supplementary Tab. 3. Antibodies used in the study.

Supplementary Table 4

Cdh5-CreERT2		
forward	5'-GCC TGC ATT ACC GGT CGA TGC AAC GA-3'	
reverse	5'-GTG GCA GAT GGC GCG GCA ACA CCA TT-3'	
amplicon size	700 bp	
PCR program		
step 1	93°C	2:00 min
step 2	93°C	0:30 min
step 3	67°C	0:30 min
step 4	72°C	0:45 min
step 5	go to 2, 35 x	
step 6	72°C	10:00 min
step 7	4°C	forever

LDLR-KO		
P1 (common)	5'-CCA TAT GCA TCC CCA GTC TT-3'	
P2 (WT)	5'-GCG ATG GAT ACA CTC ACT GC-3'	
P3 (Neo)	5'- AAT CCA TCT TGT TCA ATG GCC GAT C-3'	
WT	167 bp	
KO	350 bp	
Het	167 bp + 350 bp	
PCR program		
step 1	95°C	3:00 min
step 2	95°C	0:10 min
step 3	61°C	0:45 min
step 4	72°C	3:00 min
step 5	go to 2, 35 x	
step 6	72°C	10:00 min
step 7	4°C	forever

ALK1 floxed allel		
forward loxP 3	5'-CAG CAC CTA CAT CTT GGG TGG AGA-3'	
reverse loxP 3	5'-ACT GTT CTT CCT CGG AGC CTT GTC-3'	
amplicon size floxed	> 300 bp	
amplicon size unfloxed	187 bp	
forward loxP 6	5'-CCT GGA CAG CGA CTG TAC TAC-3'	
reverse loxP 6	5'-GCC CCA TTG CTC TCC TCA AA-3'	
amplicon size floxed	> 400 bp	
amplicon size unfloxed	356 bp	
By using forward loxP 3 and reverse loxP 6 primers the Δ-band after Cre-recombinase excision can be detected (~ 400 bp).		
PCR program		
step 1	94°C	10:00 min
step 2	94°C	0:30 min
step 3	60°C	0:40 min
step 4	72°C	0:40 min
step 5	go to 2, 34 x	
step 6	72°C	2:00 min
step 7	4°C	forever

Supplementary Tab. 4. Genotyping primers and PCR programs.

Supplementary Table 5

gene	species	primers (5'→3') forward reverse
ALK1	human	CGAGGGATGAACAGTCCTGG GTCATGTCTGAGGCGATGAAG
	murine	GGGCCTTTTGATGCTGTCG TGGCAGAATGGTCTCTTGCAG
DNM2	human	GTTTGTGCTGACTGCCGAGT TTCCAGCTGTCCACGTCTTC
GAPDH	human	CTCTCTGCTCCTCCTGTTCGAC TGAGCGATGTGGCTCGGCT
	murine	AATGTGTCCGTCGTGGATCTGA AGTGTAGCCCAAGATGCCCTTC
HMGCR	human	TGATTGACCTTTCCAGAGCAAG CTAAAATTGCCATTCCACGAGC
INSIG1	human	GCACTGCATTAAACGTGTGG GCAGCACTGAAATGAATGGA
LDLR	human	TCTGCAACATGGCTAGAGACT TCCAAGCATTCGTTGGTCCC
PCSK9	human	GGAGCTGGCCTTGAAGTTGCC ACCGTGGAGGGGTAATCCGC

Supplementary Tab. 5. Primers used for qPCR analyses.

Supplementary References

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