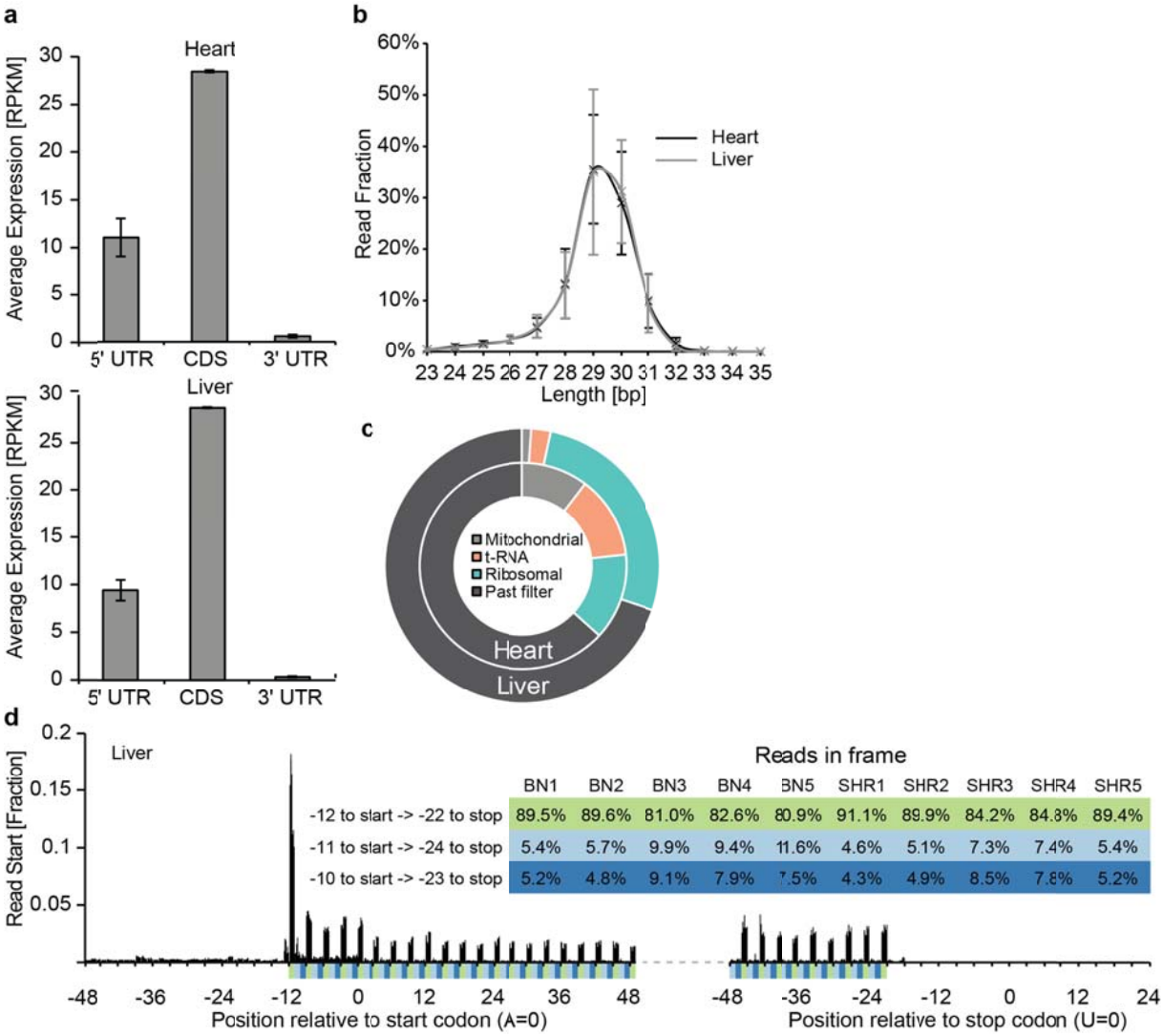
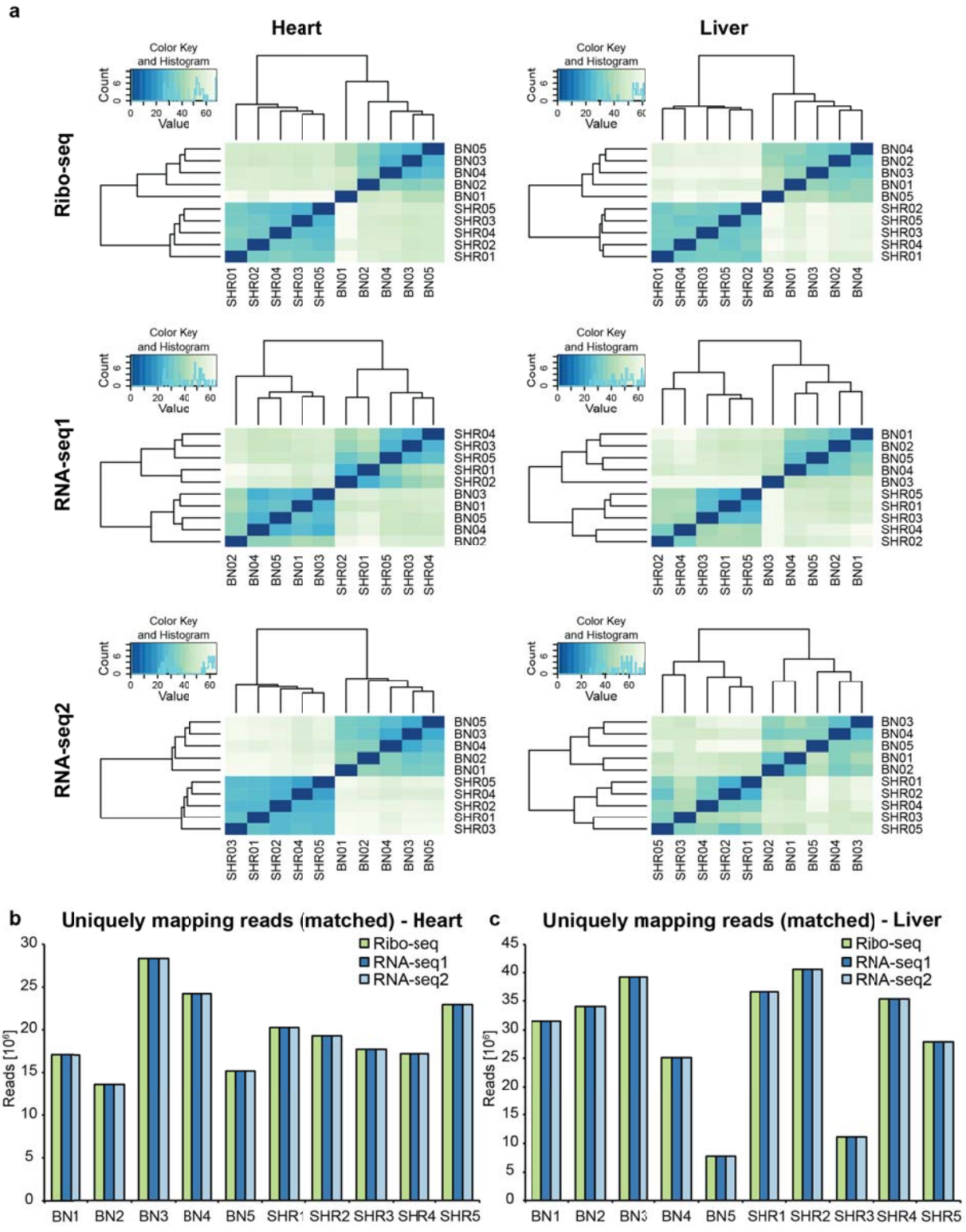
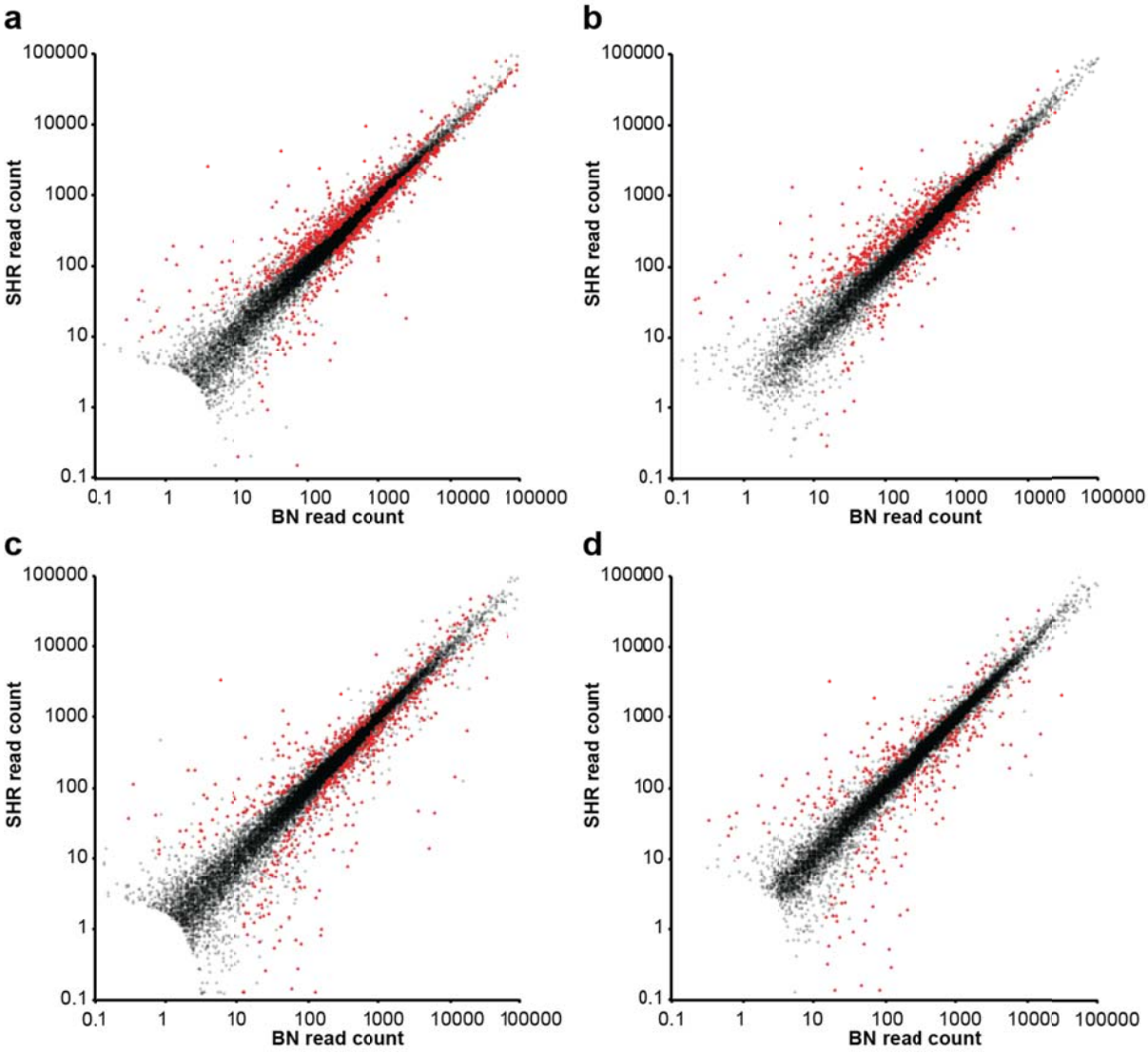


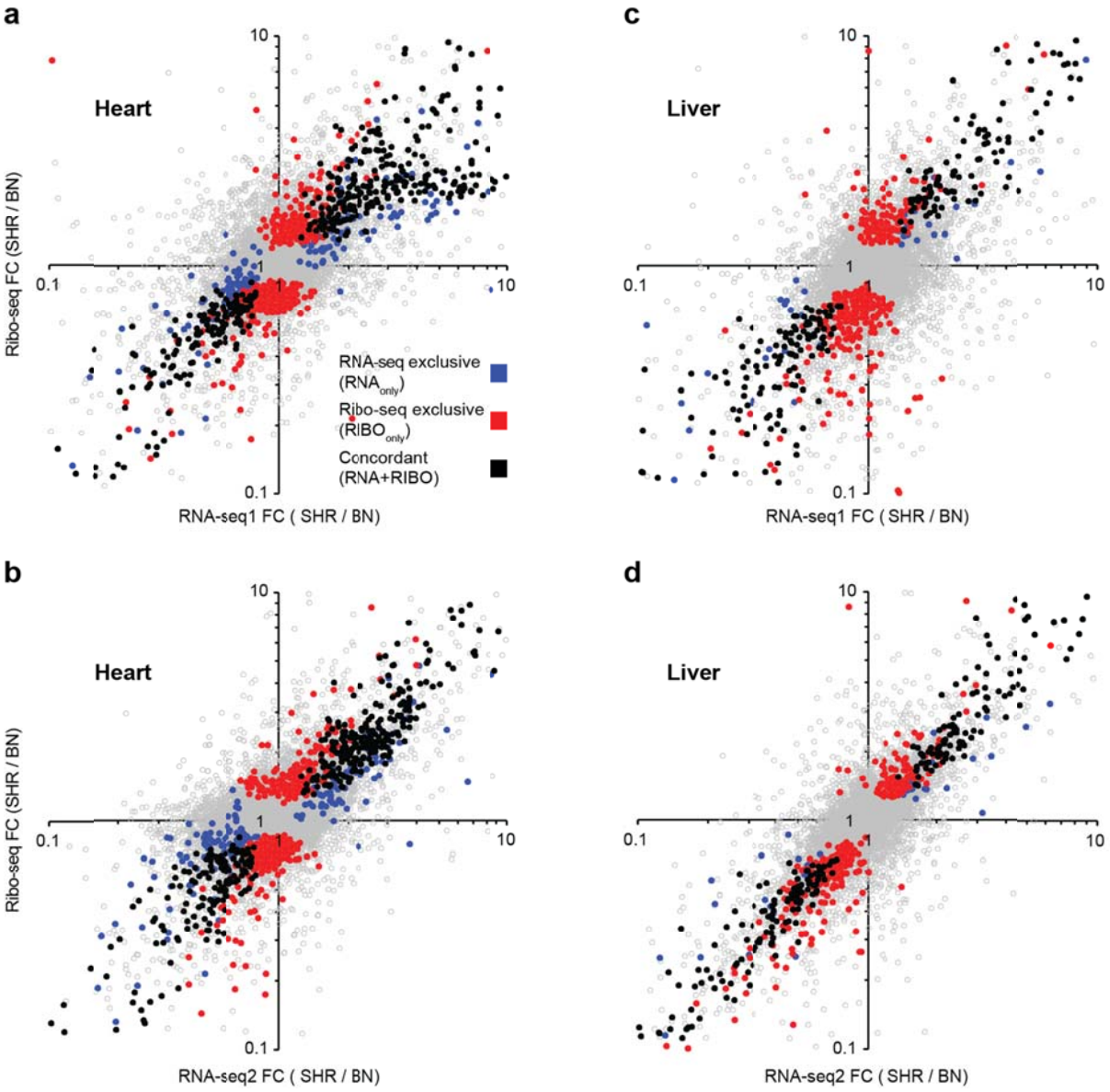
Supplementary Figure 1. General attributes and quality control for RPF libraries of frozen tissues. (**a**) Read distribution across gene bodies is shown for 10 libraries (5x SHR/Ola; 5x BN-*Lx*) for each tissue. Reads covering 5'UTR, CDS or 3'UTR were normalized to feaure length and library depth to calculate the average "reads per kilobase per million reads" RPKM. Ribosome footprints are mainly found in the coding region of transcripts and to a lesser extent in the leader sequence (5' UTR), while the average RPKM for the 3' UTR in both tissues is less than 0.5. (**b**) Average read length distribution of 10 heart (black) and 10 liver (grey) Ribo-seq libraries. Ribosomes protect mostly 29 nt on transcripts. (**c**) Pie charts illustrate the average of mitochondrial, tRNA and rRNA read fractions for heart and liver datasets. The "past filter" share denotes the reads used for downstream analysis. (**d**) Periodicity profile of RPFs in hepatic tissue at a subcodon resolution. The plot shows, for each sample, the number of RPF reads' 5' termini (read start) aligning in 48 nt windows around start and stop codons. Only reads with a length of 29 nt were considered. Ribosomes located with the P site at the start codon protected fragments starting at 12 bp upstream of the AUG codon. Ribosomes detach from transcripts once the A site of the ribosome reaches the stop codon. For each library, the fraction or reads covering each frame is shown. The majority of ribosomes are located on the codons of the open reading frame of protein coding genes. Error bars indicate s.d..



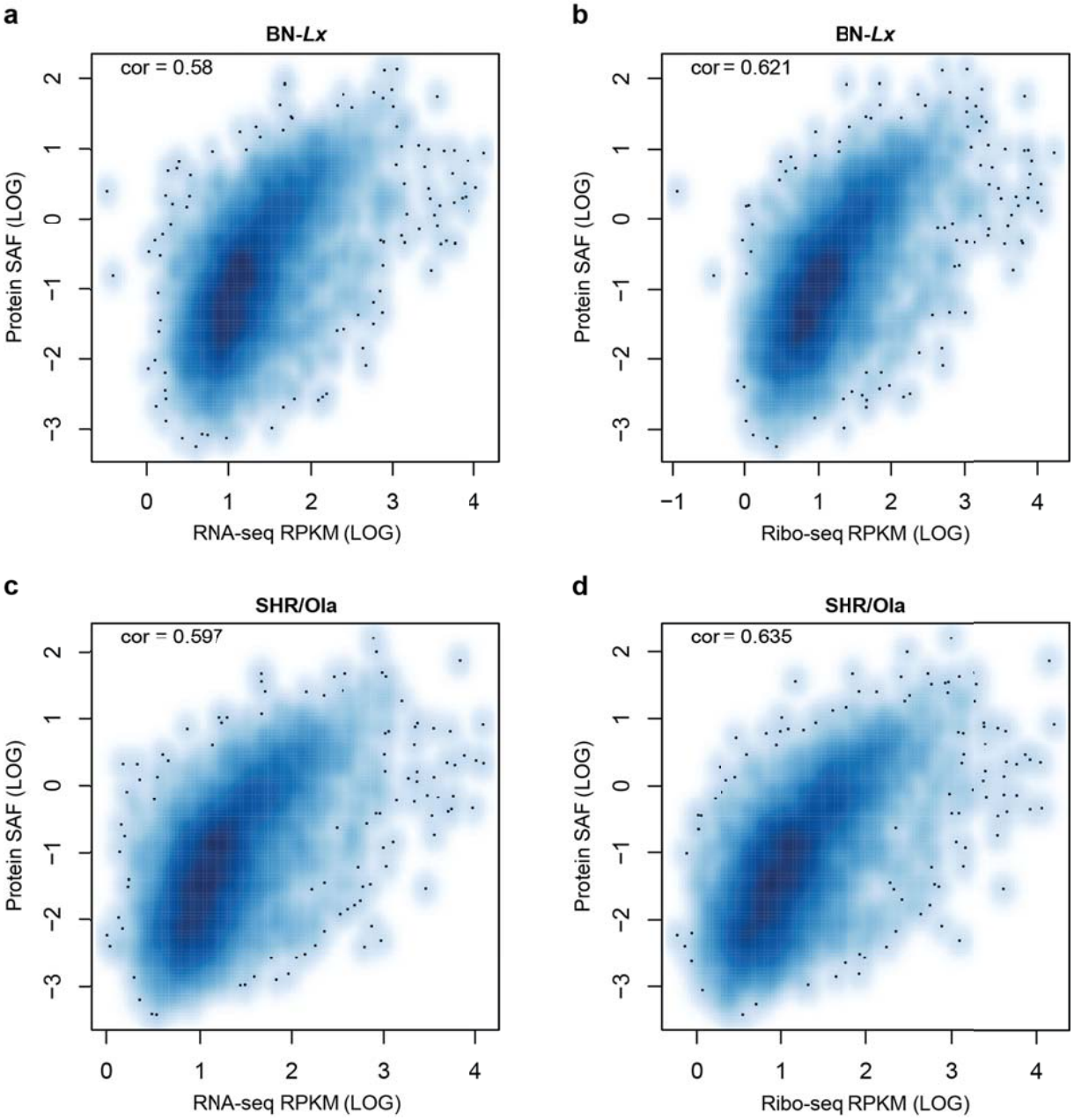
Supplementary Figure 2. Sample clustering and coverage. (**a**) Heatmaps show sample-to-sample Euclidean distance in-between replicates and strains according to DESeq2[1] for RNA-seq and Ribo-seq datasets. (**b, c**) The number of reads mapping to one unique position in the genome and located in an exon is plotted for each biological replicate in both tissues. To ensure expression differences unique to a certain technique are not influenced by library sizes, we matched the number of reads mapping uniquely and located within an exon for both tissues before estimating gene expression levels.



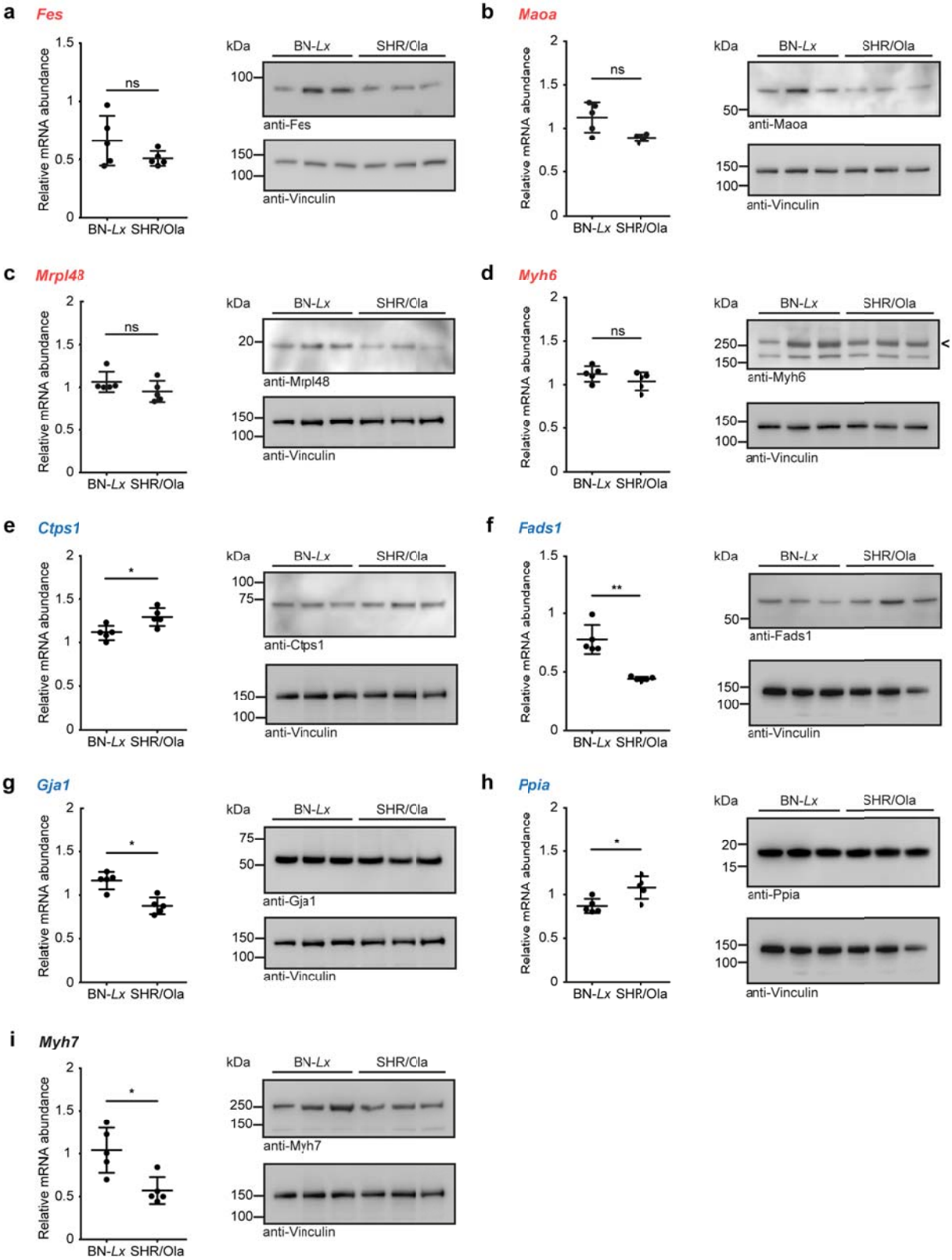
Supplementary Figure 3. Scatter plots of pairwise RNA-seq and Ribo-seq comparisons. (**a**) Heart Ribo-seq, (**b**) Heart RNA-seq; (**c**) Liver Ribo-seq and (**d**) Liver RNA-seq gene-based counts between SHR/Ola and BN-*Lx* rat strains. The red color indicates significantly different genes in-between the strains according to DESeq2 (Bonferroni correction for multiple testing, FDR ≤ 0.01). For RNA expression, we only considered genes that were detected in both RNA-seq experiments and plotted the average expression across RNA-seq1 and RNA-seq2.



Supplementary Figure 4. Comparison of fold changes between Ribo-seq and RNA-seq datasets. (**a-d**) Fold change comparisons of Ribo-seq and RNA-seq count data for buffered (RNA_{only}), forwarded (RNA+RIBO) and reinforced ($RIBO_{only}$) genes in the heart and the liver between the SHR/Ola and BN-*Lx* rat strains. (**a**) Heart Ribo-seq fold-changes compared to RNA-seq1 (polyA+ RNA-seq) data; (**b**) Heart Ribo-seq fold-changes compared to RNA-seq2 (total RNA-seq) data; (**c**) Liver Ribo-seq fold-changes compared to RNA-seq1 (polyA+ RNA-seq) data and (**d**) Liver Ribo-seq fold-changes compared to RNA-seq2 (total RNA-seq) data. Gene classes indicated for each tissue were defined as described in the supplementary material.

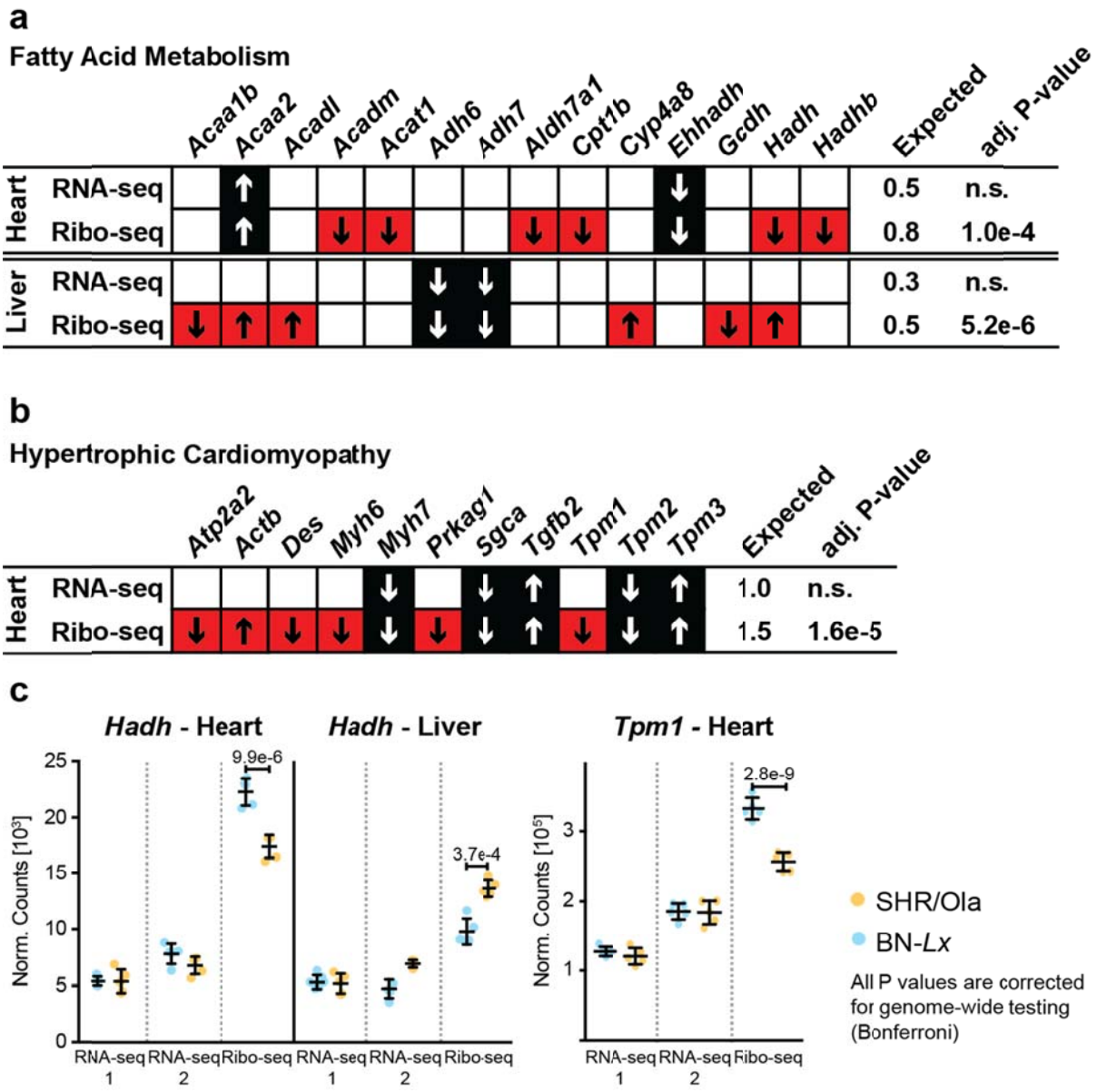


Supplementary Figure 5. Genome-wide correlation of RNA, RPF and protein abundance. Protein abundance in the liver as measured by mass spectrometry[2] is plotted against RNA-seq (BN-*Lx*: **a**, SHR/Ola: **c**) and Ribo-seq (BN-*Lx*: **b**, SHR/Ola: **d**) based RPKM values. In agreement to what has been previously reported in the literature[3], absolute protein levels show a better correlation with ribosome profiling data than with RNA-seq on the genome-wide scale.

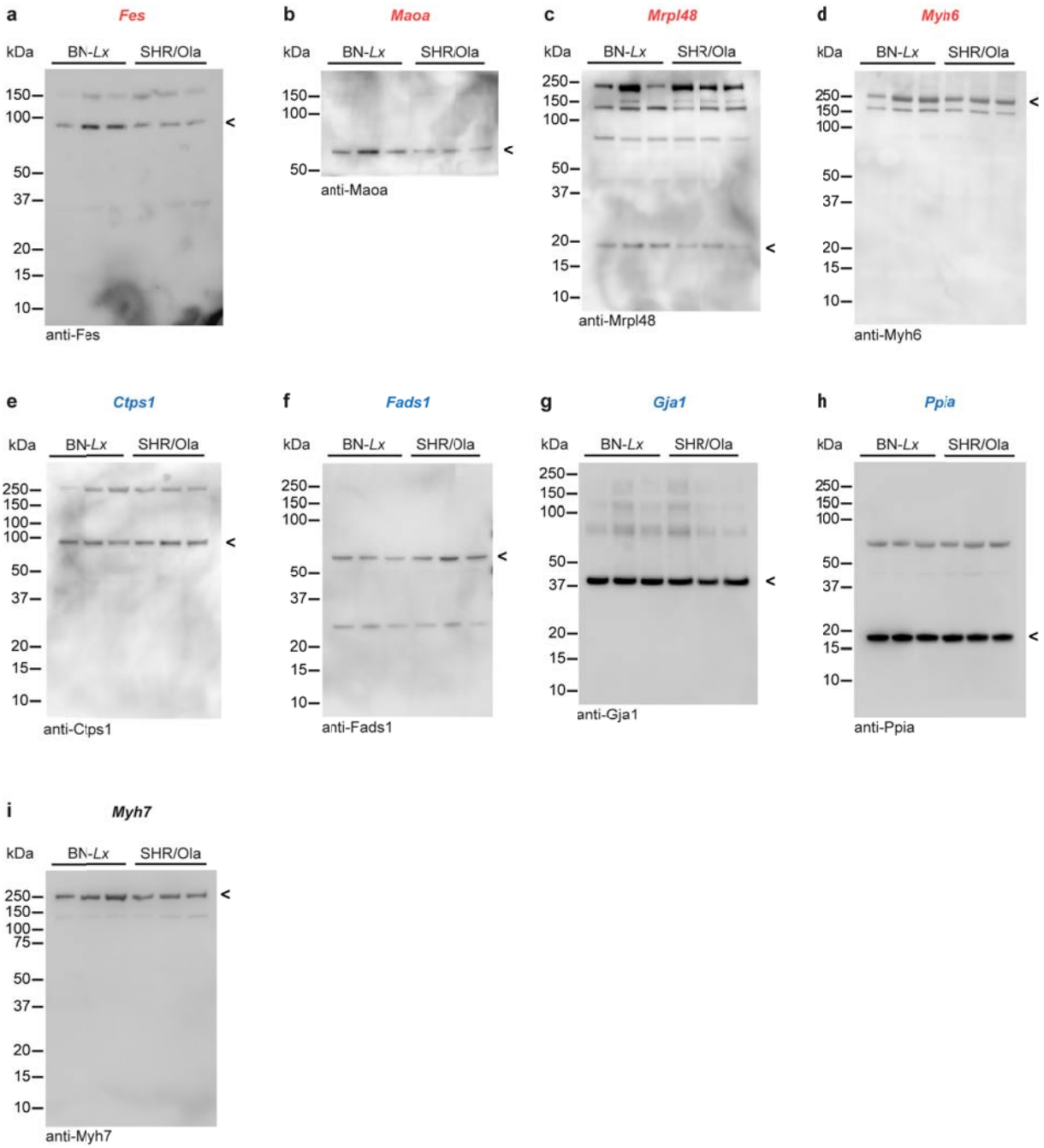


Supplementary Figure 6. Experimental validation of different modes of gene expression regulation. Genes belonging to each of the categories described in the manuscript ($RIBO_{only}$ in red, RNA_{only} in blue, RNA+RIBO in black) were validated by qRT-PCR and western blotting. For each gene, qRT-PCR results are shown on the left (error bars indicate s.d.) and western blots on the right. **(a-d)** *Fes* (liver), *Maoa*, *Mrpl48* and *Myh6* (heart), which were classified as $RIBO_{only}$ genes, show differences on the protein level in-between the strains in the absence of significant RNA

expression differences (Mann-Whitney test). **(e-h)** *Ctps1*, *Fads1*, *Gja1* and *Ppia* (heart) belong to the RNA_{only} group and quantitation by qRT-PCR shows significant differences (Mann-Whitney test, $P < 0.05$) at the RNA level between the strains, whereas comparable protein levels are detected by western blotting. **(i)** *Myh7* (heart) is classified as a RNA+RIBO gene and shows differences between BN-*Lx* and SHR/Ola both at RNA and protein levels.
In some cases the same membrane was used to detect two proteins of interest, after stripping. Therefore, the pairs Gja1-Mrpl48, Ctps1-Myh7, Ppia-Fads1 share the same loading controls.



Supplementary Figure 7. Translational and transcriptional regulation of (**a**) fatty acid and (**b**) cardiomyopathy pathways (KEGG). Arrows indicate either up- or downregulation in the SHR. All differences detected on the RNA level for these metabolic pathways were confirmed to lead to changes in protein synthesis (black; RNA+RIBO). The majority of genes are regulated on the translational level between BN and SHR (red) and can only be detected as being differentially expressed using ribosome profiling techniques. (**c**) Read counts of *Hadh* and *Tpm1* across three different sequencing strategies (Ribosome profiling (Ribo-seq), polyA+ RNA sequencing (RNA-seq1) and total RNA sequencing (RNA-seq2)) visualize how novel and reinforced strain-specific differences in gene usage can be effectively revealed by Ribo-seq in both tissues. DESeq2 based P-values are corrected for genome-wide testing (Bonferroni, FDR ≤ 0.01). Error bars indicate s.d..



Supplementary Figure 8. Full size western blots corresponding to cropped images shown in **Supplementary Figure 6**. Gja1-Mrpl48, Myh7-Ctps1 and Fads1-Ppia were detected on the same membranes after adequate stripping procedures.

Supplementary Table 1. Partial correlation analysis of RNA-seq, Ribo-seq and protein levels. Using data of each strain separately**,** each pair of variables is tested for conditional independence given the third variable as denoted in the column "conditional independence" using partial correlation. The null hypothesis of zero partial correlation coefficients is tested using the t-statistic (column "t") with the corresponding degrees of freedom ("df") (see methods).

Strain	Conditional Independence	Partial Correlation	t	df	p
BN	(Ribo ~ Protein | RNA)	0.27	19.71	4757	<2.2e-16
BN	(RNA ~ Protein | Ribo)	-0.03	-1.87	4757	0.06
BN	(RNA ~ Ribo | Protein)	0.92	156.93	4757	<2.2e-16
SHR	(Ribo ~ Protein | RNA)	0.27	19.32	4757	<2.2e-16
SHR	(RNA ~ Protein | Ribo)	-0.02	-1.29	4757	0.20
SHR	(RNA ~ Ribo | Protein)	0.92	159.00	4757	<2.2e-16

Supplementary Table 2. Overlap of strain-specific gene usage and eQTL data. Linkage analysis of the HxB/BxH RI panel[4] using RNA-seq data derived from BN-*Lx* and SHR/Ola reveals RNA expression differences under genetic control. We then compared this eQTL data with all three modes of gene expression regulation in-between the parental strains. Genes with expression differences in the parental strains (RNA_{only}; RNA+RIBO) were enriched for eQTLs. Most gene expression traits on the RNA level (eQTLs) were found to alter protein synthesis rates (RNA+RIBO) in the parental strains. Only few eQTLs were buffered in the translational level (eQTL and RNA_{only}). As expected, strain-specific usage of $RIBO_{only}$ genes was not significantly enriched for RNA expression traits since the gene expression for these genes is regulated mostly on the translational level only (eQTL and $RIBO_{only}$).

		Strain-Specific Differences			
	eQTL	**RNA_{only}**	**RNA+RIBO**	**$RIBO_{only}$**	**n.s**
Heart	FALSE	167	322	486	9211
	TRUE (EXP)	24 (4)	119 (10)	12 (11)	83
	TRUE / EXP	5.6	11.9	1.1	
Liver	FALSE	39	199	343	11921
	TRUE (EXP)	13 (1)	93 (3.2)	11 (3.9)	24
	TRUE / EXP	21	29	2.8	

Supplementary Table 3. Motifs of RNA binding proteins enriched for genetic variation in differentially translated genes across strains. We determined all motifs of RNA binding proteins[5] in the 3'UTR of genes that were under translational regulation ($RIBO_{only}$) in either heart or liver tissue between both rat strains. The motifs of 8 RNA binding proteins were more often mutated between the SHR/Ola and BN-*Lx* strains than expected (one-sided Wilcoxon-Mann-Whitney, corrected using the Benjamini-Hochberg method).

CISBP-RNA Database ID	Ensembl ID	Gene Symbol	P Value	Corrected P Value
T41133_0.6	ENSRNOG00000020271	*Tial1*	0.0012	0.0259
T41136_0.6	ENSRNOG00000020689	*Cpeb3*	0.0011	0.0259
T41220_0.6	ENSRNOG00000033169	*Cpeb4*	0.0011	0.0259
T41110_0.6	ENSRNOG00000016813	*Tia1*	0.0012	0.0259
T41117_0.6	ENSRNOG00000017405	*Raly*	0.0008	0.0259
T40997_0.6	ENSRNOG00000000702	*Sart3*	0.0024	0.0334
T41142_0.6	ENSRNOG00000021181	*Sf3b4*	0.0019	0.0334
T41078_0.6	ENSRNOG00000011621	*D4ACR0_RAT*	0.0034	0.0413

Supplementary Table 4. Expression levels of RNA binding proteins in heart and liver. The motifs of these RNA binding proteins are enriched for genetic variation in differentially translated genes across strains (**see Supplementary Table 3**). We calculated their RPKM value (average of 5 biological replicates) based on Ribo-seq data to test whether they were also translated in heart and liver tissue. If present in the tissue, they can potentially contribute to translational regulation between strains through *cis*-regulatory variation in their binding sites. We did not detect significant differential transcription or translation of these genes in-between strains.

Ensembl ID	Gene Symbol	Heart BN-*Lx* [RPKM]	Heart SHR/Ola [RPKM]	Liver BN-*Lx* [RPKM]	Liver SHR/Ola [RPKM]
ENSRNOG00000020271	*Tial1*	40.4	41.4	20.1	25
ENSRNOG00000020689	*Cpeb3*	16.2	12.9	3.6	3.6
ENSRNOG00000033169	*Cpeb4*	23.2	26.3	10.8	12.9
ENSRNOG00000016813	*Tia1*	14.7	13.7	0.9	0.9
ENSRNOG00000017405	*Raly*	219.8	229.0	91.7	88.7
ENSRNOG00000000702	*Sart3*	9.1	10.9	3.8	4.4
ENSRNOG00000021181	*Sf3b4*	17.8	22.3	12.1	12.4
ENSRNOG00000011621	*D4ACR0_RAT*	0.8	1.1	1.5	1.3

Supplementary Table 5. Differential miRNA expression and translational regulation. We determined differential miRNA expression for heart and liver tissues in-between rat strains. Differentially transcribed genes (RNA+RIBO) are not as strongly enriched for targets of differential miRNAs than genes under translational control (chi squared test, method Fisher meta P = 0.008).

	Strain-Specific Differences			
	ΔmiRNA Target	**RNA+RIBO**	**$RIBO_{only}$**	
Heart	FALSE	224	207	
	TRUE (EXP)	217 (239)	291 (269)	
Liver	FALSE	186	208	meta P = 0.008
	TRUE (EXP)	106 (114)	146 (138)	

Supplementary Table 6. GWAS candidate genes primarily under translational control ($RIBO_{only}$) in heart or liver in the SHR/Ola model for complex traits.

Gene Symbol	Human ID	Orthologue Rat ID	Tissue	Trait	GWAS
ACAA2	ENSG00000167315	ENSRNOG00000013766	Liver	HDL cholesterol	8
ACADL	ENSG00000115361	ENSRNOG00000012966	Liver	Metabolite levels	9,10
ACADM	ENSG00000117054	ENSRNOG00000009845	Heart	Metabolite levels Metabolic traits	10,11
ACOT7	ENSG00000097021	ENSRNOG00000010580	Heart	QT interval	12
ADH5	ENSG00000197894	ENSRNOG00000033854	Liver	HDL cholesterol Obesity-related traits	13
AQP9	ENSG00000103569	ENSRNOG00000015949	Liver	Metabolite levels	14
CCDC141	ENSG00000163492	ENSRNOG00000012580	Heart Liver	Blood pressure Heart rate	15,16
COL4A1	ENSG00000187498	ENSRNOG00000016281	Heart	Coronary heart/artery disease Obesity-related traits	17–19
COL4A2	ENSG00000134871	ENSRNOG00000023972	Heart	Coronary artery calcification Coronary heart/artery disease	17,19,20
CPN1	ENSG00000120054	ENSRNOG00000013439	Liver	Liver enzyme levels	21
ELMO1	ENSG00000155849	ENSRNOG00000018726	Heart	QT interval	22
EMP1	ENSG00000134531	ENSRNOG00000008676	Heart Liver	Coronary artery calcification	23
ENG	ENSG00000106991	ENSRNOG00000050190	Heart	Metabolic syndrome	24
ETFDH	ENSG00000171503	ENSRNOG00000009538	Heart Liver	Metabolite levels/traits	10,11
FADS3	ENSG00000221968	ENSRNOG00000020385	Liver	Metabolite levels HDL/LDL cholesterol Triglycerides Lipid metabolism phenotypes	13,25–28
FES	ENSG00000182511	ENSRNOG00000011683	Liver	Diastolic/Systolic Blood pressure Hypertension	29,30
GNB4	ENSG00000114450	ENSRNOG00000011070	Heart	Heart rate	16
GRB14	ENSG00000115290	ENSRNOG00000031396	Heart	Blood pressure Type 2 diabetes	31,32
KIAA1755	ENSG00000149633	ENSRNOG00000014424	Heart	Heart rate	16
KLF6	ENSG00000067082	ENSRNOG00000016885	Liver	Coronary artery calcification	23
KLF9	ENSG00000119138	ENSRNOG00000014215	Liver	Body mass index	33
LAMC2	ENSG00000058085	ENSRNOG00000002667	Heart	Coronary heart disease	34
MGMT	ENSG00000170430	ENSRNOG00000016038	Liver	Metabolite levels (X-11787)	35
MTCH2	ENSG00000109919	ENSRNOG00000008682	Heart	Body mass index	36,37
MYH6	ENSG00000197616	ENSRNOG00000025757	Heart	Heart rate	16
NEIL3	ENSG00000109674	ENSRNOG00000011688	Heart	Heart rate variability traits	38
NPC1	ENSG00000141458	ENSRNOG00000012016	Liver	Obesity	39
PDE11A	ENSG00000128655	ENSRNOG00000024457	Heart	Heart rate	16
PLD5	ENSG00000180287	ENSRNOG00000003997	Heart	Coronary artery calcification Obesity-related traits	18,23
PLEKHG1	ENSG00000120278	ENSRNOG00000016011	Heart	Blood pressure Obesity-related traits	18,40
PLEKHO2	ENSG00000241839	ENSRNOG00000029242	Heart Liver	Coronary heart disease	34
PRF1	ENSG00000180644	ENSRNOG00000000562	Heart	Obesity	41
PRKCE	ENSG00000171132	ENSRNOG00000015603	Liver	Metabolite levels (X-11787)	35
PTPRD	ENSG00000153707	ENSRNOG00000005711	Liver	Type 2 diabetes Obesity-related traits	18,42,43
RBM43	ENSG00000184898	ENSRNOG00000004673	Heart	Type 2 diabetes	44
SLC1A4	ENSG00000115902	ENSRNOG00000005248	Heart	Metabolite levels	14,28
SOX17	ENSG00000164736	ENSRNOG00000027357	Liver	LDL cholesterol	13
TNFAIP3	ENSG00000118503	ENSRNOG00000049517	Heart	Cardiac Troponin-T levels	45
WDR12	ENSG00000138442	ENSRNOG00000017340	Heart	Myocardial infarction Coronary heart/artery disease	17,19,46

Supplementary Table 7. List of primers used for qRT-PCR. F, forward; R, reverse. *Myh6* and *Myh7* share the same forward primer, but the different reverse oligos ensure the amplification of specific products.

Gene Symbol	F (5‘ – 3‘)	R (5‘ – 3‘)
Ctps1	GTTCCTTGATATCCGCCTCAC	CATCACCCACTCTTGAATTGC
Fads1	CCCACCAAGAATAAGGCGCT	TTTCATGAGGCCCATTCGCT
Fes	GCCAGCAAAGACAAGGATCG	AGTACGTAGCGGTTGTGGTG
Gja1	AGGTCTGAGAGCCTGAACTCT	CATGTCTGGGCACCTCTCTT
Maoa	AATGGGTAGATGTTGGTGGAG	CCACGGAATGGGTAAGTTTTC
Mrpl48	ATGAGCGGAACCCTGGGAAAG	CCACCTGCAGAATAAATGGGAT
Myh6	AGAGGAGAGGGCGGACATTG	AACAGCGAGGCTCTTTCTGC
Myh7	AGAGGAGAGGGCGGACATTG	GGCATCCTTAGGGTTGGGTAG
Polr2a	CACTCAAGCTGACGGATTACAGA	GAGCATGGACGCCAAAGC
Ppia	GCAGACAAAGTTCCAAAGACAG	CCATTATGGCGTGTGAAGTC
Tbp	TTCGTGCCAGAAATGCTGAA	TTCGTGGCTCTCTTATTCTCATGA

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