Supplementary Information For

METTL14 is required for exercise-induced cardiac hypertrophy and protects against myocardial ischemia-reperfusion injury

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Supplementary Tables:

Supplementary Table 1. Related to method section.

The body weights of mice before and after swim training/no training, and tibia length data, heart weights of the mice after swim training/no training in this study related to Figure 3.

	Control group		Swim group	
	AAV9-cTnT-Control	AAV9-cTnT-METTL14	AAV9-cTnT-Control	AAV9-cTnT-METTL14
Before swim				
Body Weight(g)	24.60±0.756	24.08±0.914	24.33±1.007	24.21±0.614
After swim/no training				
Body Weight(g)	25.88±1.004	25.50±0.787	22.51±0.821	22.38±0.716
Heart Weight(g)	0.098±0.016	0.097±0.002	0.124±0.006	0.107±0.006
Tibia length(cm)	1.632±0.017	1.639±0.013	1.640±0.022	1.643±0.011
HW/TL(g/cm)	0.060±0.010	0.059±0.001	0.076±0.003	0.065±0.004
HW/BW(g/g)	0.004±0.0005	0.004±0.0001	0.006±0.0004	0.005±0.0003

The body weights of mice before and after swim training/no training, and tibia length data, heart weights of the mice after swim training/no training in this study related to Figure 4.

	Control group			Swim group		
	AAV9-cTnT-Control	AAV9-cTnT-WT^{METTL14}	AAV9-cTnT-Mut^{METTL14}	AAV9-cTnT-Control	AAV9-cTnT-WT^{METTL14}	AAV9-cTnT-Mut^{METTL14}
Before swim						
Body Weight(g)	25.68±1.072	25.76±0.979	25.65±0.391	25.61±0.899	25.68±0.757	25.69±0.441
After swim/no training						
Body Weight(g)	26.74±0.788	26.68±0.699	26.46±0.934	22.53±1.406	22.66±0.615	22.43±0.692
Heart Weight(g)	0.098±0.004	0.099±0.003	0.096±0.007	0.124±0.011	0.101±0.007	0.119±0.007
Tibia length(cm)	1.774±0.004	1.774±0.003	1.774±0.004	1.775±0.004	1.774±0.003	1.775±0.002
HW/TL(g/cm)	0.055±0.002	0.056±0.002	0.054±0.004	0.070±0.006	0.057±0.004	0.067±0.004
HW/BW(g/g)	0.004±0.0002	0.004±0.0002	0.004±0.0003	0.006±0.0003	0.005±0.0003	0.005±0.0003

Supplementary Table 2. Related to method section.

Parameters of echocardiography.

	Sham		I/R 3w	
	AAV9-cTnT-shScr	AAV9-cTnT-shMETTL14	AAV9-cTnT-shScr	AAV9-cTnT-shMETTL14
Heart rate (BPM)	479±48	458±34	450±29	438±17
LVESD (mm)	2.7±0.3	2.6±0.3	3.2±0.3**	2.4±0.4$^{\#\#}$
LVEDD (mm)	3.8±0.3	3.6±0.3	3.8±0.4	3.5±0.5
LV Volume; s (μl)	27.0±8.1	24.5±5.6	39.3±6.9*	20.9±10.4$^{\#\#}$
LV Volume; d (μl)	61.9±13.9	55.8±10.3	61.1±13.3	51.6±16.9
LVAW; s (mm)	1.1±0.1	1.2±0.1	1.0±0.1	1.2±0.1$^{\#\#}$
LVAW; d (mm)	0.8±0.1	0.8±0.1	0.9±0.1	0.9±0.1
LVPW; s (mm)	1.1±0.1	1.1±0.1	0.9±0.1	1.1±0.2$^{\#}$
LVPW; d (mm)	0.8±0.1	0.8±0.1	0.7±0.1	0.8±0.2
LV Mass (mg)	103.8±20.4	98.1±7.9	105.6±22.1	98.7±21.2
LV Mass Cor (mg)	83.0±16.3	78.5±6.3	84.5±17.7	78.9±17.0
Stroke Volume (μl)	35.0±6.5	31.3±6.0	23.5±4.8**	30.7±7.9
Cardiac output (ml/min)	16.6±2.5	14.3±2.9	10.3±2.3**	13.4±3.3

Abbreviation: BPM, beat per minute; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LV Volume s, left ventricular volume systolic; LV Volume d, left ventricular volume diastolic; LVAWs, left ventricular anterior wall thickness systolic; LVAWd, left ventricular anterior wall thickness diastolic; LVPWs, left ventricular posterior wall thickness systolic; LVPWd, left ventricular posterior wall thickness diastolic; LV Mass, left ventricular mass index.

Data are presented as mean ± SD. *, $p<0.05$ compared to AAV9-cTnT-shScr +Sham; **, $p<0.01$ compared to AAV9-cTnT-shScr +Sham; $^{\#}$, $p<0.05$ compared to AAV9-cTnT-shScr +I/R 3w; $^{\#\#}$, $p<0.01$ compared to AAV9-cTnT-shScr +I/R 3w. (Two-way ANOVA, Tukey)

Supplementary Table 3. Related to method section.

The primer sequences used for quantitative PCR were as follows:

	Forward	**Reverse**
For gene expression qPCR primers		
rat-Mettl14	TGGGGATCAAAGGAACCGTG	GCCTGATAGTGCTGTCCCTC
rat-Phlpp2	GCGTCTGACGAACACAACAC	CAGACTACAGCGCCTCTCAG
mmu-Mettl14	CTGAGAGTGCGGATAGCATTG	GAGCAGATGTATCATAGGAAGCC
mmu-Anp	TCTTCCTCGTCTTGGCCTTT	CCAGGTGGTCTAGCAGGTT
mmu-Bnp	TGGGAGGTCACTCCTATCCT	GGCCATTTCCTCCGACTTT
mmu-βMhc	CGGACCTTGGAAGACCAGAT	GACAGCTCCCCATTCTCTGT
mmu-αSma	GTCCCAGACATCAGGGAGTAA	TCGGATACTTCAGCGTCAGGA
rat-Anp	GAAGATGCCGGTAGAAGATGAG	AGAGCCCTCAGTTTGCTTTTC
rat-Bnp	GGTGCTGCCCCAGATGATT	CTGGAGACTGGCTAGGACTTC
rat-βMhc	GCCCCAAATGCAGCCAT	CGCTCAGTCATGGCGGAT
18s	TCAAGAACGAAAGTCGGAGG	GGACATCTAAGGGCATCAC
rat-Gapdh	TGACAACTCCCTCAAGATTGTCA	GGCATGGACTGTGGTCATGA
mmu-Gapdh	AGGTCGGTGTGAACGGATTTG	TGTAGACCATGTAGTTGAGGTCA
mmu-Mettl14-specific for Mutant	AAAGTGGGGTTACGCAGCA	CTAGGCTTCACGGTTCCTTTGA
mmu-Phlpp2	GCTCCCGAAGAACTCTTCCAA	GTCTTCGGATCCCAAACCCC
mmu-Mettl3	CTGGGCACTTGGATTTAAGGAA	TGAGAGGTGGTGTAGCAACTT
mmu-Wtap	GAACCTCTTCCTAAAAAGGTCCG	TTAACTCATCCCGTGCCATAAC
mmu-Fto	TTCATGCTGGATGACCTCAATG	GCCAACTGACAGCGTTCTAAG
mmu-Alkbh5	CGCGGTCATCAACGACTACC	ATGGGCTTGAACTGGAACTTG
mmu-Zc3h13	AGCACTGGAAGCACAACAGA	GTAGCCTTTCCCACGAGGTG
mmu-Rbm15b	TATAGCCGCTCAGTTCGCAG	GAGTGAGTTGTCCTCCCACG
For MazF-qPCR primers		
rat-Phlpp2-1	TCACATGGATTTGCGGGACA	TCTCAACTGGTTCCGCTCAC
rat-Phlpp2-2	GCGTCTGACGAACACAACAC	CAGACTACAGCGCCTCTCAG
rat-Phlpp2-3	GACATTCATTGCTGCCGAGG	CCCAACCCCCTAGCATGTTC
rat-Phlpp2-4	CCACAGAAGCACCCAAGAGG	GGTCACGGGGGACAACAAAT
rat-Phlpp2-5	CACTGTGGGAACACTTGTCCT	AGCAGCAGCTAATGGGTCTT
mmu-Phlpp2-0	ATGTGCCAAGCTGTCCTGTG	GGGTCATGCTCCAAGCTGAA
mmu-Phlpp2-1	GCTCCCGAAGAACTCTTCCAA	GTCTTCGGATCCCAAACCCC
mmu-Mettl14-0	TGCATCGTATTTCAGTGCCC	CGGTCGAAGCCTCTCGATTT
mmu-Mettl14-1	ACTCAAAACGGAAGTGTCTGG	TCTCTTCCTCCTGCTGCATTTC
mmu-Phlpp1-0	CCACCTAGGAGCCTTTCCGT	GCAGGGCATTGCAAGATACA
mmu-Phlpp1-1	CACCTGCCAGACTGTTACGA	TCTGGGAGAGGGCATGAAGT

mmu-Phlpp2-2	GTTGAGCACTAGCAGGGTCT	GGAGTCCAACCAAGGTCCAAT
mmu-Phlpp2-3	GCCAGCGAACAGAGACAAGA	CCTCTAGGGGCACAATGGAG
mmu-Phlpp2-4	TACCTCTCGTGTGGACGCAG	ATGGTTTGAAACACTGAGGCAA

Supplementary Table 4. Related to method section.

> *Rattus* PHLPP2(Reference Sequence: NM_001109131.2)

The potential m^{6}A modification sites were browsed by RMBase 2.0 database (Species *Rattus*).

Control Amplicon primer F1/R1

TCACATGGATTTGCGGACAATCAGTTGACTGATTTGGACCTTAGCTCCT
TATGTAGCTTGGAGCAGCTGCATTGTGAGCGGAACCAGTTGAGA

Targeting Amplicon primer F2/R2

GCGTCTGACGA**A**CACAACACTGTGGGCCTGGAGACGAGCTTGCTTCCCA
GGCCTGAGAGGCGCTGTAGTCTG

Targeting Amplicon primer F3/R3

Targeting Amplicon primer F4/R4

TCTGACAATGG**A**CTGG**A**CAGTGACGATGACCAGCCTGTTGAAGGCGTCA
TAACCAATGGCAGCAGGGTTGAGGTAGAGGTAG**A**CATTCATTGCTGCCG
AGGCAGAGAGTCTGAG**A**CTCCCCTACTCTCCCGAAGAATTCTTCCTAC
CCCTGTTCAGAGGA**A**CATGCTAGGGGGTTGGGTTTTGGGATCCGAAG**A**C
AGA**A**CAGTGTGAATAGTGGTATACTTCTGCCAGTGA**A**CAAAG**A**CAAGAT
GGAGTTACAGAAGTCTCCCTCCACTTCTTGTTTGTATGGAAAGAA**A**CTCT
CCAATGGCTCCATTGTGCCCCTAGAAG**A**CAGCCTGA**A**CCTCATTGAGGTG
GCCACAGAAGCACCCAAGAGGAAA**A**CTGGCTATTTTGCTGCCCCCACTC
AGCTGGAACCAGAGGATCAATTTGTTGTCCCCCGTGACCTGGAAGACGA
AGTGAAGGAGCAAATGAAGCAGCACCAGGAGAGCAGGCCTGAGCCTGA
ACCCAGGGAAGAGG**A**CCGG**A**CAGAGCCCCTGCAGGAGTTTGATACAGC
ACTGTGA

Targeting Amplicon primer F5/R5

CACTGTGGGA**A**CACTTGTCCTATCTAGAAGCTGTCAGTGCAGTCCGTCAT
GTGCAAG**A**CCCATTAGCTGCTGCT

*mmu*PHLPP2 m^{6}A peak region in meRIP-seq:

>Chr8:109939973-109941393(+)

TGTGCACATTAGCCCAGAGCTACGGTTGTCAGGACAACGTGGGGGCAAT
GGTGGTTTATTTGAATATTGGTGAAGAAGGCTGTACCTGTGAAATGAATG
GGCTCACCCTTCCAGGCCCTGTGGGATTTGCTTCAACTGCAGCCCTCAA
GGATACTCCCAAGCCAACCACTCCCTCCTCCAGTAGTGGGATTGCCTCCG
AGTTCAGCAGTGAGATGTCCACCTCAGAGGTGAGCAGTGAAGTGGGCTC
CACGGCCTCGGATGAGCACAACACTGTGGGCCTGGAGGCGAGCTTGCTG
CCCAGGCCAGAGAGGCGCTGCAGTCTGCACCCAGCGTCCTCCGCAGGG
GTGTTCCAGCGCCAGCCTTCTTGTGCTACTTTTTCCAGCAATCAGTCTGA
CAATGGCCTGGACAGTGACGATGACCAGCCTGTTGAAGGAGTCATAACC
AACGGCAGCAGGGTTGAAGTAGAGGTAGACATCCATTGCTGCCGAGGCA
GAGAGCCAGAGAGCTCCCCTCCGCTCCCGAAGAACTCTTCCAACGCCTG
TTCAGAGGAGCGTGCTAGAGGGGCGGGGTTTGGGATCCGAAGACAGAA
CAGTGTCAACAGTGGTATACTTCTGCCAGCGAACAGAGACAAGATGGAG
CTGCAGAAGTCTCCCTCCACTTCTTGTCTGTATGGAAAGAAACTCTCCAA
TGGCTCCATTGTGCCCCTAGAGGACAGCCTGAACCTCATTGAGGTGGCC
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TGGAACCAGAGGATCAGTTTGTCGTCCCTCGAGACCTGGAAGAGGAAGT
GAAGGAGCAGATGAAGCAGCACCAGGAGGGCAGGCCTGAGCCCGAGCC
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GTGATTGTACCTCTCGTGTGGACGCAGCCTGAGGGAGGGCTGTGTGGTA
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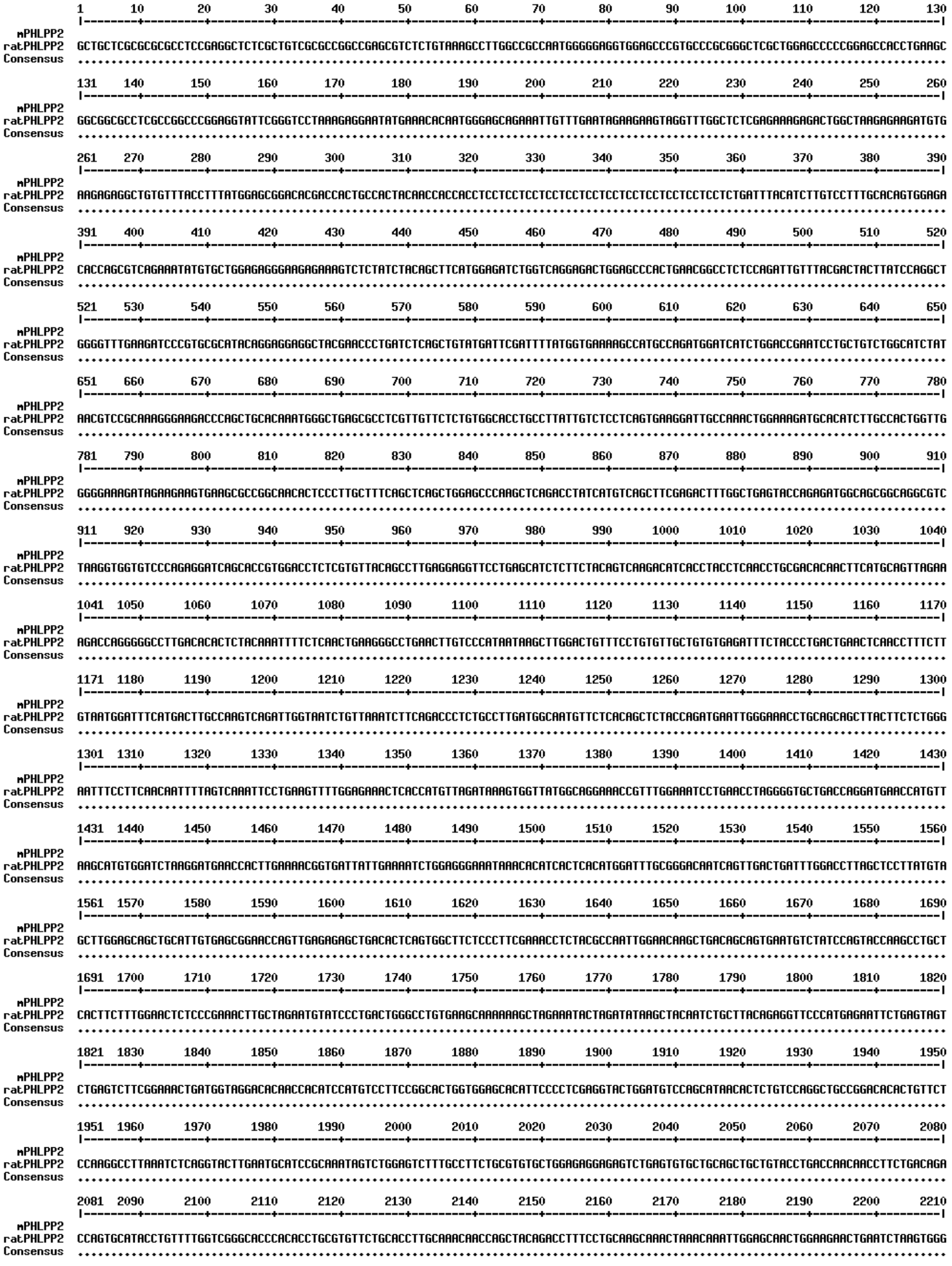
GCCTGCCTGGGCAGGAAAGGGACTATTTCTGTGGAGGAAGTAACTGAAG
GTTGATTCCCTTTACTAATTGCTGCTGATGGATCTCTGTGACAAGAGAAAT

CACCTTATCTCTCAGACTAACTAGTGGGATGTGATGTGACTAGTCACATG

GCTTTTTATTCTCTAGGAGAATACAGCCTATCAAATGTCTA

*mmu*PHLPP2 m^{6}A peak region and *Rattus* PHLPP2 (Reference Sequence: NM_001109131.2) alignment:



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          1       10        20        30        40        50        60        70        80        90       100       110       120       130
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 GCTGCTCGCGCGCGCCTCCGAGGCTCTCGCTGTCGCGCCGGCCGAGCGTCTCTGTAAAGCCTTGGCCGCCAATGGGGGAGGTGGAGCCCGTGCCCGCGGGCTCGCTGGAGCCCCCGGAGCCACCTGAAGC
Consensus ..................................................................................................................................
          131    140       150       160       170       180       190       200       210       220       230       240       250       260
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 GGCGGCGCCTCGCCGGCCCGGAGGTATTCGGGTCCTAAAGAGGAATATGAAACACAATGGGAGCAGAAATTGTTTGAATAGAAGAAGTAGGTTTGGCTCTCGAGAAAGAGACTGGCTAAGAGAAGATGTG
Consensus ..................................................................................................................................
          261    270       280       290       300       310       320       330       340       350       360       370       380       390
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 AAGAGAGGCTGTGTTTACCTTTATGGAGCGGACACGACCACTGCCACTACAACCACCACCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCTGATTTACATCTTGTCCTTTGCACAGTGGAGA
Consensus ..................................................................................................................................
          391    400       410       420       430       440       450       460       470       480       490       500       510       520
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 CACCAGCGTCAGAAATATGTGCTGGAGAGGGAAGAGAAAGTCTCTATCTACAGCTTCATGGAGATCTGGTCAGGAGACTGGAGCCCACTGAACGGCCTCTCCAGATTGTTTACGACTACTTATCCAGGCT
Consensus ..................................................................................................................................
          521    530       540       550       560       570       580       590       600       610       620       630       640       650
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 GGGGTTTGAAGATCCCGTGCGCATACAGGAGGAGGCTACGAACCCTGATCTCAGCTGTATGATTCGATTTTATGGTGAAAAGCCATGCCAGATGGATCATCTGGACCGAATCCTGCTGTCTGGCATCTAT
Consensus ..................................................................................................................................
          651    660       670       680       690       700       710       720       730       740       750       760       770       780
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 AACGTCCGCAAAGGGAAGACCCAGCTGCACAAATGGGCTGAGCGCCTCGTTGTTCTCTGTGGCACCTGCCTTATTGTCTCCTCAGTGAAGGATTGCCAAACTGGAAAGATGCACATCTTGCCACTGGTTG
Consensus ..................................................................................................................................
          781    790       800       810       820       830       840       850       860       870       880       890       900       910
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 GGGGAAAGATAGAAGAAGTGAAGCGCCGGCAACACTCCCTTGCTTTCAGCTCAGCTGGAGCCCAAGCTCAGACCTATCATGTCAGCTTCGAGACTTTGGCTGAGTACCAGAGATGGCAGCGGCAGGCGTC
Consensus ..................................................................................................................................
          911    920       930       940       950       960       970       980       990      1000      1010      1020      1030      1040
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 TAAGGTGGTGTCCCAGAGGATCAGCACCGTGGACCTCTCGTGTTACAGCCTTGAGGAGGTTCCTGAGCATCTCTTCTACAGTCAAGACATCACCTACCTCAACCTGCGACACAACTTCATGCAGTTAGAA
Consensus ..................................................................................................................................
          1041  1050      1060      1070      1080      1090      1100      1110      1120      1130      1140      1150      1160      1170
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 AGACCAGGGGGCCTTGACACACTCTACAAATTTTCTCAACTGAAGGGCCTGAACTTGTCCCATAATAAGCTTGGACTGTTTCCTGTGTTGCTGTGTGAGATTTCTACCCTGACTGAACTCAACCTTTCTT
Consensus ..................................................................................................................................
          1171  1180      1190      1200      1210      1220      1230      1240      1250      1260      1270      1280      1290      1300
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 GTAATGGATTTCATGACTTGCCAAGTCAGATTGGTAATCTGTTAAATCTTCAGACCCTCTGCCTTGATGGCAATGTTCTCACAGCTCTACCAGATGAATTGGGAAACCTGCAGCAGCTTACTTCTCTGGG
Consensus ..................................................................................................................................
          1301  1310      1320      1330      1340      1350      1360      1370      1380      1390      1400      1410      1420      1430
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 AATTTCCTTCAACAATTTTAGTCAAATTCCTGAAGTTTTGGAGAAACTCACCATGTTAGATAAAGTGGTTATGGCAGGAAACCGTTTGGAAATCCTGAACCTAGGGGTGCTGACCAGGATGAACCATGTT
Consensus ..................................................................................................................................
          1431  1440      1450      1460      1470      1480      1490      1500      1510      1520      1530      1540      1550      1560
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 AAGCATGTGGATCTAAGGATGAACCACTTGAAAACGGTGATTATTGAAAATCTGGAGGGAAATAAACACATCACTCACATGGATTTGCGGGACAATCAGTTGACTGATTTGGACCTTAGCTCCTTATGTA
Consensus ..................................................................................................................................
          1561  1570      1580      1590      1600      1610      1620      1630      1640      1650      1660      1670      1680      1690
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 GCTTGGAGCAGCTGCATTGTGAGCGGAACCAGTTGAGAGAGCTGACACTCAGTGGCTTCTCCCTTCGAAACCTCTACGCCAATTGGAACAAGCTGACAGCAGTGAATGTCTATCCAGTACCAAGCCTGCT
Consensus ..................................................................................................................................
          1691  1700      1710      1720      1730      1740      1750      1760      1770      1780      1790      1800      1810      1820
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 CACTTCTTTGGAACTCTCCCGAAACTTGCTAGAATGTATCCCTGACTGGGCCTGTGAAGCAAAAAAGCTAGAAATACTAGATATAAGCTACAATCTGCTTACAGAGGTTCCCATGAGAATTCTGAGTAGT
Consensus ..................................................................................................................................
          1821  1830      1840      1850      1860      1870      1880      1890      1900      1910      1920      1930      1940      1950
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 CTGAGTCTTCGGAAACTGATGGTAGGACACAACCACATCCATGTCCTTCCGGCACTGGTGGAGCACATTCCCCTCGAGGTACTGGATGTCCAGCATAACACTCTGTCCAGGCTGCCGGACACACTGTTCT
Consensus ..................................................................................................................................
          1951  1960      1970      1980      1990      2000      2010      2020      2030      2040      2050      2060      2070      2080
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 CCAAGGCCTTAAATCTCAGGTACTTGAATGCATCCGCAAATAGTCTGGAGTCTTTGCCTTCTGCGTGTGCTGGAGAGGAGAGTCTGAGTGTGCTGCAGCTGCTGTACCTGACCAACAACCTTCTGACAGA
Consensus ..................................................................................................................................
          2081  2090      2100      2110      2120      2130      2140      2150      2160      2170      2180      2190      2200      2210
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 CCAGTGCATACCTGTTTTGGTCGGGCACCCACACCTGCGTGTTCTGCACCTTGCAAACAACCAGCTACAGACCTTTCCTGCAAGCAAACTAAACAAATTGGAGCAACTGGAAGAACTGAATCTAAGTGGG
Consensus ..................................................................................................................................
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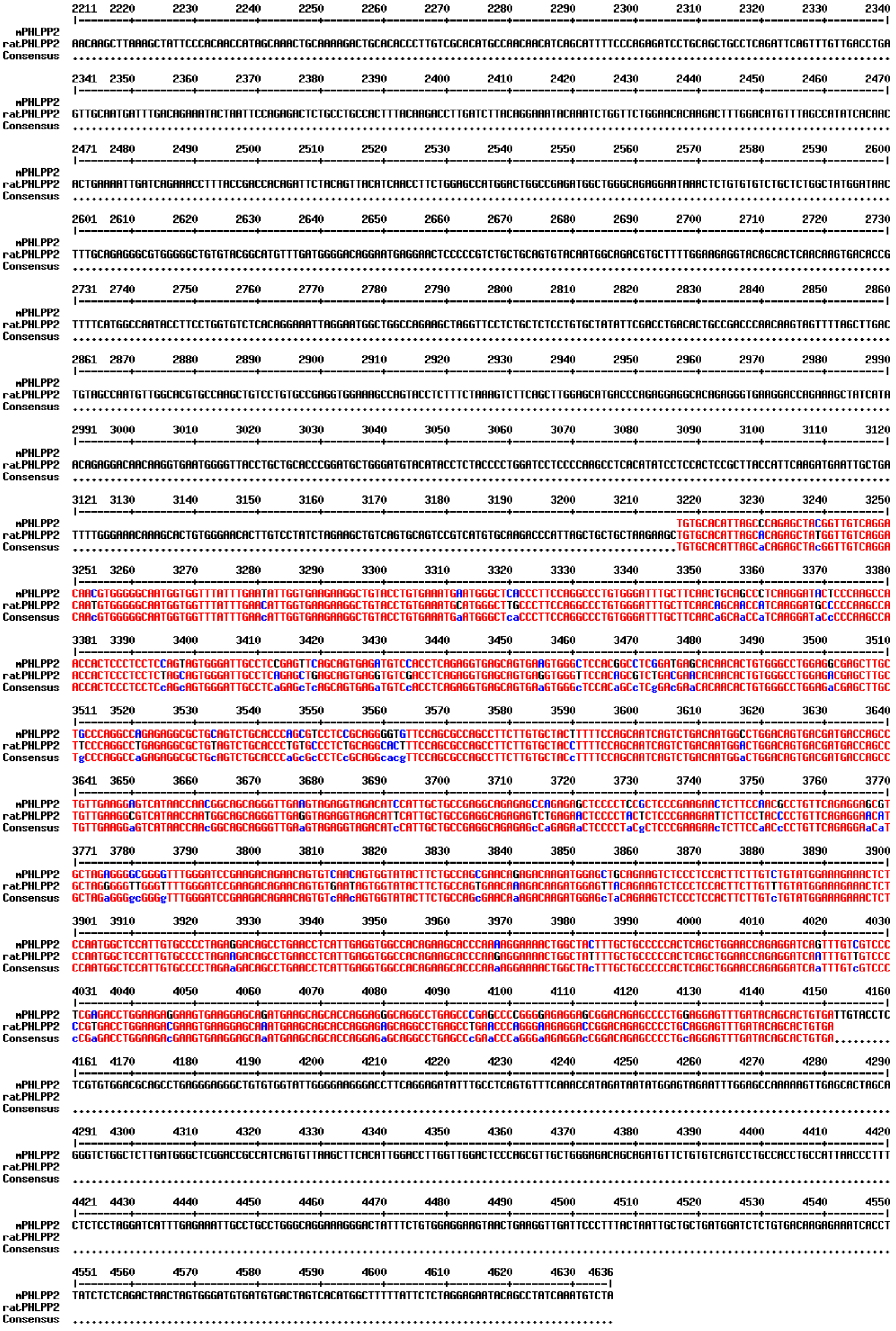

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          2211  2220      2230      2240      2250      2260      2270      2280      2290      2300      2310      2320      2330      2340
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  mPHLPP2
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Consensus ..................................................................................................................................

          2341  2350      2360      2370      2380      2390      2400      2410      2420      2430      2440      2450      2460      2470
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 GTTGCAATGATTTGACAGAAATACTAATTCCAGAGACTCTGCCTGCCACTTTACAAGACCTTGATCTTACAGGAAATACAAATCTGGTTCTGGAACACAAGACTTTGGACATGTTTAGCCATATCACAAC
Consensus ..................................................................................................................................

          2471  2480      2490      2500      2510      2520      2530      2540      2550      2560      2570      2580      2590      2600
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 ACTGAAAATTGATCAGAAACCTTTACCGACCACAGATTCTACAGTTACATCAACCTTCTGGAGCCATGGACTGGCCGAGATGGCTGGGCAGAGGAATAAACTCTGTGTGTCTGCTCTGGCTATGGATAAC
Consensus ..................................................................................................................................

          2601  2610      2620      2630      2640      2650      2660      2670      2680      2690      2700      2710      2720      2730
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 TTTGCAGAGGGCGTGGGGGCTGTGTACGGCATGTTTGATGGGGACAGGAATGAGGAACTCCCCCGTCTGCTGCAGTGTACAATGGCAGACGTGCTTTTGGAAGAGGTACAGCACTCAACAAGTGACACCG
Consensus ..................................................................................................................................

          2731  2740      2750      2760      2770      2780      2790      2800      2810      2820      2830      2840      2850      2860
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 TTTTCATGGCCAATACCTTCCTGGTGTCTCACAGGAAATTAGGAATGGCTGGCCAGAAGCTAGGTTCCTCTGCTCTCCTGTGCTATATTCGACCTGACACTGCCGACCCAACAAGTAGTTTTAGCTTGAC
Consensus ..................................................................................................................................

          2861  2870      2880      2890      2900      2910      2920      2930      2940      2950      2960      2970      2980      2990
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 TGTAGCCAATGTTGGCACGTGCCAAGCTGTCCTGTGCCGAGGTGGAAAGCCAGTACCTCTTTCTAAAGTCTTCAGCTTGGAGCATGACCCAGAGGAGGCACAGAGGGTGAAGGACCAGAAAGCTATCATA
Consensus ..................................................................................................................................

          2991  3000      3010      3020      3030      3040      3050      3060      3070      3080      3090      3100      3110      3120
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2
ratPHLPP2 ACAGAGGACAACAAGGTGAATGGGGTTACCTGCTGCACCCGGATGCTGGGATGTACATACCTCTACCCCTGGATCCTCCCCAAGCCTCACATATCCTCCACTCCGCTTACCATTCAAGATGAATTGCTGA
Consensus ..................................................................................................................................

          3121  3130      3140      3150      3160      3170      3180      3190      3200      3210      3220      3230      3240      3250
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2                                                                                                 TGTGCACATTAGCCCAGAGCTACGGTTGTCAGGA
ratPHLPP2 TTTTGGGAAACAAAGCACTGTGGGAACACTTGTCCTATCTAGAAGCTGTCAGTGCAGTCCGTCATGTGCAAGACCCATTAGCTGCTGCTAAGAAGCTGTGCACATTAGCACAGAGCTATGGTTGTCAGGA
Consensus ................................................................................................TGTGCACATTAGCaCAGAGCTAcGGTTGTCAGGA

          3251  3260      3270      3280      3290      3300      3310      3320      3330      3340      3350      3360      3370      3380
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 CAACGTGGGGGCAATGGTGGTTTATTTGAATATTGGTGAAGAAGGCTGTACCTGTGAAATGAATGGGCTCACCCTTCCAGGCCCTGTGGGATTTGCTTCAACTGCAGCCCTCAAGGATACTCCCAAGCCA
ratPHLPP2 CAATGTGGGGGCAATGGTGGTTTATTTGAACATTGGTGAAGAAGGCTGTACCTGTGAAATGCATGGGCTTGCCCTTCCAGGCCCTGTGGGATTTGCTTCAACAGCAACCATCAAGGATGCCCCCAAGCCA
Consensus CAAcGTGGGGGCAATGGTGGTTTATTTGAAcATTGGTGAAGAAGGCTGTACCTGTGAAATGaATGGGCTcaCCCTTCCAGGCCCTGTGGGATTTGCTTCAACaGCAaCCaTCAAGGATaCcCCCAAGCCA

          3381  3390      3400      3410      3420      3430      3440      3450      3460      3470      3480      3490      3500      3510
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 ACCACTCCCTCCTCCAGTAGTGGGATTGCCTCCGAGTTCAGCAGTGAGATGTCCACCTCAGAGGTGAGCAGTGAAGTGGGCTCCACGGCCTCGGATGAGCACAACACTGTGGGCCTGGAGGCGAGCTTGC
ratPHLPP2 ACCACTCCCTCCTCTAGCAGTGGGATTGCCTCAGAGCTGAGCAGTGAGGTGTCGACCTCAGAGGTGAGCAGTGAGGTGGGTTCCACAGCGTCTGACGAACACAACACTGTGGGCCTGGAGACGAGCTTGC
Consensus ACCACTCCCTCCTCcAGcAGTGGGATTGCCTCaGAGcTcAGCAGTGAGaTGTCcACCTCAGAGGTGAGCAGTGAaGTGGGcTCCACaGCcTCgGAcGAaCACAACACTGTGGGCCTGGAGaCGAGCTTGC

          3511  3520      3530      3540      3550      3560      3570      3580      3590      3600      3610      3620      3630      3640
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 TGCCCAGGCCAGAGAGGCGCTGCAGTCTGCACCCAGCGTCCTCCGCAGGGGTGTTCCAGCGCCAGCCTTCTTGTGCTACTTTTTCCAGCAATCAGTCTGACAATGGCCTGGACAGTGACGATGACCAGCC
ratPHLPP2 TTCCCAGGCCTGAGAGGCGCTGTAGTCTGCACCCTGTGCCCTCTGCAGGCACTTTCCAGCGCCAGCCTTCTTGTGCTACCTTTTCCAGCAATCAGTCTGACAATGGACTGGACAGTGACGATGACCAGCC
Consensus TgCCCAGGCCaGAGAGGCGCTGcAGTCTGCACCCaGcGcCCTCcGCAGGcacgTTCCAGCGCCAGCCTTCTTGTGCTACcTTTTCCAGCAATCAGTCTGACAATGGaCTGGACAGTGACGATGACCAGCC

          3641  3650      3660      3670      3680      3690      3700      3710      3720      3730      3740      3750      3760      3770
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 TGTTGAAGGAGTCATAACCAACGGCAGCAGGGTTGAAGTAGAGGTAGACATCCATTGCTGCCGAGGCAGAGAGCCAGAGAGCTCCCCTCCGCTCCCGAAGAACTCTTCCAACGCCTGTTCAGAGGAGCGT
ratPHLPP2 TGTTGAAGGCGTCATAACCAATGGCAGCAGGGTTGAGGTAGAGGTAGACATTCATTGCTGCCGAGGCAGAGAGTCTGAGAACTCCCCTACTCTCCCGAAGAATTCTTCCTACCCCTGTTCAGAGGAACAT
Consensus TGTTGAAGGaGTCATAACCAAcGGCAGCAGGGTTGAaGTAGAGGTAGACATcCATTGCTGCCGAGGCAGAGAGcCaGAGAaCTCCCCTaCgCTCCCGAAGAAcTCTTCCaACcCCTGTTCAGAGGAaCaT

          3771  3780      3790      3800      3810      3820      3830      3840      3850      3860      3870      3880      3890      3900
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 GCTAGAGGGGCGGGGTTTGGGATCCGAAGACAGAACAGTGTCAACAGTGGTATACTTCTGCCAGCGAACAGAGACAAGATGGAGCTGCAGAAGTCTCCCTCCACTTCTTGTCTGTATGGAAAGAAACTCT
ratPHLPP2 GCTAGGGGGTTGGGTTTTGGGATCCGAAGACAGAACAGTGTGAATAGTGGTATACTTCTGCCAGTGAACAAAGACAAGATGGAGTTACAGAAGTCTCCCTCCACTTCTTGTTTGTATGGAAAGAAACTCT
Consensus GCTAGaGGGgcGGGgTTTGGGATCCGAAGACAGAACAGTGTcAAcAGTGGTATACTTCTGCCAGcGAACAaAGACAAGATGGAGcTaCAGAAGTCTCCCTCCACTTCTTGTcTGTATGGAAAGAAACTCT

          3901  3910      3920      3930      3940      3950      3960      3970      3980      3990      4000      4010      4020      4030
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 CCAATGGCTCCATTGTGCCCCTAGAGGACAGCCTGAACCTCATTGAGGTGGCCACAGAAGCACCCAAAAGGAAAACTGGCTACTTTGCTGCCCCCACTCAGCTGGAACCAGAGGATCAGTTTGTCGTCCC
ratPHLPP2 CCAATGGCTCCATTGTGCCCCTAGAAGACAGCCTGAACCTCATTGAGGTGGCCACAGAAGCACCCAAGAGGAAAACTGGCTATTTTGCTGCCCCCACTCAGCTGGAACCAGAGGATCAATTTGTTGTCCC
Consensus CCAATGGCTCCATTGTGCCCCTAGAaGACAGCCTGAACCTCATTGAGGTGGCCACAGAAGCACCCAAaAGGAAAACTGGCTAcTTTGCTGCCCCCACTCAGCTGGAACCAGAGGATCAaTTTGTcGTCCC

          4031  4040      4050      4060      4070      4080      4090      4100      4110      4120      4130      4140      4150      4160
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 TCGAGACCTGGAAGAGGAAGTGAAGGAGCAGATGAAGCAGCACCAGGAGGGCAGGCCTGAGCCCGAGCCCCGGGGAGAGGAGCGGACAGAGCCCCTGGAGGAGTTTGATACAGCACTGTGATTGTACCTC
ratPHLPP2 CCGTGACCTGGAAGACGAAGTGAAGGAGCAAATGAAGCAGCACCAGGAGAGCAGGCCTGAGCCTGAACCCAGGGAAGAGGACCGGACAGAGCCCCTGCAGGAGTTTGATACAGCACTGTGA
Consensus cCGaGACCTGGAAGAcGAAGTGAAGGAGCAaATGAAGCAGCACCAGGAGaGCAGGCCTGAGCCcGAaCCCaGGGaAGAGGAcCGGACAGAGCCCCTGcAGGAGTTTGATACAGCACTGTGA.........

          4161  4170      4180      4190      4200      4210      4220      4230      4240      4250      4260      4270      4280      4290
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 TCGTGTGGACGCAGCCTGAGGGAGGGCTGTGTGGTATTGGGGAAGGGACCTTCAGGAGATATTTGCCTCAGTGTTTCAAACCATAGATAATATGGAGTAGAATTTGGAGCCAAAAAGTTGAGCACTAGCA
ratPHLPP2
Consensus ..................................................................................................................................

          4291  4300      4310      4320      4330      4340      4350      4360      4370      4380      4390      4400      4410      4420
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 GGGTCTGGCTCTTGATGGGCTCGGACCGCCATCAGTGTTAAGCTTCACATTGGACCTTGGTTGGACTCCCAGCGTTGCTGGGAGACAGCAGATGTTCTGTGTCAGTCCTGCCACCTGCCATTAACCCTTT
ratPHLPP2
Consensus ..................................................................................................................................

          4421  4430      4440      4450      4460      4470      4480      4490      4500      4510      4520      4530      4540      4550
          |--------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------+---------|
  mPHLPP2 CTCTCCTAGGATCATTTGAGAAATTGCCTGCCTGGGCAGGAAAGGGACTATTTCTGTGGAGGAAGTAACTGAAGGTTGATTCCCTTTACTAATTGCTGCTGATGGATCTCTGTGACAAGAGAAATCACCT
ratPHLPP2
Consensus ..................................................................................................................................

          4551  4560      4570      4580      4590      4600      4610      4620      4630  4636
          |--------+---------+---------+---------+---------+---------+---------+---------+-----|
  mPHLPP2 TATCTCTCAGACTAACTAGTGGGATGTGATGTGACTAGTCACATGGCTTTTTATTCTCTAGGAGAATACAGCCTATCAAATGTCTA
ratPHLPP2
Consensus ......................................................................................
```

> *mmu*PHLPP2 (Reference Sequence: NM_001122594.2) (Species *Mus musculus*).

Control Amplicon primer F0/R0

ATGTGCCAAGCTGTCCTGTGCCGAGGTGGGAAGCCAGTACCTCTTTCTA

AAGTCTTCAGCTTGGAGCATGACCC

Targeting Amplicon primer F1/R1

Targeting Amplicon primer F3/R3

CCTGG**A**CAGTGACGATGACCAGCCTGTTGAAGGAGTCATAACCAACGGCAGCAGGGTTGAAGTAGAGGTAGACATCCATTGCTGCCGAGGCAGAGAGCCAGAGAGCTCCCCTCCGCTCCCGAAGA**A**CTCTTCCAACGCCTGTTCAGAGGAGCGTGCTAGAGGGGCGGGGTTTGGGATCCGAAG**A**CAGA**A**CAGTGTCAACAGTGGTATACTTCTGCCAGCGA**A**CAGAG**A**CAAGATGGAGCTGCAGAAGTCTCCCTCCACTTCTTGTCTGTATGGAAAGAA**A**CTCTCCAATGGCTCCATTGTGCCCCTAGAGG**A**CAGCCTGA**A**CCTCATTGAGGTGGCCACAGAAGCACCCAAAAGGAAA**A**CTGGCTACT

Targeting Amplicon primer F2/R2

Targeting Amplicon primer F4/R4

GAGCCCGAGCCCCGGGGAGAGGAGCGG**A**CAGAGCCCCTGGAGGAGTTTGATACAGCACTGTGATTGTACCTCTCGTGTGGACGCAGCCTGAGGGAGGGCTGTGTGGTATTGGGGAAGGG**A**CCTTCAGGAGATATTTGCCTCAGTGTTTCAA**A**CCATAGATAATATGGAGTAGAATTTGGAGCCAAAAAGTTGAGCACTAGCAGGGTCTGGCTCTTGATGGGCTCGG**A**CCGCCATCAGTGTTAAGCTTCACATTGG**A**CCTTGGTTGG**A**CTCCCAGCGTTGCTGGGAG**A**CAGCAGATGTTCTGTGTCAGTCCTGCCACCTGCCATTAACCCTTTCTCTCCTAGGATCATTTGAGAAATTGCCTGCCTGGGCAGGAAAGGG**A**CTATT

Supplementary Table 5. Related to method section.

Primers used in SELECT.

Name	Sequences (5’-->3’)
mPHLPP2-m^{6}A3675-up	tagccagtaccgtagtgcgtgCTGAACAGGCGTTGGAAGAG
mPHLPP2-m^{6}A3675-down	TCTTCGGGAGCGGAGGGGAGcagaggctgagtcgctgcat
mPHLPP2-m^{6}A3733-up	tagccagtaccgtagtgcgtg CCACTGTTGACACTGTTCTG
mPHLPP2-m^{6}A3733-down	CTTCGGATCCCAAACCCCGCcagaggctgagtcgctgcat
mPHLPP2-A155-up	tagccagtaccgtagtgcgtg GGAACCAAACCTACTTCTTC
mPHLPP2-A155-down	ATTCAAACAAGTTCTGCTCCcagaggctgagtcgctgcat
qPCR for SELECT-F	ATGCAGCGACTCAGCCTCTG
qPCR for SELECT-R	TAGCCAGTACCGTAGTGCGTG

Supplementary Table 6. Related to method section.

The shRNA sequences were used in this study as follows:

	sequence
METTL14 shRNA for NRCM	F: 5’-CCGGGCTAATGTTGACATTGACTTACTCGAGTAAGTCAATGTCAACATTAGCTTTTTG-3’ R: 5’-AATTCAAAAAGCTAATGTTGACATTGACTTACTCGAGTAAGTCAATGTCAACATTAGC-3’
METTL14 shRNA for murine	F: ggtaccAAGGTATATTGCTGTTGACAGTGAGCGCAGGGCTTCCTATGATACATCTGCTTAGTGAAGCCACAG R: gaattcCGAGGCAGTAGGCACAGGGCTTCCTATGATACATCTGCTTACATCTGTGGCTTCACTAAGCAGATG
PHLPP2 shRNA for NRCM	F: 5’-CCGGAGACACCAGCGTCAGAAATATCTCGAGATATTTCTGACGCTGGTGTCTTTTTTG-3’ R: 5’-AATTCAAAAAAGACACCAGCGTCAGAAATATCTCGAGATATTTCTGACGCTGGTGTCT-3’

Supplementary Table 7. Related to method section.

The primer sequences used for generation of overexpression constructs were as follows:

	Forward	**Reverse**
For ratMettl14:		
ratMettl14-OE	ATGAGTTTGGGAGCTGAGAGT	CTACCGAGGTGTAAAGCCACCT
ratMettl14-op	gctgcaggtcgactctagagATGAGTTTGGGAGCTGAGAGT	gataagcttgatatcgaattCTACCGAGGTGTAAAGCCACCT
For ratPhlpp2:		
rat-Phlpp2-gene	F1: CGAGCGTCTCTGTAAAGCCT F2: GCATCCGCAAATAGTCTGGA	R1: TGATGTTGTTGGCATGTGCG R2: TCACAGTGCTGTATCAAACTCCTGCA R3: TCCAGACTATTTGCGGATGC
ratPhlpp2-op	gtggaggtggaggttctagaAGCGTCTCTGTAAAGCCTTG	tcagcggtttaaacttaagcttgTCACAGTGCTGTATCAAACTCCTGCA

Supplementary Table 8. Related to method section.

Antibodies used in this study.

Antibodies	Source	Catalog	lot	Application
Rabbit polyclonal anti-ZC3H13	Abcam	Cat#ab70802	GR3235168-28	Western Blot
Rabbit monoclonal anti-C/EBPβ[E299]	Abcam	Cat#ab32358	GR3232277-8	Western Blot
Rabbit Polyclonal anti-PHLPP2	ABclonal	Cat#A18218	1167720201	Western Blot
Rabbit monoclonal anti-[KO Validated] active + pro Caspase-3[ARC0133]	ABclonal	Cat#A19654	4001330002	Western Blot
Rabbit monoclonal anti-Caspase-3 p12[ARC0143]	ABclonal	Cat#A19664	4000000143	Western Blot
Rabbit monoclonal anti-Bcl-2[ARC0173]	ABclonal	Cat#A19693	4000000173	Western Blot
Rabbit polyclonal anti-[KO Validated] Bax	ABclonal	Cat#A12009	5500008806	Western Blot
Rabbit polyclonal anti-PHLPP1	ABclonal	Cat#A9542	3521609005	Western Blot
Rabbit polyclonal anti-RBM15B	ABclonal	Cat#A9873	0051800201	Western Blot
Rabbit monoclonal anti-FOXO3A [75D8]	Beyotime Biotechnology	Cat#AF609	031221210930	Western Blot
Rabbit polyclonal Phospho-FoxO3a (Ser253) Antibody	Cell Signaling Technology	Cat #9466	6	Western Blot
Rabbit polyclonal GAPDH	Bioworld Technology	Cat#AP0063	01201908	Western Blot
Rabbit monoclonal anti-METTL14 [D8K8W]	Cell Signaling Technology	Cat#51104	1	Western Blot
Rabbit monoclonal anti-METTL3 [D2I6O]	Cell Signaling Technology	Cat#96391	1	Western Blot
Rabbit monoclonal	Cell Signaling	Cat#4060	38	Western Blot

anti-Phospho-Akt (Ser473) [D9E] XP	Technology			
Rabbit monoclonal anti-Phospho-Akt (Thr308)[D25E6]XP	Cell Signaling Technology	Cat#13038	18	Western Blot
Rabbit monoclonal anti-FTO [D2V1I]	Cell Signaling Technology	Cat#45980	1	Western Blot
Rabbit monoclonal anti-ALKBH5 [E5Y7C]	Cell Signaling Technology	Cat#80283	1	Western Blot
Rabbit monoclonal anti-Phospho-Akt2 (Ser474) [D3H2]	Cell Signaling Technology	Cat#8599	2	Western Blot
Mouse monoclonal anti-Akt2 [L79B2]	Cell Signaling Technology	Cat#5239	4	Western Blot
Rabbit monoclonal anti-Phospho-GSK-3β (Ser9) [D85E12] XP	Cell Signaling Technology	Cat#5558	10	Western Blot
Rabbit monoclonal anti-GSK-3β [D5C5Z] XP	Cell Signaling Technology	Cat#12456	8	Western Blot
Rabbit monoclonal anti-PI3 Kinase p110α [C73F8]	Cell Signaling Technology	Cat#4249	11	Western Blot
Rabbit Polyclonal WTAP polyclonal antibody	Proteintech	Cat#10200-1-AP	00048586	Western Blot
Rabbit Polyclonal AKT polyclonal antibody	Proteintech	Cat#10176-2-AP	00099352	Western Blot
Mouse Monoclonal Beta Actin antibody[2D4H5]	Proteintech	Cat#66009-1-Ig	10004156	Western Blot
Rabbit polyclonal IGF-1 antibody	Proteintech	Cat#28530-1-AP	00085177	Western Blot
Rabbit Polyclonal Phospho-Histone H3 (Ser10) antibody	Thermo Fisher Scientific	Cat#PA5-17869	WC3216175A	Immunofluorescence
Rabbit monoclonal Ki67 antibody [SP6]	Abcam	Cat#ab16667	GR3375640-18	Immunofluorescence
Monoclonal Anti-alpha-Actinin [EA-53] (Sarcomeric)	Sigma-Aldrich	Cat#A7811	0000120831	Immunofluorescence

antibody				
Cy3 AffiniPure Donkey Anti-Mouse IgG (H+L)	Jackson ImmunoResearch Labs	Cat#715-165-151	155867	Immunofluorescence
Alexa Fluor 488-conjugated Affinipure Goat Anti-Mouse IgG(H+L)	Jackson ImmunoResearch Labs	Cat#115-545-003	158218	Immunofluorescence
Alexa Fluor 488-AffiniPure Goat Anti-Rabbit IgG (H+L) antibody	Jackson ImmunoResearch Labs	Cat#111-545-003	146644	Immunofluorescence
Anti-m6A antibody	Synaptic Systems	Cat#202 003	2-125	Immunoprecipitation
Rabbit polyclonal anti-YTHDF1	Proteintech	Cat#17479-1-AP	00102690	Immunoprecipitation
Normal Rabbit-IgG	Sigma-Aldrich	Cat#NI01	3238429	Immunoprecipitation
Rabbit polyclonal anti-METTL14	ABclonal	Cat#A8530	5500003462	Immunoprecipitation

Supplementary Table 9. Related to method section.

***mmu*PHLPP2-WT-pGL3** Cloning vector (Insert site): pGL3-Basic(gccgtg/taattc) >*mmu*PHLPP2-WT-pGL3 GGAGGCGGCGGAAGCTCTGACAATGGCCTGGACAGTGACGATGACCAGCCTGTTG AAGGAGTCATAACCAACGGCAGCAGGGTTGAAGTAGAGGTAGACATCCATTGCTGC CGAGGCAGAGAGCCAGAGAGCTCCCCTCCGCTCCCGAAGAACTCTTCCAACGCCTG TTCAGAGGAGCGTGCTAGAGGGGCGGGGTTTGGGATCCGAAGACAGAACAGTGTC AACAGTGGTATACTTCTGCCAGCGAACAGAGACAAGATGGAGCTGCAGAAGTCTCC CTCCACTTCTTGTCTGTATGGAAAGAAACTCTCCAATGGCTCCATTGTGCCCCTAGA GGACAGCCTGAACCTCATTGAGGTGGCCACAGAAGCACCCAAAAGGAAAACTGGC TACTTTGCTGCCCCCACTCAGCTGGAACCAGAGGATCAGTTTGTCGTCCCTCGAGAC CTGGAAGAGGAAGTGAAGGAGCAGATGAAGCAGCACCAGGAGGGCAGGCCTGAG CCCGAGCCCCGGGGAGAGGAGCGGACAGAGCCCCTGGAGGAGTTTGATACAGCAC TGTGATTGTACCTCTCGTGTGGACGCAGCCTGAGGGAGGGCTGTGTGGTATTGGGG AAGGGACCTTCAGGAGATATTTGCCTCAGTGTTTCAAACCATAGATAATATGGAGTA GAATTTGGAGCCAAAAAGTTGAGCACTAGCAGGGTCTGGCTCTTGATGGGCTCGGA CCGCCATCAGTGTTAAGCTTCACATTGGACCTTGGTTGGACTCCCAGCGTTGCTGGG AGACAGCAGATGTTCTGTGTCAGTCCTGCCACCTGCCATTAACCCTTTCTCTCCTAG GATCATTTGAGAAATTGCCTGCCTGGGCAGGAAAGGGACTATTTCTGTGGAGGAAG TAACTGAAGGTTGATTCCCTTTACTAATTGCTGCTGATGGATCTCTGTGACAAGAGA AATCACCTTATCTCTCAGACTAACTAGTGGGATGTGATGTGACTAGTCACATGGCTTT TTATTCTCTAGGAGAATACAGCCTATCAAATGTCTA
***mmu*PHLPP2-mut-pGL3** Cloning vector (Insert site): pGL3-Basic(gccgtg/taattc) >*mmu*PHLPP2-mut-pGL3 GGAGGCGGCGGAAGCTCTGACAATGGCCTGGTCAGTGACGATGACCAGCCTGTTGA AGGAGTCATAACCAACGGCAGCAGGGTTGAAGTAGAGGTAGTCATCCATTGCTGCC GAGGCAGAGAGCCAGAGAGCTCCCCTCCGCTCCCGAAGATCTCTTCCAACGCCTGT TCAGAGGAGCGTGCTAGAGGGGCGGGGTTTGGGATCCGAAGTCAGATCAGTGTCAA CAGTGGTATACTTCTGCCAGCGATCAGAGTCAAGATGGAGCTGCAGAAGTCTCCCTC CACTTCTTGTCTGTATGGAAAGAATCTCTCCAATGGCTCCATTGTGCCCCTAGAGGTC AGCCTGATCCTCATTGAGGTGGCCACAGAAGCACCCAAAAGGAAATCTGGCTACTT TGCTGCCCCCACTCAGCTGGATCCAGAGGATCAGTTTGTCGTCCCTCGAGTCCTGGA AGAGGAAGTGAAGGAGCAGATGAAGCAGCACCAGGAGGGCAGGCCTGAGCCCGA GCCCCGGGGAGAGGAGCGGTCAGAGCCCCTGGAGGAGTTTGATACAGCACTGTGAT TGTACCTCTCGTGTGGACGCAGCCTGAGGGAGGGCTGTGTGGTATTGGGGAAGGGT CCTTCAGGAGATATTTGCCTCAGTGTTTCAATCCATAGATAATATGGAGTAGAATTTG GAGCCAAAAAGTTGAGCACTAGCAGGGTCTGGCTCTTGATGGGCTCGGTCCGCCAT CAGTGTTAAGCTTCACATTGGTCCTTGGTTGGTCTCCCAGCGTTGCTGGGAGTCAGC AGATGTTCTGTGTCAGTCCTGCCACCTGCCATTAACCCTTTCTCTCCTAGGATCATTT GAGAAATTGCCTGCCTGGGCAGGAAAGGGTCTATTTCTGTGGAGGAAGTAACTGAA GGTTGATTCCCTTTACTAATTGCTGCTGATGGATCTCTGTGACAAGAGAAATCACCTT

ATCTCTCAGTCTAACTAGTGGGATGTGATGTGACTAGTCACATGGCTTTTATTCTCT
AGGAGAATACAGCCTATCAAATGTCTA

mmuPHLPP1-WT-pGL3

Cloning vector (Insert site): pGL3-Basic(gccgtg/taattc)

>*mmu*PHLPP1-WT-pGL3
GGAGGCGGCGGAAGCGGCATGGCATCTGAGATCAGCAGTGAACTGTCTACCTCCGA
GATGAGTAGTGAGGTGGGCTCCACAGCCTCTGATGAGCCCCCGTCTGGAGTCCTGA
ATGAGAGCAGCCCTGCCTACCCCAACGAGCAGCGCTGCATGCTCCACCCTGTCTGC
CTGTCTAACTCCTTCCAACGTCAGCTGTCCAGCGCTACTTTCTCCAGCGCGTTCTCT
GACAACGGCCTTGACAGTGACGATGAAGAACCCATTGAGGGGGTGTTCAGCAACG
GCAGCCGGGTTGAGGTGGAAGTAGACATCCACTGCAGCAGGGCCAAGGAAAAGGA
GAGACAGCAGCACCTACTTCAGGTGCCAGCTGAGGCCAGTGATGAGGGCATTGTCA
TCAGTGCCAATGAGGATGAGTCAGGTCTGTCCAAGAAGGCAGACTTTTCTGCTGTG
GGAACCATTGGACGACGCAGGGCTAATGGCTCTGTAGCTCCCCAGGAAAGGAGCCA
TAATGTGATAGAGGTTGCTGCAGATGCGCCTCTCCGGAAGCCAGGAGGCTATTTTGC
AGCCCCTGCTCAGCCAGATCCAGATGATCAGTTTATCATCCCCCCAGAGCTGGAAGA
GGAAGTCAAAGAAATCATGAAACATCACCAGGAGCAGCAGCAGCAGCAGCAGCAG
CAGCAGCTGCCACCACCACCCCAGCCGCCACAGCCACAGCCACAGCCACAGCCAC
AGCCACAGCCACAGCCACAGCGGCACTTCCAAATGGATCACCTGCCAGACTGTTAC
GATACACCGCTATGACCCAGCCTGAGTACTGTTTTAAACAATAAACTAACCAGAGAG
ACTGAGAGTCTCCCAGGCTCACATTAAACCAGGGGTGTTAACTTCATGCCCTCTCCC
AGACACTGCCCCACCTGTCTCTGCAGCTCATCTGTAGGTTCTCTTTGTATTGGTTACT
TTTAACAATTAACCACTTTTCTTCTAGTGATACTTTACCAATATGATTTAAATGTGCAG
ATAATGTGGCCCTGTTCTCGGGAACCCAGAACCTTTTACAGACATTTTTTAATTGTGT
TCCTTCCTGCTGCCACAATCAGCATGACTGTATAGAGTCCCTTATACCATCTACACAT
CCAGAGTTATATGGAAGCAGAATGCCC

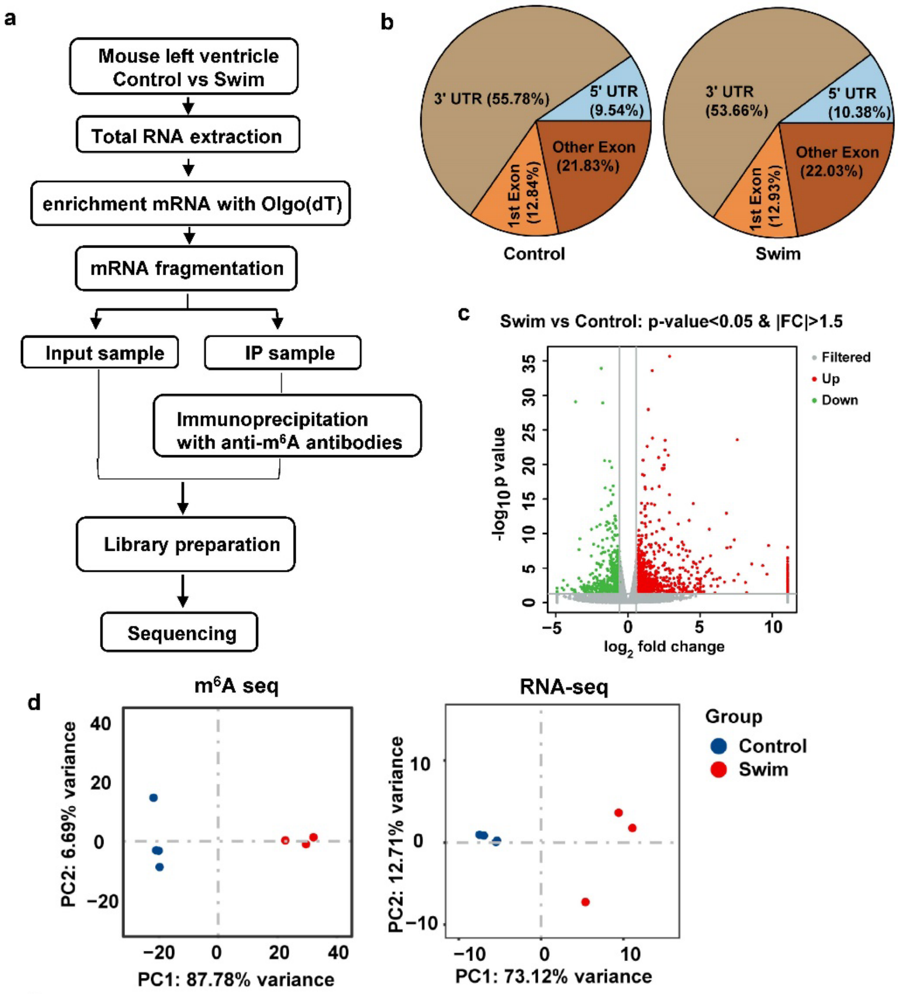
mmuPHLPP1-mut-pGL3

Cloning vector (Insert site): pGL3-Basic(gccgtg/taattc)

>*mmu*PHLPP1-mut-pGL3
GGAGGCGGCGGAAGCGGCATGGCATCTGAGATCAGCAGTGATCTGTCTACCTCCGA
GATGAGTAGTGAGGTGGGCTCCACAGCCTCTGATGAGCCCCCGTCTGGAGTCCTGA
ATGAGAGCAGCCCTGCCTACCCCAACGAGCAGCGCTGCATGCTCCACCCTGTCTGC
CTGTCTAACTCCTTCCAACGTCAGCTGTCCAGCGCTACTTTCTCCAGCGCGTTCTCT
GACAACGGCCTTGACAGTGACGATGAAGATCCCATTGAGGGGGTGTTCAGCAACGG
CAGCCGGGTTGAGGTGGAAGTAGTCATCCACTGCAGCAGGGCCAAGGAAAAGGAG
AGTCAGCAGCACCTACTTCAGGTGCCAGCTGAGGCCAGTGATGAGGGCATTGTCAT
CAGTGCCAATGAGGATGAGTCAGGTCTGTCCAAGAAGGCAGTCTTTTCTGCTGTGG
GAACCATTGGACGACGCAGGGCTAATGGCTCTGTAGCTCCCCTGGAAAGGAGCCAT
AATGTGATAGAGGTTGCTGCAGATGCGCCTCTCCGGAAGCCAGGAGGCTATTTTGCA
GCCCCTGCTCAGCCAGATCCAGATGATCAGTTTATCATCCCCCCAGAGCTGGAAGAG
GAAGTCAAAGAAATCATGAATCATCACCAGGAGCAGCAGCAGCAGCAGCAGCAGC
AGCAGCTGCCACCACCACCCCAGCCGCCACAGCCACAGCCACAGCCACAGCCACA
GCCACAGCCACAGCCACAGCGGCACTTCCAAATGGATCACCTGCCAGTCTGTTACG
ATACACCGCTATGACCCAGCCTGAGTACTGTTTTAATCAATAATCTAACCAGAGAGTC

TGAGAGTCTCCCAGGCTCACATTAATCCAGGGGTGTTAACTTCATGCCCTCTCCCAGTCACTGCCCCACCTGTCTCTGCAGCTCATCTGTAGGTTCTCTTTGTATTGGTTACTTTTAACAATTAACCACTTTTCTTCTAGTGATACTTTACCAATATGATTTAAATGTGCAGATAATGTGGCCCTGTTCTCGGGATCCCAGATCCTTTTACAGTCATTTTTTAATTGTGTTCCTTCCTGCTGCCACAATCAGCATGACTGTATAGAGTCCCTTATACCATCTACACATCCAGAGTTATATGGAAGCAGAATGCCC
***Rattus* PHLPP2-WT-pGL3** Cloning vector (Insert site): pGL3-Basic(gccgtg/taattc) >*Rattus* PHLPP2-WT-pGL3 GGAGGCGGCGGAAGCTCTGACAATGGACTGGACAGTGACGATGACCAGCCTGTTGAAGGCGTCATAACCAATGGCAGCAGGGTTGAGGTAGAGGTAGACATTCATTGCTGCCGAGGCAGAGAGTCTGAGAACTCCCCTACTCTCCCGAAGAATTCTTCCTACCCCTGTTCAGAGGAACATGCTAGGGGGTTGGGTTTTGGGATCCGAAGACAGAACAGTGTGAATAGTGGTATACTTCTGCCAGTGAACAAAGACAAGATGGAGTTACAGAAGTCTCCCTCCACTTCTTGTTTGTATGGAAAGAAACTCTCCAATGGCTCCATTGTGCCCCTAGAAGACAGCCTGAACCTCATTGAGGTGGCCACAGAAGCACCCAAGAGGAAAACTGGCTATTTTGCTGCCCCCACTCAGCTGGAACCAGAGGATCAATTTGTTGTCCCCCGTGACCTGGAAGACGAAGTGAAGGAGCAAATGAAGCAGCACCAGGAGAGCAGGCCTGAGCCTGAACCCAGGGAAGAGGACCGGACAGAGCCCCTGCAGGAGTTTGATACAGCACTGTGA
***Rattus* PHLPP2-mut-pGL3** Cloning vector (Insert site): pGL3-Basic(gccgtg/taattc) >*Rattus* PHLPP2-mut-pGL3 GGAGGCGGCGGAAGCTCTGACAATGGTCTGGTCAGTGACGATGACCAGCCTGTTGAAGGCGTCATAACCAATGGCAGCAGGGTTGAGGTAGAGGTAGTCATTCATTGCTGCCGAGGCAGAGAGTCTGAGATCTCCCCTACTCTCCCGAAGAATTCTTCCTACCCCTGTTCAGAGGATCATGCTAGGGGGTTGGGTTTTGGGATCCGAAGTCAGATCAGTGTGAATAGTGGTATACTTCTGCCAGTGATCAAAGTCAAGATGGAGTTACAGAAGTCTCCCTCCACTTCTTGTTTGTATGGAAAGAATCTCTCCAATGGCTCCATTGTGCCCCTAGAAGTCAGCCTGATCCTCATTGAGGTGGCCACAGAAGCACCCAAGAGGAAATCTGGCTATTTTGCTGCCCCCACTCAGCTGGAACCAGAGGATCAATTTGTTGTCCCCCGTGACCTGGAAGACGAAGTGAAGGAGCAAATGAAGCAGCACCAGGAGAGCAGGCCTGAGCCTGATCCCAGGGAAGAGGTCCGGTCAGAGCCCCTGCAGGAGTTTGATACAGCACTGTGA

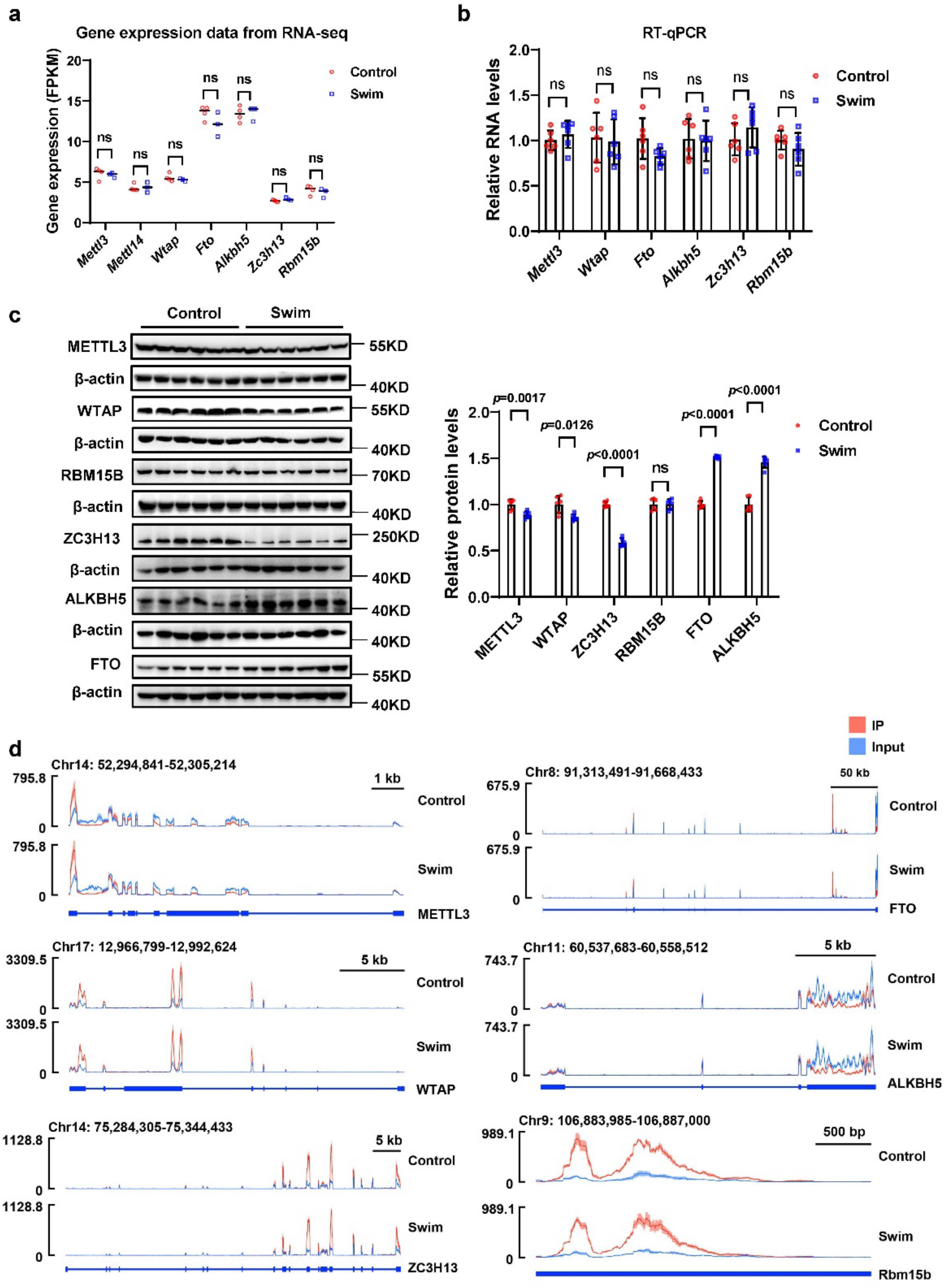
Supplementary Figures



e

Differentially methylated peaks	swim-vs-control
Number of Peaks	475
Number of genes	436
Total Length of Peaks(bp)	1252289
Average Length of Peaks(bp)	2636.4
Median Length of Peaks(bp)	299
Minimum Length of Peaks(bp)	140
Maximum Length of Peaks(bp)	284643
Percentage of Genome(%)	0.05

Supplementary Fig. 1: Identifying m^{6}A RNA methylome of the exercised murine hearts by MeRIP-seq and RNA-seq. (**a**) Diagram of meRIP-seq experiment. (**b**) Pie charts showing the distribution of m^{6}A RNA methylation in the swim and control murine hearts, respectively. (**c**) Volcano plot of the RNA-seq. Transcripts with significantly increased peak (red) and decreased peak (green) changes are highlighted (*p*-value<0.05, fold change>1.5). Negative binomial test (two-sided). (**d**) PCA plots of MeRIP-seq and RNA-seq. (**e**) Statistics of the differential methylation peaks which were detected by meRIP in the swim and control hearts. Seq, sequencing. IP, immunoprecipitation.

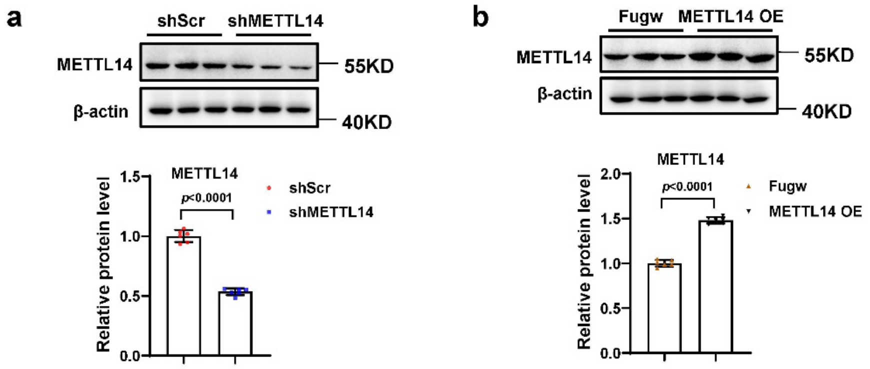


e

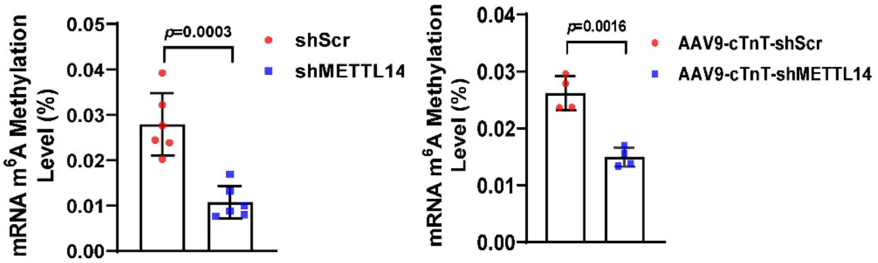
chr	chromStart	chromEnd	Name	diff.lg(p)	diff.log$_2$(FC)
Chr3	123368443	123368741	*Mettl14*	-4.11	-0.749
Chr3	123380298	123383616	*Mettl14*	-1.45	-0.719

Supplementary Fig. 2: The regulation of m^{6}A effectors in response to exercise. (**a**) Gene expression data of m^{6}A effectors (METTL3, METTL14, WTAP, FTO, ALKBH5, ZC3H13, and RBM15B) from RNA-seq (n=4:3 independent biological samples). (**b**) qPCR analysis of *Mettl3*, *Wtap*, *Fto*, *Alkbh5*, *Zc3h13*, and *Rbm15b* mRNA expression levels in the hearts with or without swim training (n=6 mice/group). (**c**) Representative western blot and statistical data displaying the knockdown of m^{6}A effectors (METTL3, WTAP, FTO, ALKBH5, ZC3H13, and

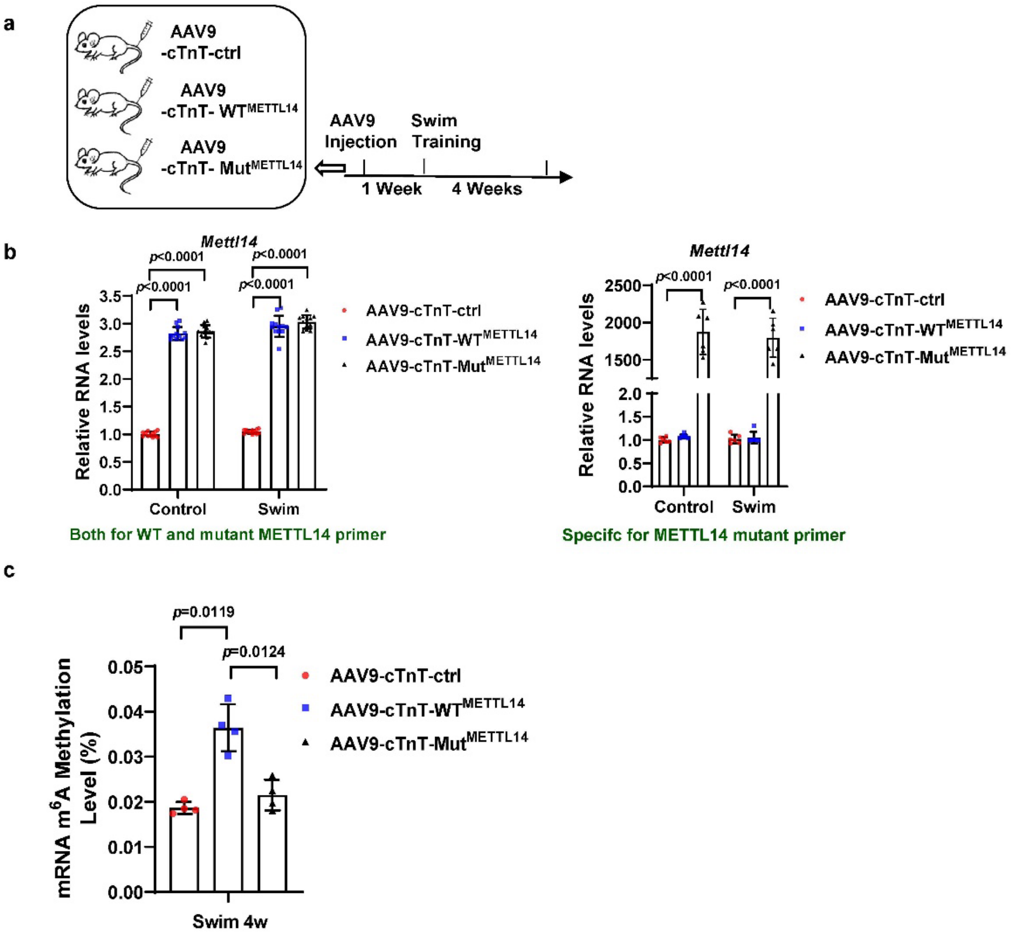
RBM15B) in whole lysates isolated from the hearts of swim and control murine (n=6 mice/group). (**d**) Integrative genomics viewer (IGV) tracks revealing the results of meRIP-seq (Red) and RNA-seq (Blue) reads distributions in *Mettl3*, *Wtap*, *Fto*, *Alkbh5*, *Zc3h13*, and *Rbm15b* mRNA of the swim and control. Seq, sequencing. (**e**) m^6A peaks on *Mettl14* mRNA in the hearts with or without swim training determined using meRIP-seq. IP, immunoprecipitation. RT-qPCR, quantitative reverse transcription polymerase chain reaction. ns, nonstatistically significant. All data are expressed as means ± SD. (**b** and **c**, independent-sample t-test, two-sided.) Source data are provided as a Source Data file.



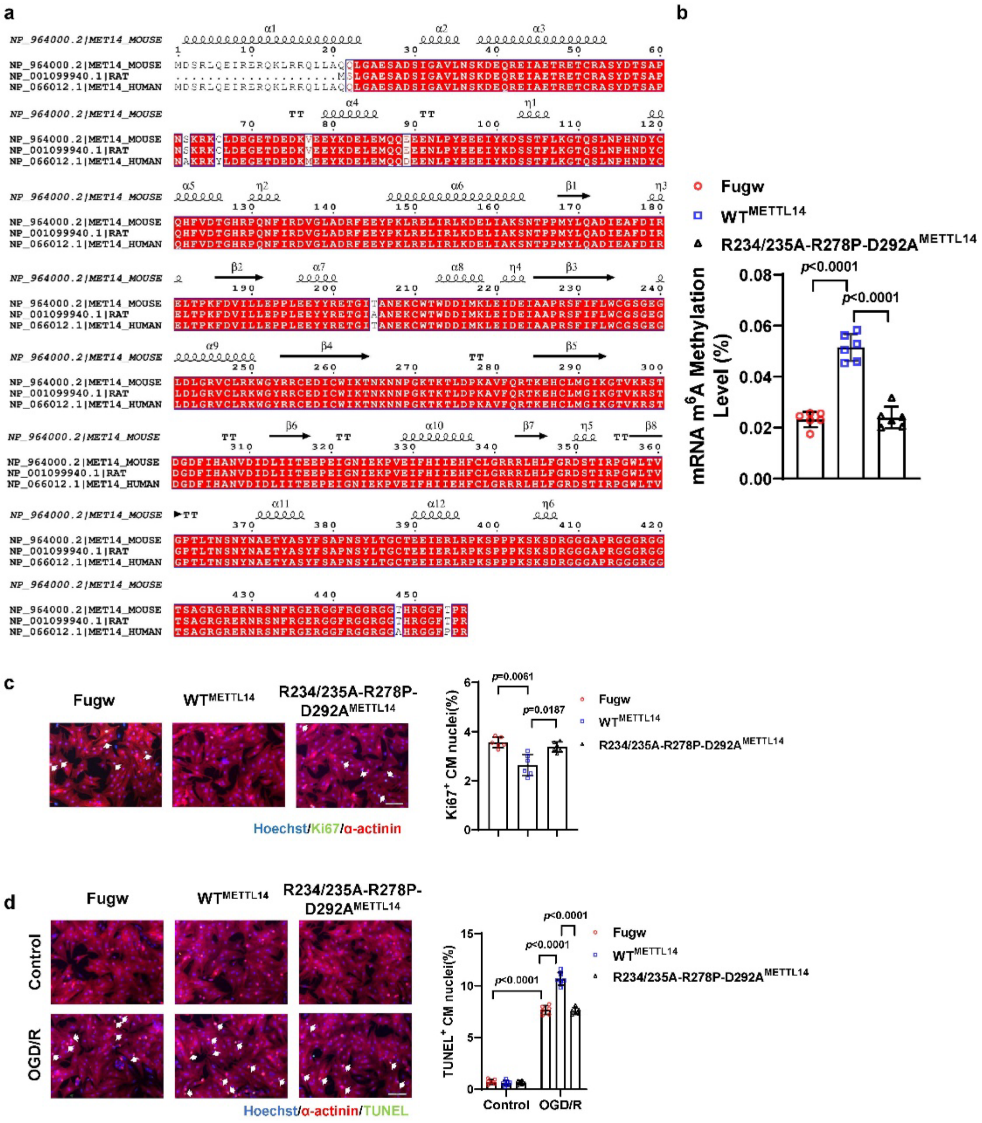
Supplementary Fig. 3: Overexpression and inhibition of METTL14 in NRCMs. (**a**) Representative western blot and statistical data displaying the knockdown of METTL14 in NRCMs by shMETTL14 (n=6 wells/group). (**b**) Representative western blot and statistical data displaying the overexpression of METTL14 in NRCMs via transfecting with METTL14 overexpression construct (n=6 wells/group). NRCM, neonatal rat cardiomyocyte. Fugw, control without METTL14 overexpression; METTL14 OE, METTL14 overexpression; shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14. All data are expressed as means ± SD. (**a** and **b**, independent-sample t-test, two-sided.) Source data are provided as a Source Data file.



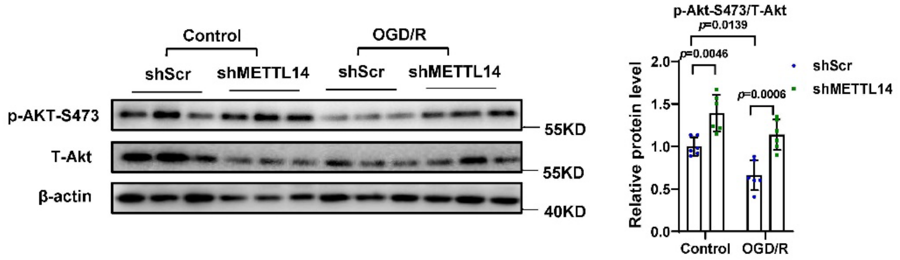
Supplementary Fig. 4: METTL14 inhibition reduces the mRNA m^{6}A level in NRCM. The relative mRNA m^{6}A level with or without METTL14 knockdown in NRCM (n=6 /group) or mice hearts (n=4 /group). NRCM, neonatal rat cardiomyocyte. shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14; AAV9-cTnT-shScr, cardiac-specific troponin-T promoter-driven Scramble AAV9; AAV9-cTnT-shMETTL14, cardiac-specific troponin-T promoter-driven METTL14 knockdown AAV9. All data are expressed as means ± SD. (Independent-sample t-test, two-sided.) Source data are provided as a Source Data file.



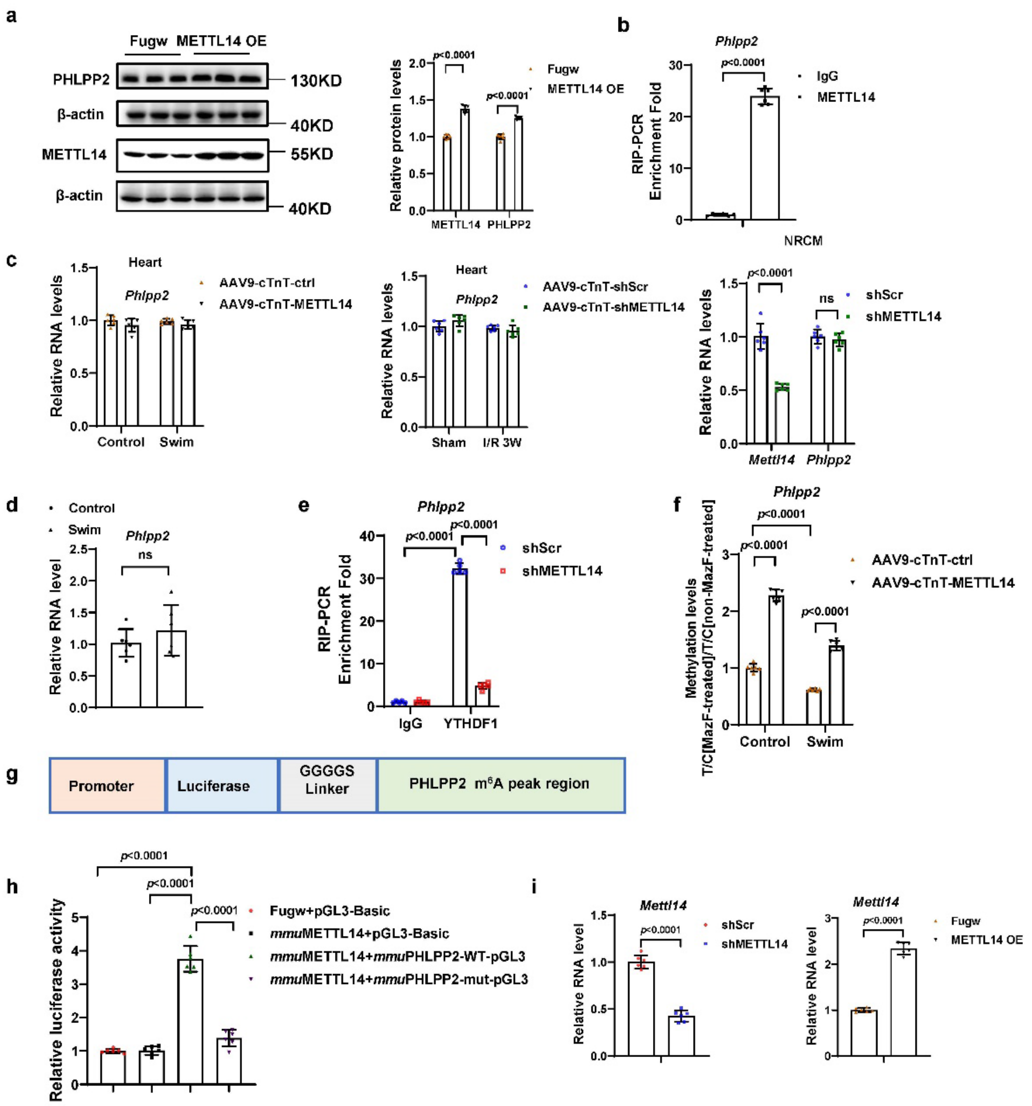
Supplementary Fig. 5: Mutant METTL14 abolishes the cardiac m^{6}A methylation elevation after swimming training. (**a**) The schedule of virus injection and swim-induced mice physiological cardiac hypertrophy model establishment. WT^{METTL14}, wild -type METTL14 overexpression. Mut^{METTL14}, METTL14 R254/R255A-R298P-D312A mutant overexpression. (**b**) qPCR analysis of *Mettl14* mRNA expression levels in mice hearts treated as indicated groups. Left panel, primer, which was used to PCR, for both WT and mutant METTL14 (n=12 /group). Right panel, primer, which was used to PCR, specific for mutant METTL14 (n=6 /group). (**c**) The relative mRNA m^{6}A level in hearts treated as indicated (n=4 /group). AAV9-cTnT-ctrl, cardiac-specific troponin-T promoter-driven control AAV9; AAV9-cTnT-WT^{METTL14}, cardiac-specific troponin-T promoter-driven wild-type METTL14 overexpression AAV9; AAV9-cTnT- Mut^{METTL14}, cardiac-specific troponin-T promoter-driven METTL14 R254/R255A-R298P-D312A mutant overexpression AAV9. All data are expressed as means ± SD. (**b**, two-way ANOVA followed by Tukey's post hoc test; **c**, one-way ANOVA followed by Bonferroni test.) Source data are provided as a Source Data file.



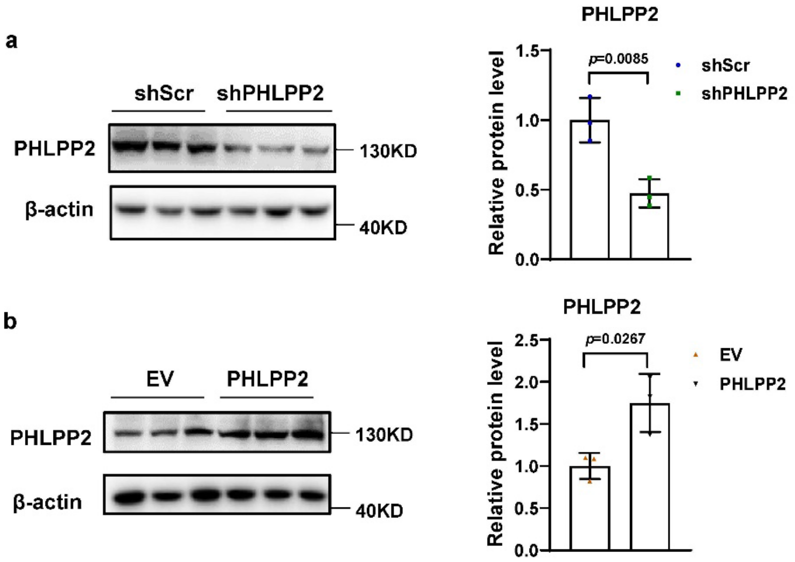
Supplementary Fig. 6: The pro-apoptosis and antiproliferative effects of WT^{METTL14} overexpression on NRCM are disrupted by mut^{METTL14} overexpression. (**a**) Protein alignment of METTL14 across mammalian species. Protein alignment was generated by CLUSTALW and ESPript 3.0. PDB file of murine METTL14 was download from AlphaFold Protein Structure Database. (**b**) The relative mRNA m^{6}A level in NRCM treated as indicated (n=6 /group). (**c**) Representative images of immunofluorescence staining and quantification of the Ki67 positive cardiomyocytes treated as indicated (n=6 wells/group). Scale bar: 100 μm. (**d**) Representative images of immunofluorescence staining and quantification of the TUNEL positive cardiomyocytes treated as indicated (n=6 wells/group). Scale bar: 100 μm. NRCM, neonatal rat cardiomyocyte. OGD/R, oxygen-glucose deprivation/reperfusion. Fugw, control without METTL14 overexpression; WT^{METTL14}, NRCM treated with wild-type METTL14 overexpression; R234/235A-R278P-D292A^{METTL14}, NRCM treated with METTL14 mutant overexpression. All data are expressed as means ± SD. (**b**, one-way ANOVA followed by Bonferroni test; **c**, one-way ANOVA followed by Dunnett T3 test; **d**, two-way ANOVA followed by Tukey's post hoc test.) Source data are provided as a Source Data file.



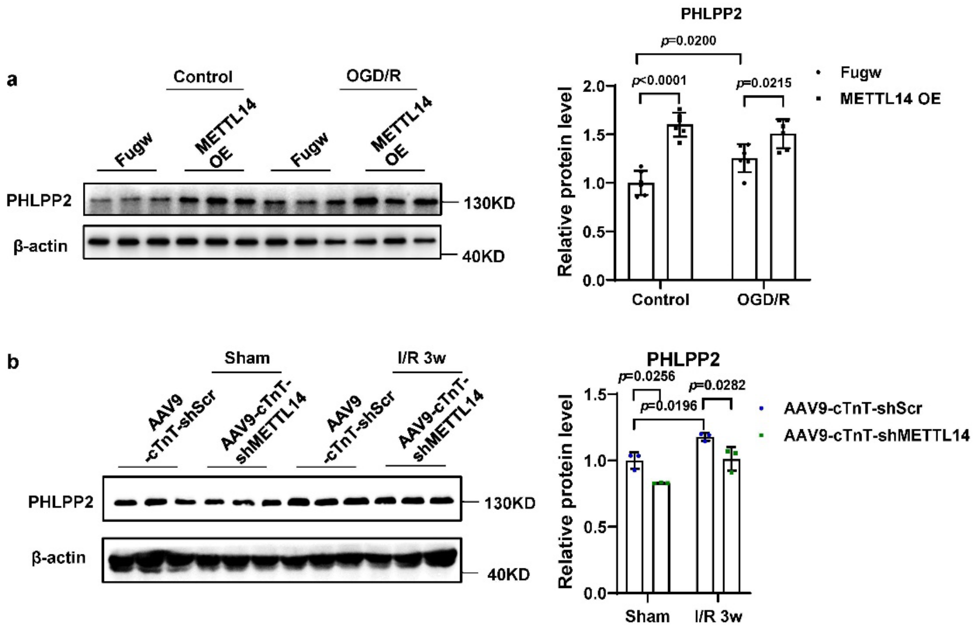
Supplementary Fig. 7: The activation of Akt-S473 presented in OGD/R treated NRCM is regulated by METTL14. Representative western blot and statistical data of the phosphorylation levels of Akt-S473 in OGD/R induced NRCM apoptosis model treated with shMETTL14 or scrambled control (n=6 wells/group). NRCM, neonatal rat cardiomyocyte. shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14; OGD/R, oxygen-glucose deprivation/reperfusion. All data are expressed as means ± SD. (Two-way ANOVA followed by Tukey's post hoc test.) Source data are provided as a Source Data file.



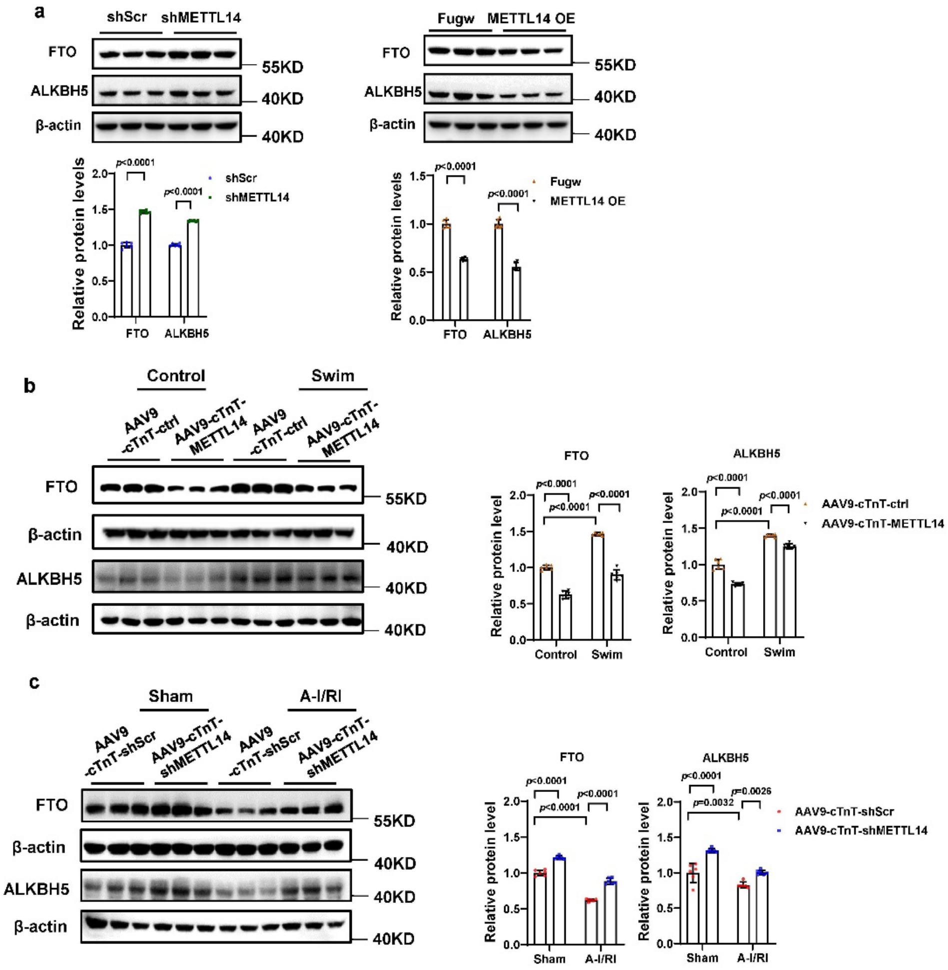
Supplementary Fig. 8: The regulation of METTL14 on PHLPP2. (**a**) Western blot analyses of PHLPP2 and METTL14 in NRCM with or without METTL14 overexpression (n=6 wells/group). (**b**) Validation of *Phlpp2* mRNA binding to METTL14 in H9C2 cardiomyocytes using RIP-qPCR (n=6/group). (**c**) qPCR analysis of *Phlpp2* mRNA expression levels in the hearts or NRCM treated as indicated (n=6 mice or wells/group). (**d**) qPCR analysis of *Phlpp2* mRNA expression levels in the hearts with or without swimming training (n=6 mice/group). (**e**) The binding of *Phlpp2* mRNA to YTHDF1 in H9C2 cardiomyocytes with or without METTL14 knockdown (n=5/group). (**f**) The methylation levels of *Phlpp2* mRNA in mice hearts treated as indicated measured by MazF-qPCR (n=6 mice/group). (**g**) Scheme of WT-PHLPP2 or Mut-PHLPP2 luciferase reporter gene. (**h**) Relative luciferase activity of mouse PHLPP2 wild type (PHLPP2-WT-pGL3) or m^{6}A mutant (PHLPP2-mut-pGL3) reporter gene with or without mouse METTL14 overexpression (n=6/group). (**i**) qPCR analysis of *Mettl14* expression with METTL14 overexpression or knockdown, related to MazF-qPCR in Fig. 7k (n=6/group). NRCM, neonatal rat cardiomyocyte; RIP, RNA immunoprecipitation assay; Fugw, control without METTL14 overexpression; METTL14 OE, METTL14 overexpression; shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14; AAV9-cTnT-ctrl, cardiac-specific troponin-T promoter-driven control AAV9; AAV9-cTnT-METTL14, cardiac-specific troponin-T promoter-driven METTL14 overexpression AAV9; AAV9-cTnT-shScr, cardiac-specific troponin-T promoter-driven Scramble AAV9; AAV9-cTnT-shMETTL14, cardiac-specific troponin-T promoter-driven METTL14 knockdown AAV9. ns, nonstatistically significant. All data are expressed as means ± SD. (**a**-**b**, **d**, and **i**, independent-sample t-test, two-sided; **c**, **e**-**f**, two-way ANOVA followed by Tukey's post hoc test; **h**, one-way ANOVA followed by Dunnett T3 test.) Source data are provided as a Source Data file.



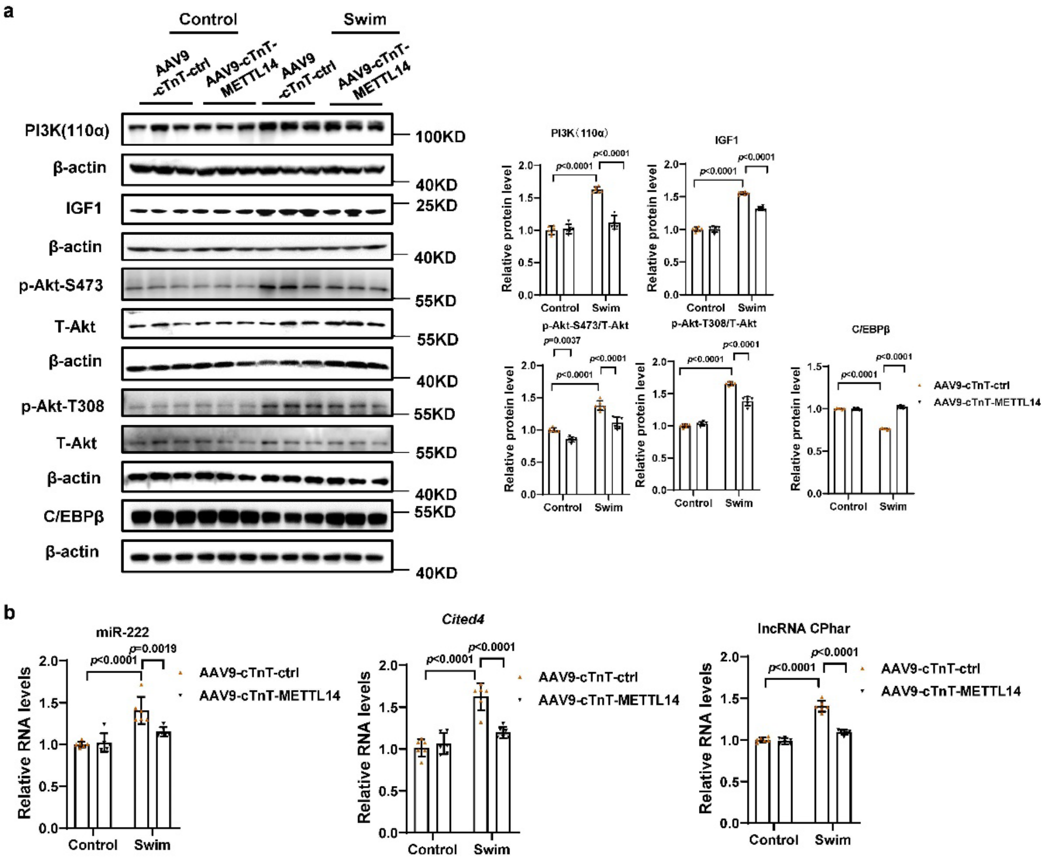
Supplementary Fig. 9: Overexpression and inhibition of PHLPP2 in NRCMs. (**a**) Representative western blot and statistical data displaying the knockdown of PHLPP2 in NRCMs by shPHLPP2 (n=3 wells/group). (**b**) Representative western blot and statistical data displaying the overexpression of PHLPP2 in NRCMs via transfecting with PHLPP2 overexpression construct (n=3 wells/group). NRCM, neonatal rat cardiomyocyte. EV, Empty vector without PHLPP2 overexpression; PHLPP2, PHLPP2 overexpression; shScr, Scramble short hairpin RNA; shPHLPP2, PHLPP2 short hairpin RNA to knockdown PHLPP2. All data are expressed as means ± SD. (**a** and **b**, independent-sample t-test, two-sided.) Source data are provided as a Source Data file.



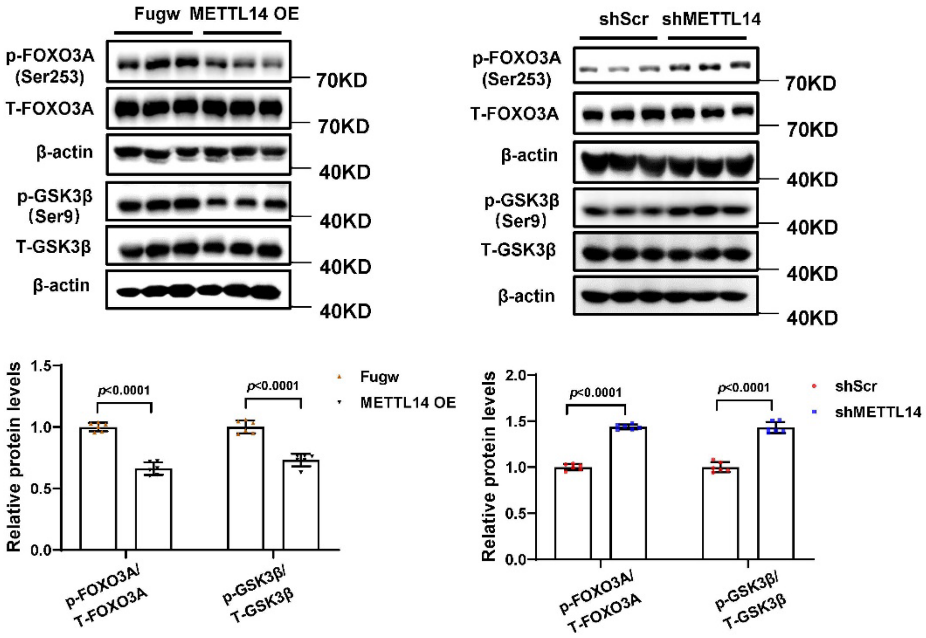
Supplementary Fig. 10: The expression of PHLPP2 were positively regulated by METTL14. (**a**) Representative western blot and statistical data of PHLPP2 expression levels in the NRCMs treated as indicated (n=6 wells /group). (**b**) Representative western blot and statistical data of PHLPP2 expression levels in the mice hearts treated as indicated (n=3 mice/group). NRCM, neonatal rat cardiomyocyte; OGD/R, oxygen-glucose deprivation/reperfusion; Fugw, control without METTL14 overexpression; METTL14 OE, METTL14 overexpression; AAV9-cTnT-shScr, cardiac-specific troponin-T promoter-driven Scramble AAV9; AAV9-cTnT-shMETTL14, cardiac-specific troponin-T promoter-driven METTL14 knockdown AAV9. All data are expressed as means ± SD. (**a** and **b**, Two-way ANOVA followed by Tukey's post hoc test.) Source data are provided as a Source Data file.



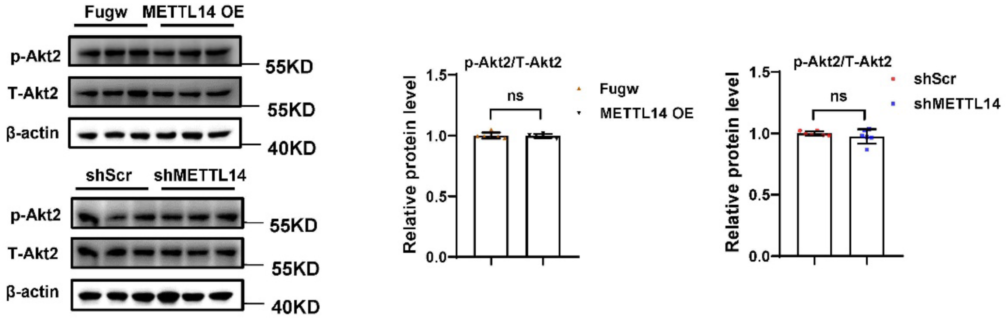
Supplementary Fig. 11: Demethylase FTO and ALKBH5 were negatively regulated by METTL14 alteration. (**a**) Representative western blot and statistical data of FTO and ALKBH5 in NRCMs with METTL14 knockdown or METTL14 overexpression (n=6 wells/group). (**b-c**) Representative western blot and statistical data of FTO and ALKBH5 expression levels in the mice hearts treated as indicated (n=6 mice/group). Fugw, control without METTL14 overexpression; METTL14 OE, METTL14 overexpression; shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14; AAV9-cTnT-shScr, cardiac-specific troponin-T promoter-driven Scramble AAV9; AAV9-cTnT-shMETTL14, cardiac-specific troponin-T promoter-driven METTL14 knockdown AAV9; AAV9-cTnT-ctrl, cardiac-specific troponin-T promoter-driven control AAV9; AAV9-cTnT-METTL14, cardiac-specific troponin-T promoter-driven METTL14 overexpression AAV9. A-I/RI, acute myocardial ischemia-reperfusion injury. All data are expressed as means ± SD. (**a**, independent-sample t-test, two-sided; **b** and **c**, Two-way ANOVA followed by Tukey's post hoc test.) Source data are provided as a Source Data file.



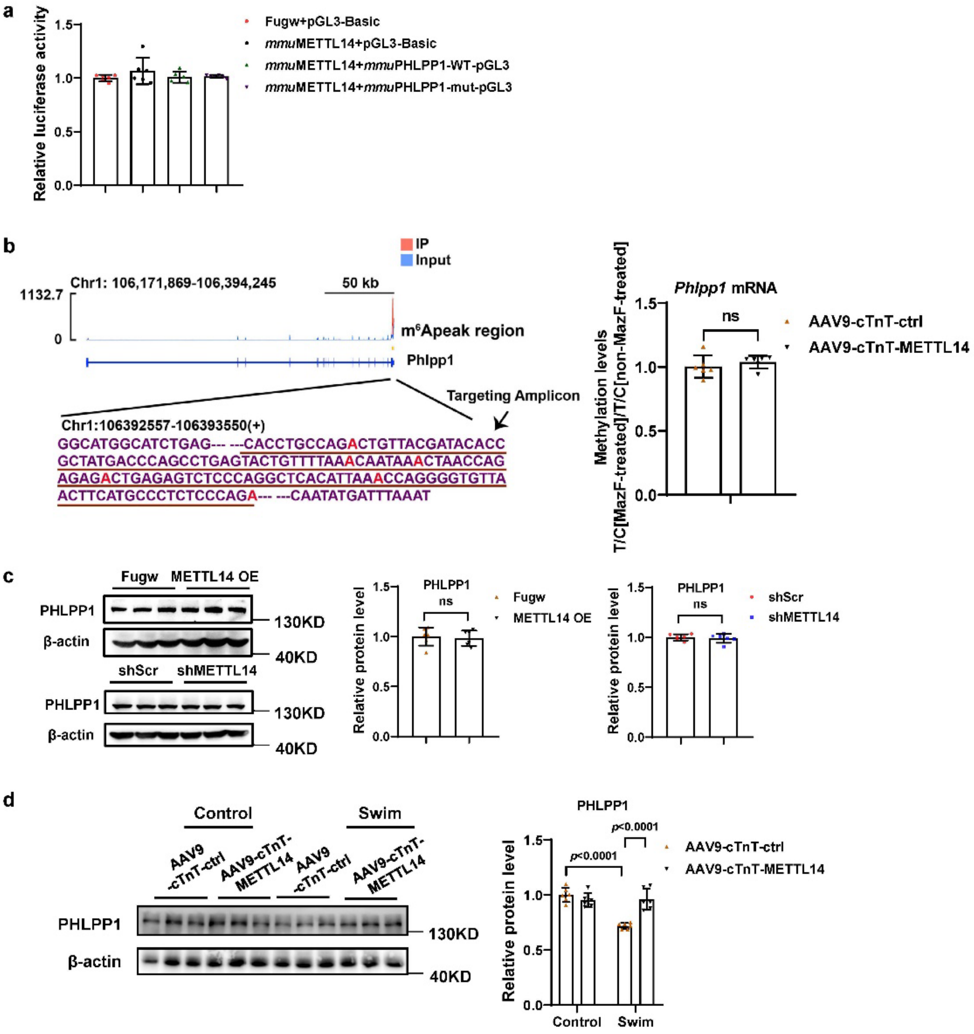
Supplementary Fig. 12: Expression of previously reported factors and signaling pathways known to be involved in exercise-induced cardiac hypertrophy. (**a**) Representative western blot and statistical data of IGF1/PI3K/Akt signaling and C/EBPβ expression levels in the mice hearts treated as indicated (n=6 mice/group). (**b**) qPCR analysis of miR-222, *Cited4*, and lncRNA CPhar expression levels in the hearts treated as indicated (n=6 mice/group). AAV9-cTnT-ctrl, cardiac-specific troponin-T promoter-driven control AAV9; AAV9-cTnT-METTL14, cardiac-specific troponin-T promoter-driven METTL14 overexpression AAV9. All data are expressed as means ± SD. (**a** and **b**, Two-way ANOVA followed by Tukey's post hoc test.) Source data are provided as a Source Data file.



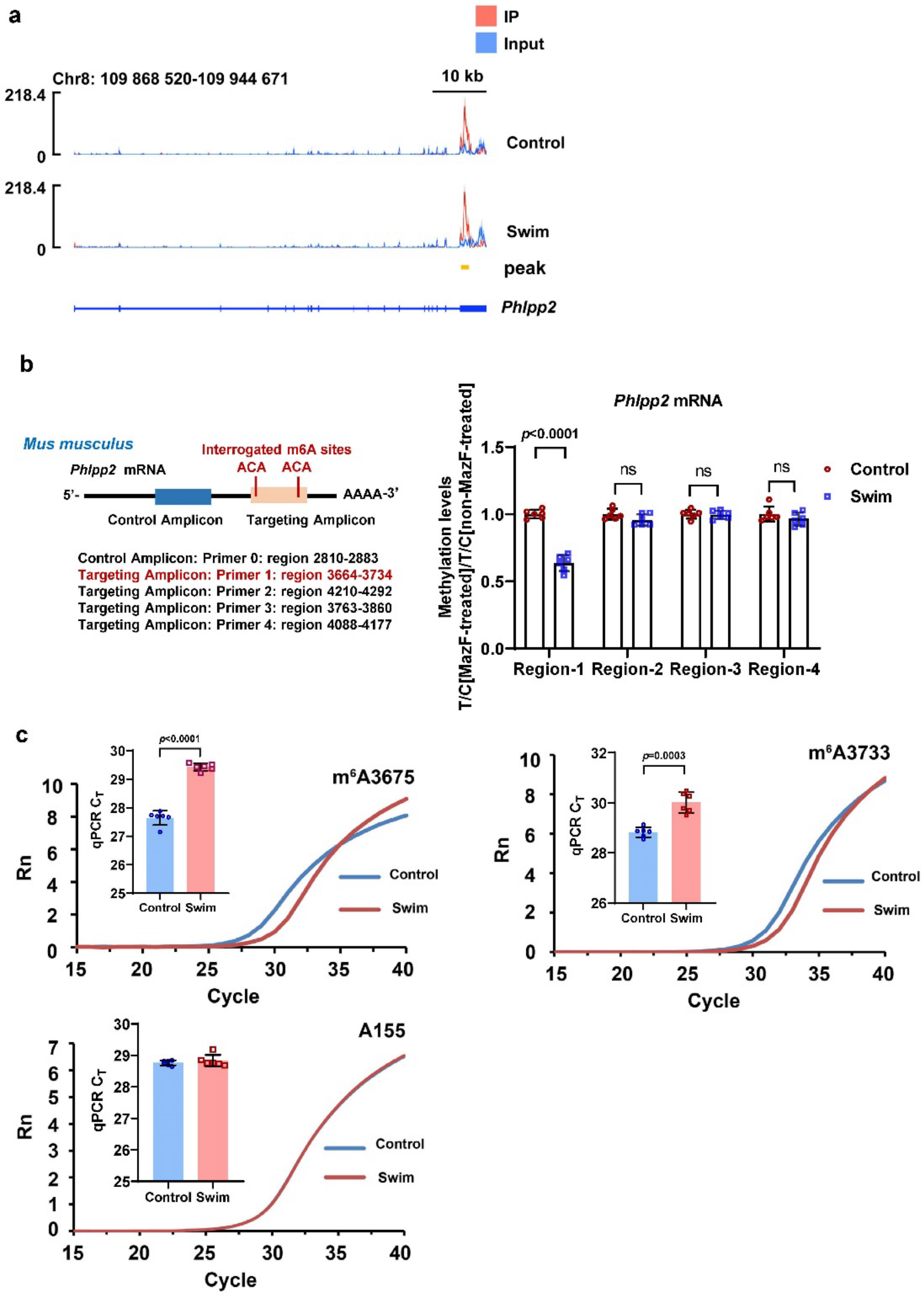
Supplementary Fig. 13: The phosphorylation levels of Akt substrates including FOXO3a, and GSK3β. Representative western blot and statistical data of phosphorylation levels of FOXO3a, and GSK3β in NRCMs with METTL14 knockdown or METTL14 overexpression (n=6 wells/group). Fugw, control without METTL14 overexpression; METTL14 OE, METTL14 overexpression; shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14. All data are expressed as means ± SD. (Independent-sample t-test, two-sided.) Source data are provided as a Source Data file.



Supplementary Fig. 14: The phosphorylation levels of Akt2 in NRCMs with METTL14 knockdown or METTL14 overexpression (n=6 wells/group). Fugw, control without METTL14 overexpression; METTL14 OE, METTL14 overexpression; shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14. ns, nonstatistically significant. All data are expressed as means ± SD. (Independent-sample t-test, two-sided.) Source data are provided as a Source Data file.



Supplementary Fig. 15: *Phlpp1* mRNA m^{6}A level and protein level were not affected by METTL14. (**a**) Relative luciferase activity of mouse PHLPP1 wild type (PHLPP1-WT-pGL3) or m^{6}A mutant (PHLPP1-mut-pGL3) reporter gene with or without mouse METTL14 overexpression (n=6/group). (**b**) The methylation levels of *Phlpp1* mRNA in mice hearts treated as indicated measured by MazF-qPCR (n=6 mice/group). (**c**) Representative western blot and statistical data of PHLPP1 in NRCMs with METTL14 knockdown or METTL14 overexpression (n=6 wells/group). (**d**) Representative western blot and statistical data of PHLPP1 expression level in the mice hearts treated as indicated (n=6 mice/group). Fugw, control without METTL14 overexpression; METTL14 OE, METTL14 overexpression; shScr, Scramble short hairpin RNA; shMETTL14, METTL14 short hairpin RNA to knockdown METTL14; AAV9-cTnT-ctrl, cardiac-specific troponin-T promoter-driven control AAV9; AAV9-cTnT-METTL14, cardiac-specific troponin-T promoter-driven METTL14 overexpression AAV9. ns, nonstatistically significant. All data are expressed as means ± SD. (**a**, one-way ANOVA followed by Dunnett T3 test; **b** and **c**, independent-sample t-test, two-sided; **d**, Two-way ANOVA followed by Tukey's post hoc test.) Source data are provided as a Source Data file.



Supplementary Fig. 16: RNA m^{6}A modifications regulation in *Phlpp2* mRNA in response to exercise training in mouse heart. (**a**) Integrative genomics viewer (IGV) tracks revealing the results of meRIP-seq (Red) and RNA-seq (Blue) reads distributions in *Phlpp2* mRNA of the swim and control. Seq, sequencing. (**b**) MazF-qPCR identified the methylation modification region of *Phlpp2* mRNA which is specifically regulated in response to swimming training (n=6 mice/group). (**c**) Real-time fluorescence amplification curves and bar plot of the threshold cycle (C_T) of qPCR showing SELECT results for detecting m^{6}A3675, m^{6}A3733 and A155 sites (for input control) in *Phlpp2* mRNA between control and swim mice hearts (n=6 /group). ns, nonstatistically significant; All data are expressed as means ± SD. (**b** and **c**, independent-sample t-test, two-sided.) Source data are provided as a Source Data file.