

Supplementary Tables

Table S1. The conserved miRNA precursors that are duplicated or single-copy in humans (excel file).

Table S2. The 574 mature miRNAs and their average expression level (RPM) across the 181 datasets

miRNA	RPM	miRNA	RPM	miRNA	RPM
hsa-miR-21-5p	82106.27	hsa-miR-421	190.72	hsa-miR-766-3p	22.83
hsa-let-7f-5p	66056.48	hsa-miR-452-5p	185.38	hsa-miR-105-5p	22.35
hsa-let-7a-5p	57991.92	hsa-miR-429	177.51	hsa-miR-1225-5p	21.80
hsa-miR-143-3p	52248.75	hsa-miR-331-3p	172.79	hsa-miR-1304-3p	21.69
hsa-miR-486-5p	38969.27	hsa-miR-455-3p	172.68	hsa-miR-548av-3p	21.66
hsa-miR-26a-5p	37256.47	hsa-miR-17-3p	167.00	hsa-miR-513c-5p	21.62
hsa-miR-92a-3p	33787.35	hsa-miR-96-5p	160.07	hsa-miR-378a-5p	21.29
hsa-miR-181a-5p	32284.11	hsa-miR-378d	159.81	hsa-miR-1301-3p	21.28
hsa-miR-22-3p	30377.68	hsa-miR-508-3p	159.10	hsa-miR-409-5p	21.23
hsa-miR-451a	29245.08	hsa-miR-20b-5p	156.90	hsa-miR-655-3p	21.00
hsa-let-7b-5p	21680.38	hsa-miR-656-3p	156.55	hsa-miR-509-3p	20.73
hsa-miR-378c	16756.89	hsa-miR-193a-3p	156.02	hsa-miR-873-3p	20.72
hsa-miR-9-5p	16459.67	hsa-miR-33a-5p	155.92	hsa-miR-592	20.70
hsa-miR-16-5p	15424.42	hsa-miR-7704	150.60	hsa-miR-3609	20.68
hsa-miR-30a-5p	15246.96	hsa-miR-339-5p	149.20	hsa-miR-195-3p	20.39
hsa-let-7g-5p	14301.91	hsa-miR-302b-3p	148.61	hsa-miR-3176	20.04
hsa-miR-378a-3p	14108.16	hsa-miR-137	144.83	hsa-miR-200b-5p	20.02
hsa-miR-101-3p	13627.95	hsa-miR-502-3p	141.83	hsa-miR-1269b	19.86
hsa-miR-103a-3p	13581.60	hsa-miR-671-3p	140.64	hsa-miR-664a-5p	19.63
hsa-miR-191-5p	12167.02	hsa-miR-487b-3p	139.57	hsa-miR-377-5p	19.60
hsa-miR-148a-3p	12015.82	hsa-miR-767-5p	138.74	hsa-miR-346	19.55
hsa-miR-375	10757.46	hsa-miR-369-3p	136.28	hsa-miR-3065-5p	19.42
hsa-miR-24-3p	9894.80	hsa-miR-301b-3p	134.41	hsa-miR-145-3p	19.26
hsa-miR-10a-5p	9273.11	hsa-miR-190a-5p	132.74	hsa-miR-576-5p	19.08
hsa-let-7c-5p	9259.19	hsa-miR-885-5p	130.23	hsa-miR-26b-3p	18.87
hsa-miR-155-5p	8731.76	hsa-miR-708-5p	129.98	hsa-miR-33a-3p	18.77
hsa-let-7i-5p	8590.47	hsa-miR-148a-5p	129.65	hsa-miR-487a-3p	18.33
hsa-miR-30d-5p	8224.59	hsa-miR-134-5p	129.09	hsa-miR-299-3p	18.21
hsa-miR-146b-5p	8105.41	hsa-miR-330-3p	128.34	hsa-miR-1468-5p	18.07
hsa-miR-30e-5p	8048.91	hsa-miR-33b-5p	121.46	hsa-miR-101-5p	17.74
hsa-miR-192-5p	7602.45	hsa-miR-326	119.36	hsa-miR-92b-5p	17.63
hsa-miR-125b-5p	7312.12	hsa-miR-125b.1-3p	119.27	hsa-miR-154-5p	17.24
hsa-miR-27b-3p	6945.81	hsa-miR-542-3p	117.39	hsa-miR-138.1-3p	17.19
hsa-miR-10b-5p	6916.87	hsa-miR-361-3p	116.15	hsa-miR-302a-3p	17.08
hsa-miR-19b-3p	6905.83	hsa-miR-376a-5p	114.40	hsa-miR-187-3p	16.97
hsa-miR-124-3p	6518.43	hsa-miR-214-3p	112.85	hsa-miR-758-3p	16.84
hsa-miR-128-3p	6447.18	hsa-miR-5683	109.59	hsa-miR-940	16.81
hsa-miR-126-5p	6318.05	hsa-miR-27b-5p	107.00	hsa-miR-34a-3p	16.58
hsa-miR-320a	6117.64	hsa-miR-148b-5p	105.70	hsa-miR-374b-3p	16.38
hsa-miR-1-3p	5485.72	hsa-miR-495-3p	103.44	hsa-miR-24.1-5p	16.20
hsa-miR-29a-3p	5391.40	hsa-miR-345-5p	103.29	hsa-miR-1247-5p	16.19
hsa-miR-127-3p	5190.86	hsa-miR-374c-5p	102.96	hsa-miR-329-3p	16.06
hsa-miR-122-5p	5165.02	hsa-miR-129.2-3p	102.18	hsa-miR-942-5p	15.95
hsa-miR-182-5p	5096.56	hsa-miR-511-3p	100.03	hsa-miR-891a-5p	15.87
hsa-miR-140-3p	4949.02	hsa-miR-7974	99.51	hsa-miR-1269a	15.72
hsa-miR-100-5p	4845.23	hsa-miR-577	99.21	hsa-miR-376a-3p	15.42
hsa-miR-99b-5p	4756.92	hsa-miR-133a-3p	97.77	hsa-miR-23b-5p	15.13
hsa-miR-26b-5p	4732.29	hsa-miR-18b-5p	93.08	hsa-miR-627-5p	15.13
hsa-miR-29b-3p	4373.79	hsa-miR-324-5p	92.79	hsa-miR-302d-3p	15.04
hsa-let-7e-5p	4336.70	hsa-miR-582-3p	92.61	hsa-miR-431-3p	14.97
hsa-miR-25-3p	4332.90	hsa-let-7i-3p	91.42	hsa-miR-675-3p	14.69
hsa-miR-186-5p	4170.00	hsa-miR-382-5p	91.08	hsa-let-7f.1-3p	14.68
hsa-miR-92b-3p	4092.26	hsa-miR-455-5p	90.52	hsa-miR-128.1-5p	14.64
hsa-miR-151a-3p	4037.93	hsa-let-7a-3p	88.48	hsa-miR-19b.1-5p	14.54

hsa-miR-144-5p	3905.17	hsa-miR-378f	87.55	hsa-miR-548ay-5p	14.49
hsa-miR-23a-3p	3833.48	hsa-miR-550a-3p	87.00	hsa-miR-2110	14.47
hsa-miR-150-5p	3566.48	hsa-miR-509-5p	83.24	hsa-miR-296-5p	14.19
hsa-miR-423-5p	3544.75	hsa-miR-106a-5p	82.71	hsa-miR-125a-3p	14.13
hsa-miR-9-3p	3399.33	hsa-miR-125b.2-3p	81.24	hsa-miR-181b-3p	13.94
hsa-miR-27a-3p	3311.14	hsa-miR-485-5p	81.19	hsa-miR-1271-5p	13.54
hsa-miR-181b-5p	3237.83	hsa-miR-130b-5p	80.35	hsa-miR-196b-3p	13.46
hsa-miR-126-3p	3091.17	hsa-miR-136-5p	77.26	hsa-miR-376b-3p	13.41
hsa-miR-151a-5p	3077.65	hsa-miR-27a-5p	76.71	hsa-miR-98-3p	13.38
hsa-let-7d-5p	3028.21	hsa-miR-106b-3p	75.89	hsa-miR-548d-5p	13.28
hsa-miR-222-3p	2835.61	hsa-miR-320b	74.59	hsa-miR-222-5p	13.26
hsa-miR-142-5p	2798.26	hsa-miR-590-5p	74.26	hsa-miR-15a-3p	13.24
hsa-miR-93-5p	2786.34	hsa-miR-31-3p	74.05	hsa-miR-584-5p	13.00
hsa-miR-423-3p	2765.64	hsa-miR-432-5p	74.00	hsa-miR-548e-3p	12.89
hsa-miR-142-3p	2654.04	hsa-miR-324-3p	69.15	hsa-miR-202-3p	12.83
hsa-miR-30c-5p	2644.06	hsa-miR-25-5p	68.94	hsa-miR-2467-5p	12.82
hsa-miR-99a-5p	2400.29	hsa-miR-654-3p	68.72	hsa-let-7e-3p	12.81
hsa-miR-146a-5p	2301.50	hsa-miR-543	66.57	hsa-miR-200a-5p	12.68
hsa-miR-20a-5p	2296.82	hsa-miR-22-5p	66.29	hsa-miR-208b-3p	12.68
hsa-miR-29c-3p	2149.65	hsa-miR-320c	64.79	hsa-miR-210-5p	12.66
hsa-miR-17-5p	2113.61	hsa-miR-29c-5p	64.05	hsa-miR-1298-3p	12.65
hsa-miR-23b-3p	2042.44	hsa-miR-494-3p	63.34	hsa-miR-154-3p	12.47
hsa-miR-30b-5p	2004.13	hsa-miR-1248	61.65	hsa-miR-550a.3-5p	12.34
hsa-miR-7-5p	1972.57	hsa-miR-671-5p	61.58	hsa-miR-628-3p	12.30
hsa-miR-106b-5p	1935.49	hsa-miR-330-5p	60.72	hsa-miR-548o-3p	12.29
hsa-miR-98-5p	1897.49	hsa-miR-193a-5p	60.07	hsa-miR-539-5p	12.14
hsa-miR-28-3p	1881.81	hsa-miR-212-3p	59.30	hsa-miR-103a.2-5p	12.00
hsa-miR-200c-3p	1753.30	hsa-miR-877-5p	58.77	hsa-miR-34c-3p	11.15
hsa-miR-19a-3p	1735.56	hsa-miR-371a-5p	58.37	hsa-miR-4677-3p	11.15
hsa-miR-145-5p	1679.74	hsa-miR-3615	57.84	hsa-miR-18a-3p	10.99
hsa-miR-21-3p	1594.85	hsa-miR-3607-5p	57.76	hsa-miR-4732-3p	10.75
hsa-miR-181c-5p	1524.96	hsa-miR-590-3p	57.60	hsa-miR-331-5p	10.66
hsa-miR-130a-3p	1519.24	hsa-miR-320d	55.95	hsa-miR-10a-3p	10.64
hsa-miR-31-5p	1474.11	hsa-miR-1323	55.77	hsa-miR-29b.1-5p	10.62
hsa-miR-34c-5p	1465.48	hsa-miR-3613-5p	55.51	hsa-miR-299-5p	10.61
hsa-miR-148b-3p	1341.62	hsa-miR-493-5p	55.27	hsa-miR-515-5p	10.57
hsa-miR-144-3p	1337.97	hsa-miR-95-3p	54.69	hsa-miR-4454	10.48
hsa-miR-15a-5p	1209.07	hsa-miR-488-3p	54.17	hsa-miR-1197	10.47
hsa-miR-340-5p	1199.71	hsa-miR-887-3p	53.96	hsa-miR-483-5p	10.24
hsa-miR-204-5p	1182.04	hsa-miR-99a-3p	53.38	hsa-miR-514b-5p	10.12
hsa-miR-1246	1137.60	hsa-miR-216b-5p	53.25	hsa-miR-1973	10.09
hsa-miR-129-5p	1102.44	hsa-miR-664a-3p	52.89	hsa-let-7f.2-3p	10.03
hsa-miR-221-3p	1075.13	hsa-miR-516b-5p	52.82	hsa-miR-1299	10.02
hsa-miR-125a-5p	1034.59	hsa-miR-30c.2-3p	52.43	hsa-miR-16.1-3p	9.89
hsa-miR-15b-5p	1022.10	hsa-miR-372-3p	51.73	hsa-miR-502-5p	9.69
hsa-miR-185-5p	961.24	hsa-miR-383-5p	51.07	hsa-miR-542-5p	9.58
hsa-miR-199a-5p	957.25	hsa-miR-449a	50.87	hsa-miR-26a.2-3p	9.45
hsa-miR-342-3p	945.15	hsa-miR-99b-3p	50.53	hsa-miR-4326	9.44
hsa-miR-374a-3p	924.12	hsa-miR-29a-5p	50.14	hsa-miR-449c-5p	9.33
hsa-miR-381-3p	920.05	hsa-miR-92a.1-5p	50.09	hsa-miR-744-3p	9.20
hsa-miR-425-5p	867.08	hsa-miR-1225-3p	48.22	hsa-miR-491-5p	9.06
hsa-miR-183-5p	858.09	hsa-miR-532-3p	47.94	hsa-miR-3909	9.05
hsa-miR-769-5p	855.04	hsa-miR-127-5p	47.93	hsa-miR-516a-5p	8.96
hsa-miR-30e-3p	826.18	hsa-miR-30c.1-3p	47.28	hsa-miR-4461	8.87
hsa-miR-200b-3p	823.44	hsa-miR-339-3p	46.41	hsa-miR-146b-3p	8.87
hsa-miR-210-3p	800.38	hsa-miR-1180-3p	45.71	hsa-miR-1306-5p	8.66
hsa-miR-199b-5p	794.91	hsa-miR-378b	45.60	hsa-miR-885-3p	8.59
hsa-miR-361-5p	791.94	hsa-miR-370-3p	45.19	hsa-miR-641	8.59
hsa-miR-141-3p	779.51	hsa-miR-499a-5p	45.11	hsa-miR-3912-3p	8.54
hsa-miR-130b-3p	754.56	hsa-miR-342-5p	44.35	hsa-miR-152-5p	8.49
hsa-miR-195-5p	753.79	hsa-miR-424-3p	44.09	hsa-miR-190b	8.44
hsa-miR-107	750.05	hsa-miR-378g	43.45	hsa-miR-1277-3p	8.42
hsa-miR-152-3p	735.41	hsa-miR-1298-5p	42.93	hsa-miR-3194-5p	8.37
hsa-miR-1307-5p	702.07	hsa-miR-15b-3p	42.87	hsa-miR-548ah-3p	8.34
hsa-miR-484	696.63	hsa-miR-708-3p	42.29	hsa-miR-874-5p	8.30
hsa-miR-181a-3p	693.08	hsa-miR-16.2-3p	42.16	hsa-miR-381-5p	8.28
hsa-miR-223-3p	687.83	hsa-miR-485-3p	42.03	hsa-miR-6075	8.24
hsa-miR-138-5p	677.80	hsa-miR-486-3p	42.03	hsa-miR-185-3p	8.20
hsa-miR-132-3p	665.62	hsa-miR-625-5p	41.88	hsa-miR-548ba	7.95

hsa-miR-323a-3p	614.80	hsa-miR-561-5p	40.93	hsa-miR-769-3p	7.55
hsa-miR-30a-3p	614.51	hsa-miR-4485-3p	40.88	hsa-miR-338-5p	7.55
hsa-miR-379-5p	607.88	hsa-miR-132-5p	40.32	hsa-miR-30b-3p	7.53
hsa-miR-34a-5p	595.21	hsa-miR-450b-5p	40.18	hsa-miR-1270	7.49
hsa-miR-181a.2-3p	572.97	hsa-miR-377-3p	40.18	hsa-miR-302c-3p	7.37
hsa-miR-205-5p	558.00	hsa-miR-551b-3p	39.94	hsa-miR-642a-5p	7.21
hsa-miR-301a-3p	549.78	hsa-miR-24.2-5p	39.81	hsa-miR-654-5p	7.19
hsa-miR-410-3p	506.24	hsa-miR-548k	39.52	hsa-miR-1303	7.17
hsa-miR-218-5p	504.07	hsa-miR-7.1-3p	39.44	hsa-miR-642b-3p	7.15
hsa-miR-215-5p	492.99	hsa-miR-582-5p	39.36	hsa-miR-3158-3p	7.14
hsa-miR-18a-5p	489.20	hsa-miR-30d-3p	38.97	hsa-miR-545-3p	7.11
hsa-miR-532-5p	486.05	hsa-miR-340-3p	38.78	hsa-miR-1251-5p	7.11
hsa-miR-411-5p	483.52	hsa-miR-362-5p	37.71	hsa-miR-3928-3p	7.08
hsa-miR-193b-3p	477.54	hsa-miR-450a-5p	37.62	hsa-miR-23c	7.05
hsa-miR-501-3p	474.06	hsa-miR-628-5p	37.46	hsa-miR-1911-5p	6.91
hsa-miR-217	462.54	hsa-miR-3200-3p	37.18	hsa-miR-6500-3p	6.83
hsa-miR-219a.2-3p	448.18	hsa-miR-93-3p	37.04	hsa-miR-203a-5p	6.83
hsa-miR-200a-3p	439.41	hsa-miR-629-5p	36.48	hsa-miR-3065-3p	6.79
hsa-miR-136-3p	421.51	hsa-miR-3653-5p	35.83	hsa-miR-337-5p	6.78
hsa-miR-203a-3p	413.99	hsa-miR-539-3p	35.17	hsa-miR-7114-5p	6.67
hsa-miR-194-5p	399.52	hsa-miR-625-3p	34.59	hsa-miR-124-5p	6.67
hsa-miR-424-5p	391.16	hsa-miR-20a-3p	34.28	hsa-miR-518c-3p	6.64
hsa-miR-135a-5p	390.42	hsa-miR-514a-3p	34.27	hsa-miR-576-3p	6.63
hsa-miR-196b-5p	390.18	hsa-miR-7706	34.20	hsa-miR-483-3p	6.60
hsa-miR-335-3p	381.96	hsa-miR-4521	33.71	hsa-miR-2355-5p	6.57
hsa-miR-433-3p	374.65	hsa-miR-378e	33.61	hsa-miR-337-3p	6.53
hsa-miR-139-5p	373.65	hsa-miR-204-3p	33.24	hsa-miR-1276	6.48
hsa-miR-224-5p	368.49	hsa-miR-1249-3p	32.55	hsa-miR-4746-5p	6.44
hsa-miR-874-3p	362.45	hsa-miR-873-5p	31.83	hsa-miR-365a-5p	6.39
hsa-miR-497-5p	353.79	hsa-miR-188-5p	31.63	hsa-miR-1287-5p	6.39
hsa-miR-181d-5p	349.93	hsa-miR-382-3p	31.07	hsa-miR-550a-5p	6.38
hsa-miR-760	349.80	hsa-miR-944	30.75	hsa-miR-301a-5p	6.35
hsa-miR-1260b	341.89	hsa-miR-212-5p	30.44	hsa-miR-380-3p	6.31
hsa-miR-335-5p	339.26	hsa-miR-141-5p	30.29	hsa-miR-4662a-5p	6.27
hsa-miR-328-3p	331.57	hsa-miR-1268b	30.20	hsa-let-7c-3p	6.20
hsa-miR-140-5p	331.10	hsa-miR-193b-5p	30.16	hsa-miR-449b-5p	6.16
hsa-miR-500a-3p	330.92	hsa-miR-139-3p	29.74	hsa-miR-371a-3p	6.16
hsa-miR-660-5p	330.04	hsa-miR-505-3p	29.73	hsa-miR-411-3p	6.14
hsa-miR-32-5p	321.42	hsa-miR-589-5p	29.17	hsa-miR-3934-5p	6.12
hsa-miR-135b-5p	311.08	hsa-miR-133b	29.14	hsa-miR-33b-3p	6.11
hsa-miR-216a-5p	304.18	hsa-miR-1285-3p	28.91	hsa-miR-619-5p	6.10
hsa-miR-206	303.78	hsa-miR-155-3p	28.83	hsa-miR-766-5p	6.06
hsa-miR-153-3p	302.22	hsa-miR-143-5p	28.82	hsa-miR-378i	6.00
hsa-miR-1296-5p	297.92	hsa-miR-589-3p	28.16	hsa-miR-1185.1-3p	5.96
hsa-miR-744-5p	291.39	hsa-miR-362-3p	28.08	hsa-miR-548b-5p	5.94
hsa-miR-363-3p	290.84	hsa-miR-615-3p	27.85	hsa-miR-365b-5p	5.89
hsa-miR-338-3p	286.05	hsa-miR-425-3p	27.52	hsa-miR-211-5p	5.87
hsa-miR-28-5p	282.55	hsa-let-7g-3p	27.31	hsa-miR-1226-3p	5.86
hsa-miR-196a-5p	273.54	hsa-miR-454-5p	26.65	hsa-miR-3613-3p	5.84
hsa-miR-409-3p	252.68	hsa-miR-501-5p	26.63	hsa-miR-670-3p	5.82
hsa-miR-373-3p	244.30	hsa-miR-223-5p	26.36	hsa-miR-1910-5p	5.81
hsa-miR-889-3p	235.73	hsa-let-7b-3p	26.33	hsa-miR-4517	5.79
hsa-miR-221-5p	232.85	hsa-miR-574-5p	26.24	hsa-miR-1179	5.78
hsa-miR-1224-5p	230.84	hsa-miR-500a-5p	26.02	hsa-miR-7976	5.77
hsa-miR-574-3p	229.12	hsa-miR-652-5p	25.98	hsa-miR-4446-3p	5.68
hsa-miR-219a-5p	228.20	hsa-miR-1185-5p	25.28	hsa-miR-4433b-3p	5.66
hsa-miR-149-5p	227.79	hsa-miR-518b	24.81	hsa-miR-135b-3p	5.59
hsa-miR-941	223.84	hsa-miR-493-3p	24.67	hsa-miR-3117-3p	5.59
hsa-miR-454-3p	223.43	hsa-miR-512-3p	24.20	hsa-miR-219a.1-3p	5.58
hsa-miR-374a-5p	223.28	hsa-miR-214-5p	23.92	hsa-miR-6511a-3p	5.48
hsa-miR-652-3p	219.80	hsa-miR-503-5p	23.89	hsa-miR-504-5p	5.44
hsa-miR-509.3-5p	218.42	hsa-miR-505-5p	23.76	hsa-miR-3620-3p	5.35
hsa-miR-598-3p	217.57	hsa-miR-129.1-3p	23.44	hsa-miR-665	5.30
hsa-miR-374b-5p	217.43	hsa-miR-323b-3p	23.39	hsa-miR-190a-3p	5.27
hsa-miR-197-3p	213.92	hsa-miR-100-3p	23.33	hsa-miR-548g-3p	5.26
hsa-miR-376c-3p	213.13	hsa-miR-29b.2-5p	23.28	hsa-miR-487a-5p	5.10
hsa-let-7d-3p	197.06	hsa-miR-202-5p	23.22	hsa-miR-518e-3p	5.04
hsa-miR-1307-3p	195.58	hsa-miR-490-3p	23.21		
hsa-miR-184	191.33	hsa-miR-3607-3p	23.16		

Table S3. The 181 publicly available small RNA libraries for human tissues and cell lines

Accession.ID	Sample	Accession.ID	Sample	Accession.ID	Sample
SRR772343	adipose tissue	SRR772350	adipose tissue	SRR772376	adipose tissue
SRR772381	adipose tissue	SRR772414	adipose tissue	SRR772416	adipose tissue
SRR772418	adipose tissue	SRR772427	adipose tissue	SRR772435	adipose tissue
SRR772437	adipose tissue	SRR772453	adipose tissue	SRR772461	adipose tissue
SRR772472	adipose tissue	SRR772475	adipose tissue	SRR772499	adipose tissue
SRR772509	adipose tissue	SRR772511	adipose tissue	SRR772512	adipose tissue
SRR772528	adipose tissue	SRR772560	adipose tissue	SRR772589	adipose tissue
SRR772593	adipose tissue	SRR772595	adipose tissue	SRR772605	adipose tissue
SRR772620	adipose tissue	SRR772623	adipose tissue	SRR772624	adipose tissue
SRR772631	adipose tissue	SRR772657	adipose tissue	SRR772667	adipose tissue
SRR772674	adipose tissue	SRR772675	adipose tissue	SRR772678	adipose tissue
SRR772681	adipose tissue	SRR1028924	alpha cell	SRR1012314	B-cell lymphoma
SRR1012315	B-cell lymphoma	SRR1012316	B-cell lymphoma	SRR1012318	B-cell lymphoma
SRR1012328	B-cell lymphoma	SRR1028925	beta cell	DRR013040	bladder cancer
DRR013042	bladder cancer	DRR013043	bladder cancer	DRR013044	bladder cancer
DRR013039	bladder epithelia	SRR804662	blood	SRR804669	Blood
SRR804672	Blood	SRR804676	blood	SRR804678	Blood
SRR804682	Blood	SRR804688	blood	SRR353655	blood cell
SRR353656	blood cell	SRR353657	blood cell	SRR353659	blood cell
ERR038406	Brain	ERR038407	brain	ERR038409	Brain
SRR1103939	Brain	SRR1103941	brain	SRR1103942	Brain
SRR1103946	Brain	SRR1103948	brain	SRR095854	Brain
SRR531683	Brain embryonal tumor	SRR531684	Brain embryonal tumor	SRR531685	Brain embryonal tumor
SRR531686	Brain embryonal tumor	SRR531707	Brain embryonal tumor	SRR531708	Brain embryonal tumor
SRR531709	Brain embryonal tumor	SRR531713	Brain embryonal tumor	SRR531687	Brain germ cell tumor
SRR531688	Brain germ cell tumor	SRR531689	Brain germ cell tumor	SRR531690	Brain germ cell tumor
SRR531691	Brain germ cell tumor	SRR531711	Brain germ cell tumor	SRR531715	Brain germ cell tumor
SRR531692	Brain glioma	SRR531693	Brain glioma	SRR531694	Brain glioma
SRR531695	Brain glioma	SRR531696	Brain glioma	SRR531697	Brain glioma
SRR531698	Brain glioma	SRR531699	Brain glioma	SRR531700	Brain glioma
SRR531701	Brain glioma	SRR531702	Brain glioma	SRR531703	Brain glioma
SRR531704	Brain glioma	SRR531705	Brain glioma	SRR531706	Brain glioma
SRR531710	Brain glioma	SRR1024134	Cingulate gyrus (grey matter)	SRR1024136	Cingulate gyrus (grey matter)
SRR1012319	follicle center lymphoma	SRR1012320	follicle lymphoma	ERR038425	Heart
SRR1241600	HEK293T cell	SRR1241604	HEK293T cell	SRR1241605	HEK293T cell
SRR1241606	HEK293T cell	SRR1241607	HEK293T cell	SRR1241608	HEK293T cell
SRR1241609	HEK293T cell	SRR1241612	HEK293T cell	SRR1241613	HEK293T cell
SRR628450	Hela cell	SRR628451	Hela cell	SRR628453	Hela cell
SRR628454	Hela cell	ERR038420	kidney	ERR038421	Kidney
ERR038422	Kidney	ERR038412	liver	SRR950887	liver + miR-302d

SRR372612	Lung	SRR372614	Lung	SRR372615	Lung
SRR372616	Lung	SRR372618	Lung	SRR372619	Lung
SRR372620	Lung	SRR372621	Lung	SRR372622	Lung
SRR372623	Lung	SRR372624	Lung	SRR372625	Lung
SRR372626	Lung	SRR372628	Lung	SRR372631	Lung
SRR372632	Lung	SRR372635	Lung	SRR372637	Lung
SRR372639	Lung	SRR372640	Lung	SRR372641	Lung
SRR372643	Lung	SRR372646	Lung	SRR372647	Lung
SRR1013967	Lung Cancer Cell Line A549	SRR1013979	Lung Cancer Cell Line H1264	SRR1013971	Lung Cancer Cell Line H460
SRR1013975	Lung Cancer Cell Line H520	SRR1013983	Lung Cancer Cell Line RVH6849	SRR1013969	Lung Xenograft A549
SRR1013981	Lung Xenograft H1264	SRR1013973	Lung Xenograft H460	SRR1013978	Lung Xenograft H520
SRR1013985	Lung Xenograft RVH6849	SRR592690	lymphoblastoid cells	SRR592692	lymphoblastoid cells
SRR592693	lymphoblastoid cells	SRR592694	lymphoblastoid cells	SRR592695	lymphoblastoid cells
SRR1290798	lymphoblastoid SUP-T1 cells	SRR1290809	lymphoblastoid SUP-T1 cells	SRR873389	MCF-7 cell
SRR060986	memory B cell	SRR950877	miRQC A repeat	SRR950878	miRQC B
SRR950881	miRQC C repeat	SRR950883	miRQC D repeat	SRR060985	naive B cell
SRR015358	Naive B Cell(Naive39)	SRR1028933	whole islet	SRR926589	Peripheral blood
SRR1012334	peripheral blood B-cells	SRR060983	pre-germinal center B cell	SRR491355	Renal
SRR1028935	whole islet	ERR328151	testis	SRR1028926	whole islet
SRR1028927	whole islet	SRR1028930	whole islet	SRR1028931	whole islet
SRR1028932	whole islet				

These small RNA libraries were downloaded from the NCBI SRA website

(www.ncbi.nlm.nih.gov/sra, last accessed 16 May 2016).

Table S4. The publicly available small RNA libraries for tissues of five species

Accession.ID	Sample	Accession.ID	Sample	Accession.ID	Sample
SRR553572	Human Frontal Cortex	SRR553573	Human Cerebellum	SRR553574	Human Heart
SRR553575	Human Kidney	SRR553576	Human Testis	SRR553577	Macaque Frontal Cortex
SRR553578	Macaque Cerebellum	SRR553579	Macaque Heart	SRR553580	Macaque Kidney
SRR553581	Macaque Testis	SRR553582	Mouse Frontal Cortex	SRR553583	Mouse Cerebellum
SRR553584	Mouse Heart	SRR553585	Mouse Kidney	SRR553586	Mouse Testis
SRR553587	Opossum Frontal Cortex	SRR553588	Opossum Cerebellum	SRR553589	Opossum Heart
SRR553590	Opossum Kidney	SRR553591	Opossum Testis	SRR553597	Chicken Frontal Cortex
SRR553598	Chicken Cerebellum	SRR553600	Chicken Kidney	SRR553601	Chicken Testis
SRR553599	Chicken Heart				

Table S5. The numbers of canonical target sites for the broadly conserved SCUmIRs and DmiR families

Family	Mature miRNAs	Seed	Category	All targets	P _{CT} > 0.5	Fraction (P _{CT} > 0.5)
mir-122	miR-122-5p	GGAGTGT	hetero-seed	6883	15	0.002
mir-214	miR-214-3p	CAGCAGG	hetero-seed	9111	0	0.000
mir-216	miR-216a-5p	AATCTCA	hetero-seed	5546	103	0.019
mir-216	miR-216b-5p	AATCTCT	hetero-seed	5253	97	0.018
mir-10	miR-100-5p/99a-5p/99b-5p	ACCCGTA	HH-seed	374	0	0.000
mir-10	miR-10a-5p/10b-5p	ACCCTGT	HH-seed	4736	166	0.035
mir-10	miR-125b-5p	CCCTGAG	HH-seed	6400	717	0.112
mir-17	miR-106a-5p/106b-5p/17-5p/20a-5p/20b-5p/93-5p	AAAGTGC	HH-seed	9459	1219	0.129
mir-17	miR-18a-5p/18b-5p	AAGGTGC	HH-seed	3473	143	0.041
mir-219	miR-219a-5p	GATTGTC	HH-seed	2839	332	0.117
mir-34	miR-34a-5p/34c-5p	GGCAGTG	HH-seed	5826	661	0.113
mir-34	miR-34b-5p	AGGCAGT	HH-seed	5296	0	0.000
mir-449	miR-449a/449b-5p	GGCAGTG	HH-seed	5826	661	0.113
mir-8	miR-200b-3p/200c-3p/429	AATACTG	HH-seed	6666	836	0.125
mir-8	miR-141-3p/200a-3p	AACACTG	HH-seed	6905	225	0.033
let-7	let-7a-5p/7b-5p/7c-5p/7d-5p/7e-5p/7f-5p/7g-5p/7i-5p/98-5p	GAGGTAG	homo-seed	4129	1266	0.307
mir-1	miR-1-3p/206	GGAATGT	homo-seed	5559	782	0.141
mir-101	miR-101-3p	ACAGTAC	homo-seed	5537	516	0.093
mir-103	miR-103a-3p/107	GCAGCAT	homo-seed	6035	433	0.072
mir-124	miR-124-3p	AAGGCAC	homo-seed	5898	1969	0.334
mir-128	miR-128-3p	CACAGTG	homo-seed	8148	947	0.116
mir-129	miR-129-5p	TTTTTGC	homo-seed	14645	0	0.000
mir-130	miR-130a-3p/130b-3p/301a-3p/301b-3p	AGTGCAA	homo-seed	4856	962	0.198
mir-132	miR-132-3p/212-3p	AACAGTC	homo-seed	5029	131	0.026
mir-133	miR-133a-3p/133b	TTGGTCC	homo-seed	3567	647	0.181
mir-135	miR-135a-5p/135b-5p	ATGGCTT	homo-seed	4875	644	0.132
mir-138	miR-138-5p	GCTGGTG	homo-seed	5306	473	0.089
mir-146	miR-146a-5p/146b-5p	GAGAACT	homo-seed	5087	0	0.000
mir-148	miR-148a-3p/148b-3p/152-3p	CAGTGCA	homo-seed	5110	567	0.111
mir-15	miR-15a-5p/15b-5p/16-5p/195-5p	AGCAGCA	homo-seed	7661	1474	0.192
mir-153	miR-153-3p	TGCATAG	homo-seed	4180	805	0.193
mir-181	miR-181a-5p/181b-5p/181d-5p	ACATTCa	homo-seed	7605	937	0.123
mir-19	miR-19a-3p/19b-3p	GTGCAAA	homo-seed	5120	1204	0.235
mir-190	miR-190a-5p/190b	GATATGT	homo-seed	3133	31	0.010
mir-192	miR-192-5p/215-5p	TGACCTA	homo-seed	3145	0	0.000
mir-193	miR-193a-3p/193b-3p	ACTGGCC	homo-seed	3542	74	0.021
mir-194	miR-194-5p	GTAACAG	homo-seed	4977	193	0.039
mir-196	miR-196a-5p/196b-5p	AGGTAGT	homo-seed	2665	265	0.099
mir-199	miR-199a-5p/199b-5p	CCAGTGT	homo-seed	5533	346	0.063
mir-199	miR-199a-3p/199b-3p	CAGTAGT	homo-seed	3669	347	0.095
mir-204	miR-204-5p/211-5p	TCCTTTT	homo-seed	7779	0	0.000
mir-208	miR-208a-3p/208b-3p	TAAGACG	homo-seed	2967	0	0.000
mir-218	miR-218-5p	TGTGCTT	homo-seed	5233	978	0.187
mir-221	miR-221-3p/222-3p	GCTACAT	homo-seed	3796	181	0.048
mir-23	miR-23a-3p/23b-3p	TCACATT	homo-seed	8284	279	0.034
mir-24	miR-24-3p	GGCTCAG	homo-seed	10528	264	0.025
mir-25	miR-25-3p/92a-3p/92b-3p	ATTGCAC	homo-seed	5184	966	0.186
mir-26	miR-26a-5p/26b-5p	TCAAGTA	homo-seed	6607	0	0.000
mir-27	miR-27a-3p/27b-3p	TCACAGT	homo-seed	7660	1097	0.143
mir-29	miR-29a-3p/29b-3p/29c-3p	AGCACCA	homo-seed	4495	1289	0.287
mir-30	miR-30a-5p/30b-5p/30c-5p/30d-5p/30e-5p	GTAAACA	homo-seed	5770	1595	0.276
mir-302	miR-302a-3p/302b-3p/302c-3p/302d-3p	AAGTGCT	homo-seed	8109	777	0.096
mir-33	miR-33a-5p/33b-5p	TGCATTG	homo-seed	5540	22	0.004
mir-365	miR-365a-3p/365b-3p	AATGCCC	homo-seed	3558	79	0.022
mir-7	miR-7-5p	GGAAGAC	homo-seed	6789	245	0.036
mir-9	miR-9-5p	CTTTGGT	homo-seed	5948	1331	0.224
mir-21	miR-21-5p	AGCTTAT	Convergence	3302	141	0.043
mir-32	miR-32-5p	ATTGCAC	Convergence	5184	966	0.186
mir-363	miR-363-3p	ATTGCAC	Convergence	5184	966	0.186
mir-367	miR-367-3p	ATTGCAC	Convergence	5184	966	0.186
mir-454	miR-454-3p	AGTGCAA	Convergence	4856	962	0.198
mir-96	miR-96-5p	TTGGCAC	Convergence	5321	1206	0.227
mir-126	miR-126-3p	CGTACCG	SC-unique	240	0	0.000
mir-1306	miR-1306-5p	CACCTCC	SC-unique	6492	0	0.000
mir-137	miR-137	TATTGCT	SC-unique	4609	1244	0.270
mir-140	miR-140-5p	AGTGGTT	SC-unique	3659	242	0.066
mir-142	miR-142-5p	ATAAAGT	SC-unique	8094	229	0.028
mir-143	miR-143-3p	GAGATGA	SC-unique	6643	64	0.010
mir-144	miR-144-3p	ACAGTAT	SC-unique	6336	242	0.038
mir-145	miR-145-5p	TCCAGTT	SC-unique	5992	628	0.105
mir-150	miR-150-5p	CTCCCAA	SC-unique	11817	0	0.000
mir-155	miR-155-5p	TAATGCT	SC-unique	4284	123	0.029

mir-182	miR-182-5p	TTGGCAA	SC-unique	5922	989	0.167
mir-183	miR-183-5p	ATGGCAC	SC-unique	4359	280	0.064
mir-184	miR-184	GGACGGA	SC-unique	1087	0	0.000
mir-187	miR-187-3p	CGTGTCT	SC-unique	888	0	0.000
mir-191	miR-191-5p	AACGGAA	SC-unique	843	0	0.000
mir-202	miR-202-5p	TCCTATG	SC-unique	4418	0	0.000
mir-205	miR-205-5p	CCTTCAT	SC-unique	5976	85	0.014
mir-210	miR-210-3p	TGTGCGT	SC-unique	898	0	0.000
mir-217	miR-217	ACTGCAT	SC-unique	5379	59	0.011
mir-22	miR-22-3p	AGCTGCC	SC-unique	4743	349	0.074
mir-223	miR-223-3p	GTCAGTT	SC-unique	3910	6	0.002
mir-31	miR-31-5p	GGCAAGA	SC-unique	5147	68	0.013
mir-338	miR-338-3p	CCAGCAT	SC-unique	6351	0	0.000
mir-375	miR-375	TTGTTTCG	SC-unique	4057	0	0.000
mir-383	miR-383-5p	GATCAGA	SC-unique	3337	0	0.000
mir-425	miR-425-5p	ATGACAC	SC-unique	4473	0	0.000
mir-451	miR-451a	AACCGTT	SC-unique	558	0	0.000
mir-455	miR-455-5p	ATGTGCC	SC-unique	3723	75	0.020
mir-490	miR-490-5p	CATGGAT	SC-unique	4201	0	0.000
mir-499	miR-499a-5p	TAAGACT	SC-unique	4285	0	0.000
mir-129	miR-129-3p	AGCCCTT	homo-seed	3789	298	0.079

SCUmiR: single-copy miRNAs that have unique seeds.

Only the miRNAs that are broadly conserved and originated before the split of mammals and fish/bird/frog are considered.

The target sites were downloaded from the TargetScan7.0 website (www.targetscan.org), and all the three types of target sites (8mer, 7mer-A1 and 7mer-m8) were considered.

Table S6. Summary of mRNA-seq data in the cellular transfection experiments in this study

Samples	Total reads	Mapping rate (%)	Unique mapping rate (%)
293FT _mock-rep1	12,910,622	89.74	62.45
293FT _mock-rep2	20,093,471	90.10	61.61
293FT _NC-32h-rep1	54,547,365	91.88	73.84
293FT _NC-32h-rep2	12,249,445	89.73	56.86
293FT _let-7a-12h-rep1	35,711,844	91.94	75.03
293FT _let-7a-12h-rep2	10,917,691	92.59	46.53
293FT _let-7a-32h-rep1	36,819,475	91.23	73.10
293FT _let-7a-32h-rep2	18,815,462	84.23	52.49
293FT _let-7b-12h-rep1	51,464,381	91.88	74.08
293FT _let-7b-12h-rep2	23,167,851	93.80	45.51
293FT _let-7b-32h-rep1	55,993,539	90.39	72.14
293FT _let-7b-32h-rep2	19,824,065	91.03	53.69
LLC-MK2_mock-rep1	11,439,785	89.63	67.68
LLC-MK2_mock-rep2	11,633,984	89.62	67.70
LLC-MK2_NC-32h-rep1	9,177,301	87.22	66.64
LLC-MK2_NC-32h-rep2	9,356,480	87.19	66.65
LLC-MK2_let-7a-32h-rep1	8,551,711	94.28	71.33
LLC-MK2_let-7a-32h-rep2	8,440,910	94.32	71.32
LLC-MK2_let-7b-32h-rep1	11,853,145	92.54	69.90
LLC-MK2_let-7b-32h-rep2	11,570,514	92.50	69.86
CV-1_mock-rep1	11,698,547	82.97	69.73
CV-1_mock-rep2	11,547,428	83.57	70.11
CV-1_NC-32h-rep1	7,305,436	82.09	67.00
CV-1_NC-32h-rep2	7,532,426	81.92	66.87
CV-1_let-7a-32h-rep1	11,285,902	84.97	70.70
CV-1_let-7a-32h-rep2	11,388,888	84.97	70.67
CV-1_let-7b-32h-rep1	8,382,903	84.54	71.01
CV-1_let-7b-32h-rep2	8,340,124	84.55	70.99
NRK_mock-rep1	10,100,682	92.85	57.43
NRK_mock-rep2	10,283,414	92.82	57.46
NRK_NC-32h-rep1	10,232,835	93.92	54.22
NRK_NC-32h-rep2	18,770,931	94.38	61.99
NRK_let-7a-32h-rep1	28,231,775	91.54	47.64
NRK_let-7a-32h-rep2	38,518,472	91.59	56.56
NRK_let-7b-32h-rep1	21,582,629	94.69	60.98
NRK_let-7b-32h-rep2	21,034,315	93.22	56.49

Table S7. Primers for qRT-PCR

ID	Oligo sequence (5'-to-3')
ACTB-F	GCCAACCGCGAGAAGATGA
ACTB-R	CCAGAGGCGTACAGGGATAG
EIF4G2-F	GGTGGCAGCTGCTGAGTT
EIF4G2-R	CGGCTTGACAACGAAGAATC
TIMM17B-F	ACTATGGGTGTCATCGGTGG
TIMM17B-R	TCCTCACAGCATTGGCACTA
SLC25A4-F	AGAGGGTCAAACCTGCTGCTG
SLC25A4-R	CCCTGCTCCTTAGGGATTCT
MAPK6-F	TCGATGAGTCGGAGAAGTCC
MAPK6-R	TAGTGATCAGGTGGCTCCAG
USP38-F	ATGCAAGTATGACCCAAGCC
USP38-R	CAGTCCTTTCAGGAGTGCAA
IGDCC4-F	TTGACCTTCTGCCTGTTGG
IGDCC4-R	CAGGATCACTGCAGTGGC
DCR1-F	CTGAAACTGCAACGGACCTG
DCR1-R	GCCCACTTCTGTCAGTAAATGG
TMEM8A-F	AAACACACCGTCCATGATGC
TMEM8A-R	CGTTCACACAGGCCACTATG
TARBP2-F	GCCCACCAGCCTAATTCAC
TARBP2-R	CTTTGAGGTGTTTGAGGGCC
TTL4-F	GGTGGCCGTGATCTCTAGAA
TTL4-R	GGGAACGTTGGGAAAGAGAC
PBX2-F	ACATCTATGCTGTCAAGACCG
PBX2-R	GAGAGATTGAAAGAGCCGCC
miR-221-3p-F*	AGCTACATTGTCTGCTGGGTTTC
miR-15-5p-F*	TAGCAGCACATAATGGTTTGTG
miR-103a-3p-F*	AGCAGCATTGTACAGGGCTATGA
miR-17-5p-F*	CAAAGTGCTTACAGTGCAGGTAG

* The miRNA reverse primer was included in the Mir-X miRNA First-Strand Synthesis Kit.

Table S8. Primers for luciferase reporter assays

ID	Oligo sequence (5'-to-3')
EIF4G2-F	AAGGAAAAAAGCGGCCGAGAACCCAGCCAAAGCC
EIF4G2-R	CCGCTCGAGTCACTACATCAAGTATCAC
TIMM17B-F	AAGGAAAAAAGCGGCCGCGGAAGCCACTGCCACCATGG
TIMM17B-R	CCGCTCGAGGGCATTTCAAACGGGCTTTA
SLC25A4-F	AAGGAAAAAAGCGGCCGCTGTAATTAACACAAAGTTCACAG
SLC25A4-R	CCGCTCGAGCCACCTCTGCCTCCCAAAGT
MAPK6-F	AAGGAAAAAAGCGGCCGCAACTCAGCAGACATTT
MAPK6-R	CCGCTCGAGTGTATTTGCTGGCCATG
USP38-F	AAGGAAAAAAGCGGCCGCTCTGAGAGAGTCCAAAATG
USP38-R	CCGCTCGAGCATCAGATTTTACTTCTGG
IGDCC4-F	AAGGAAAAAAGCGGCCGCTAGTGTTCTGTCTCCCAG
IGDCC4-R	CCGCTCGAGTCAAGTCAAGCCTCACAGG

Supplementary Figures

A Homo-seed family (*let-7*)

Guide (5p)

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hsa-let-7a-1 -----UGGGAUGAGGUGAGUAGGUUUAUUUUUAGGGU-----CACACCCACCACUGGGAGAUUAACUAACAUCUACUGUCUUUUCCA-----
hsa-let-7f-2 -----UG.....A.....A.....G.....U.....AU.....U.....G.....C.....CG-----
hsa-let-7g -----A.....C.....U.....C.....GAG.....UCUAUG-AU.....CA.....CGGUACA.....G.....GG.....C.....C.....G.....A-----
hsa-let-7i -----CU.....C.....U.....GCU.....GG.....C.....UGUG-A.....UUG.....CG.....UG.....GCG.....G.....C.....G.....UA-----
hsa-let-7a-3 -----G.....G.....C.....C.....G.....C.....C.....G.....C.....C.....G.....C.....U.....UG.....CUGCU-AU.....G.....G.....C.....C.....G.....A-----
hsa-let-7f-1 -----UCA.....AG.....A.....G.....AGUG-AUUUUUA.....CUGUUA.....U.....C.....C.....GA-----
hsa-let-7b -----C.....G.....G.....G.....CAGUG-AUGUUU.....C-UUC.....A.....G.....C.....C.....C.....G-----
hsa-let-7d -----CC.....A.....A.....C.....CAGGG-AUUUUG.....C.....AA.....G.....G.....C.....G.....C.....U.....GG-----
hsa-let-7a-2 -----A.....U.....G.....AG.....AUUACA-----UCAAG-----G.....G.....C.....C.....AG-----
hsa-let-7c -----GCAUCC.....U.....G.....AG.....UUACA-----C.....UG-----U.....G.....C.....U.....AG.....UGGAGC-----
hsa-let-7e -----CCC.....C.....G.....GAGGA.....ACA-----C.....A.....C.....G.....C.....AG.....CCAGG-----
hsa-mir-98 -----AGGAUUCUGCUCAUGCCA.....G.....A.....U.....GUGG.....UAGGGAUUUAGG.....C.....A.....U.....A.....C.....CU.....A.....CUGGUGUGUGGCCAUUUUA

```

B Hetero-seed family (*mir-188*)

Guide (5p)

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hsa-mir-188 -----UGCUCUUCUUCUCAUCCCUUGCAUGGUGGAGGGGUGAGGUUUUCUGAAAACCCUCCCAUGCAGGGUUUGCAGGAUGGCGAGCC-----
hsa-mir-660 -----C.....U.....C.....U.....C.....A.....AUC.....U.....U.....A.....C.....A.....U.....G.....U.....A.....A.....U.....U.....UUGUCAUCUGU
hsa-mir-532 -----CGACU.....UU.....CUC.....G.....AG.....UA.....CC.....UG.....A.....CU.....A.....UU.....C.....C.....A.....C.....A.....A.....U-----

```

C Homo-hetero-seed family (*mir-17*)

Guide (5p)

```

hsa-mir-93 -----CUGGGGGCUCAAGUGCUGUUCGUGCAGGUAGUGUGAUUACCC--AAACUACUGCUGAGCUAGCAGCUUCCGAGCCCGG-----
hsa-mir-106b -----C.....CC.....GG.....U.....ACA.....A.....GUCC.....CU.....GUG.....C.....ACU.....UGG.....U.....G.....U.....CU.....AG.....A.....G-----
hsa-mir-20b -----A.....UA.....CA.....A.....U.....UGGC.....UG-----CU.....U.....UA.....UAUG.....A.....UA.....U-----
hsa-mir-20a -----UA.....A.....U.....UA.....A.....UUAGUU-----U.....A.....AUUAUG.....AAA.....UA.....UG-----
hsa-mir-106a -----CCU.....CCAUGUA.....UACA.....CU.....UU.....G.....G.....U.....AAU.....UA.....UUACA.....U.....AUGG-----
hsa-mir-17 -----GUCAGAAUUAUGU.....UACA.....AU.....GUG-----U.....A.....U.....A.....G.....GUA.....CAUUUG.....UGAC-----
hsa-mir-18a -----U.....U.....U.....G.....AUC.....A.....AAG.....AGAUUAGC.....U.....CCUAA.....U.....C.....U.....U.....GCA-----
hsa-mir-18b -----U.....UGUU.....G.....AUC.....A.....U.....AAGCAG.....UUAG.....U.....CCUAA.....U.....C.....C.....U.....GCA-----

```

D Convergence (*mir-21* and *mir-590*)

Guide (5p)

```

hsa-mir-21 -----UGUCGGG--UAGCUUAU-CAGACUGAUGUUGACUGUUGAAUCUCAUGGCAACACCAAGUCGAUGGGCUG--UCUGACA-----
hsa-mir-590 -----UAGCCA.....A.....AAAUG.....U.....U.....AAAG.....CA.....UA.....G.....GUCA.....CUGU.....AUUUUA.....GU.....AA.....AGUC.....UUGAAAACUAGCAGCA

```

Figure S1. Examples of DmiR family of different categories (A-C) and convergence (D).

(A) *let-7* is a homo-seed family in which all miRNAs share common seed (GAGGUAG).

(B) *mir-188* is a hetero-seed family that all three miRNAs in this family have distinct seeds (*miR-188-5p*: AUCCCUU; *miR-660-5p*: ACCCAU; *miR-532-5p*: AUGCCCU).

(C) *mir-17* family is a homo-hetero-seed (HH-seed) family. Eight different miRNAs share three distinct seeds (*miR-17-5p/20a-5p/20b-5p/93-5p/106a-5p/106b-5p*: AAAGUGC; *miR-18a-5p/18b-5p*: AAGGUGC).

(D) *mir-21* and *mir-590* are not homologous in the precursor sequences but *miR-21-5p* and *miR-590-5p* share the same seed (AGCUUAU) due to convergent evolution. For each set of miRNAs, the sequence alignments of the precursors are shown. The mature sequences (guide strands) are in bold, and the seed sequences are in the red.

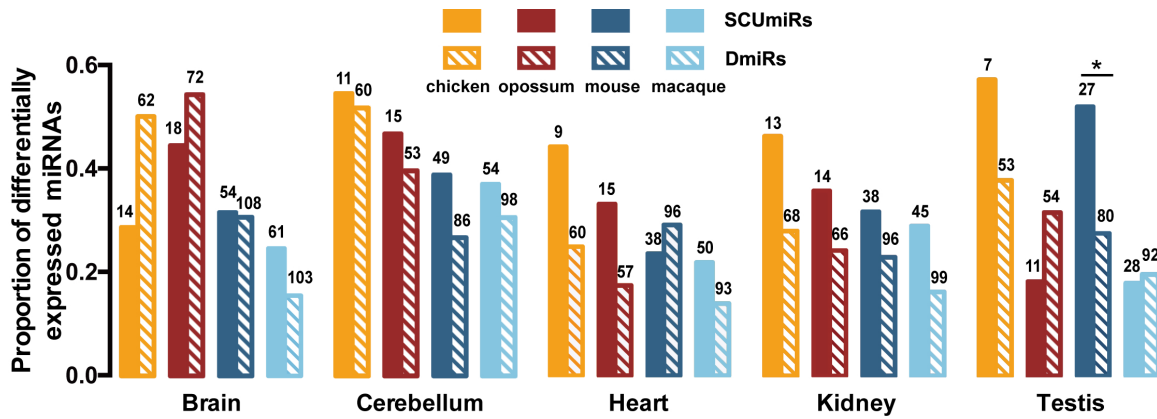


Figure S2 The proportion of SCUmIRs and DmiRs that are differentially expressed by at least 4-fold (y-axis) in five tissues between human and macaque, mouse, opossum, or chicken. The number above each box represents the number of SCUmIRs and DmiRs that are conserved and expressed in both humans and the other species. The miRNAs that are conserved in the vertebrate species, whenever applicable, were considered in each comparison.

```

dme-miR-34-5p      .UGGCAGUGUGGUUAGCUGGUUGUG
hsa-miR-34a-5p    .UGGCAGUGUC.UUAGCUGGUUGU.
hsa-miR-34c-5p    .AGGCAGUGUAGUUAGCUGAUUGC.
hsa-miR-34b-5p    UAGGCAGUGUCAUUAGCUGAUUG..
                    *****  *****  ***

```

Figure S3. Shifting of the seed sequence in *mir-34* family. The seed of *dme-miR-34* and *has-miR-34a/34c* is GGCAGUG, whereas the seed of *has-miR-34b* is AGGCAGU due to one nucleotide shift. The *dme-miR-34* (from *D. melanogaster*) serves as outgroup and represents the ancestral state.

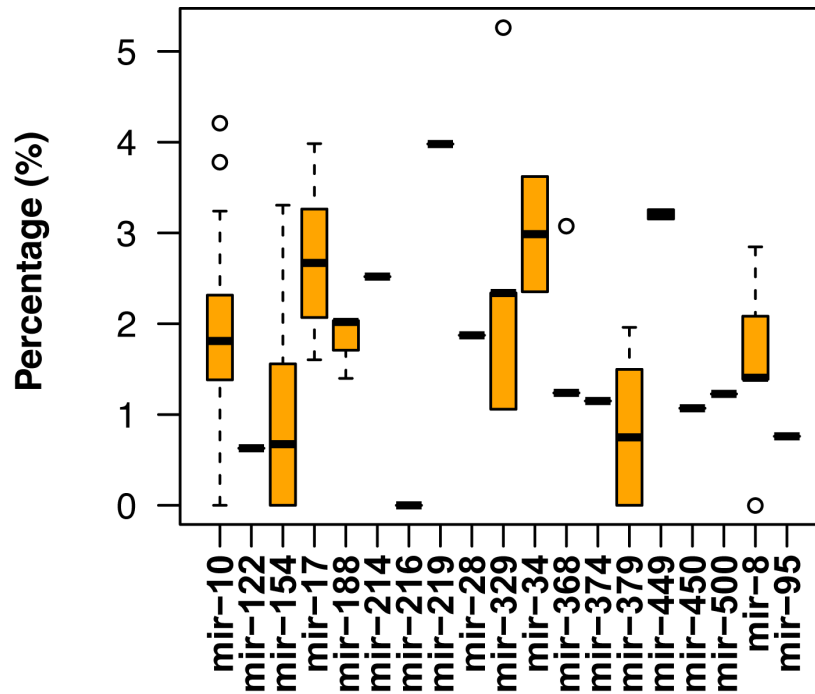
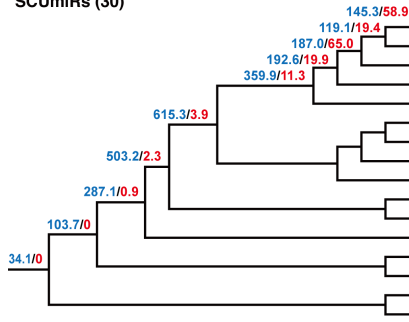


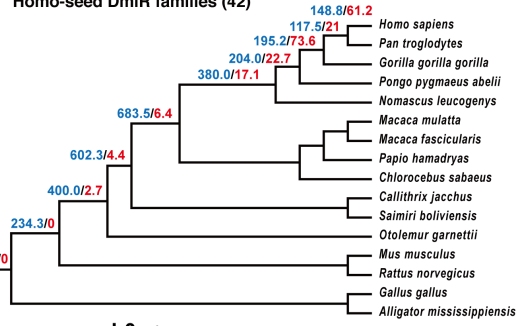
Figure S4. Paralogous miRNAs that have different seeds share a very low fraction of target genes in common. The *x*-axis is a distinct miRNA family, and the *y*-axis is the boxplot for the percentage (%) of the target sites shared between two paralogous miRNAs divided by the mean number of target sites for the two miRNAs. The target sites were predicted with TargetScan Context++ Score < -0.3.

A

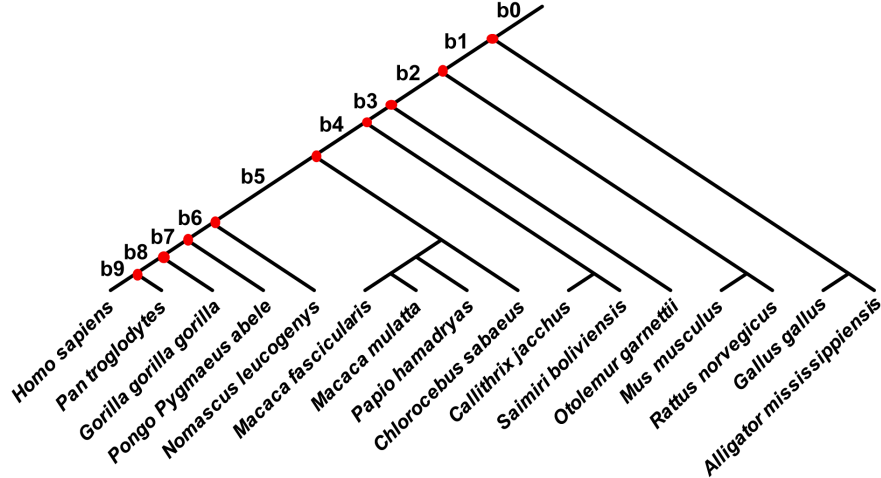
SCUmiRs (30)



Homo-seed DmiR families (42)



B



SCUmiRs (30)

Seed	Family	b0	b1	b2	b3	b4	b5	b6	b7	b8	b9
AACCGTT	mir-451	1	12	10	17	50	45	38	64	39	72
AACGGAA	mir-191	4	23	30	46	83	89	69	115	71	109
ACAGTAT	mir-144	96	133	403	679	753	495	244	259	149	173
ACTGCAT	mir-217	30	81	317	554	752	468	240	276	145	214
AGCTGCC	mir-22	46	225	513	726	752	382	231	208	107	159
AGTGGTT	mir-140	31	121	360	473	612	298	151	194	91	129
ATAAAGT	mir-142	80	239	626	919	1053	627	333	288	186	204
ATGACAC	mir-425	17	67	225	427	602	354	175	197	105	138
ATGGCAC	mir-183	73	103	245	390	497	386	196	216	155	164
ATGTGCC	mir-455	16	62	176	398	525	365	194	221	137	164
CACCTCC	mir-1306	5	90	393	789	1081	703	382	371	270	292
CATGGAT	mir-490	6	40	239	433	544	303	194	196	102	117
CCAGCAT	mir-338	24	94	280	628	740	464	270	281	161	188
CCTTCAT	mir-205	38	117	287	547	715	378	224	187	92	118
CGTACCG	mir-126	0	2	3	3	3	2	4	5	6	6
CGTGTCT	mir-187	2	7	12	39	103	87	85	108	72	104
CTCCCAA	mir-150	9	107	467	1695	2327	1373	705	529	566	467
GAGATGA	mir-143	27	130	405	677	774	461	243	227	142	178
GATCAGA	mir-383	3	55	270	425	465	233	120	125	51	91
GGACGGA	mir-184	2	13	29	45	89	89	56	88	60	99
GGCAAGA	mir-31	35	108	379	680	744	405	201	231	116	177
GTCAGTT	mir-223	31	74	250	407	451	249	131	155	77	101
TAAGACT	mir-499	27	74	316	514	551	317	163	144	80	104
TAATGCT	mir-155	44	103	402	554	588	335	172	157	98	92
TATTGCT	mir-137	194	292	357	469	509	324	163	107	87	93
TCCAGTT	mir-145	78	199	439	630	715	396	198	206	139	175
TCCTATG	mir-202	9	53	162	309	454	280	189	171	81	124
TGTGCGT	mir-210	1	15	31	27	96	80	85	116	80	149
TTGGCAA	mir-182	94	244	484	690	633	377	159	151	93	135
TTGTTCC	mir-375	0	3	5	18	36	33	24	40	29	26

C

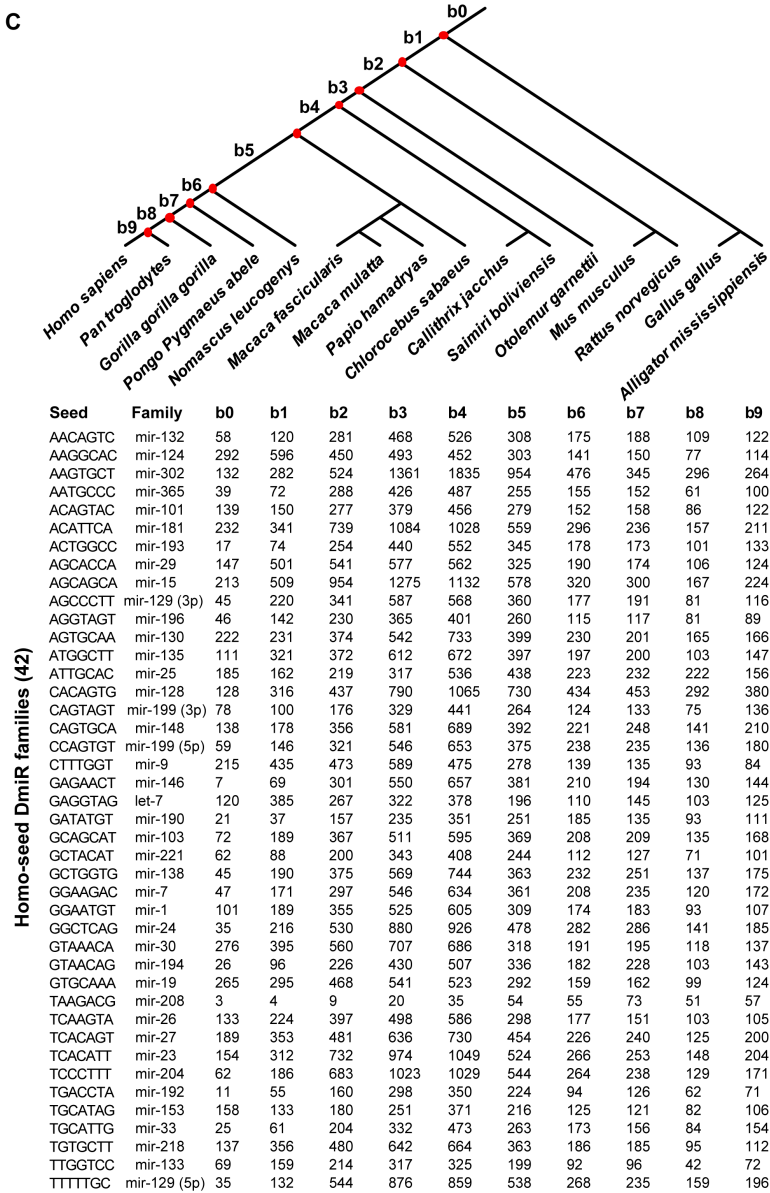


Figure S5. The evolutionary dynamics of canonical target sites in the branches leading to extant humans for the broadly conserved SCUmRNAs (30 miRNAs) and homo-seed DmiR families (42 families). (A) The average gains and losses of canonical target sites *per* seed in the branches leading to extant humans. The numbers of gain and loss events in each branch are in blue and red, respectively. The branch is named the same as in Fig. 4B. **(B-C)** the detailed net-gained target sites for each SCUmRNA **(B)** and homo-seed DmiR family **(C)**. Only the target sites with perfect seed matching (7mer-m8 and 8mer in TargetScan) were considered in the analysis. The number of target sites in branch b0 is the target sites that are ancient and conserved in all the 16 species.

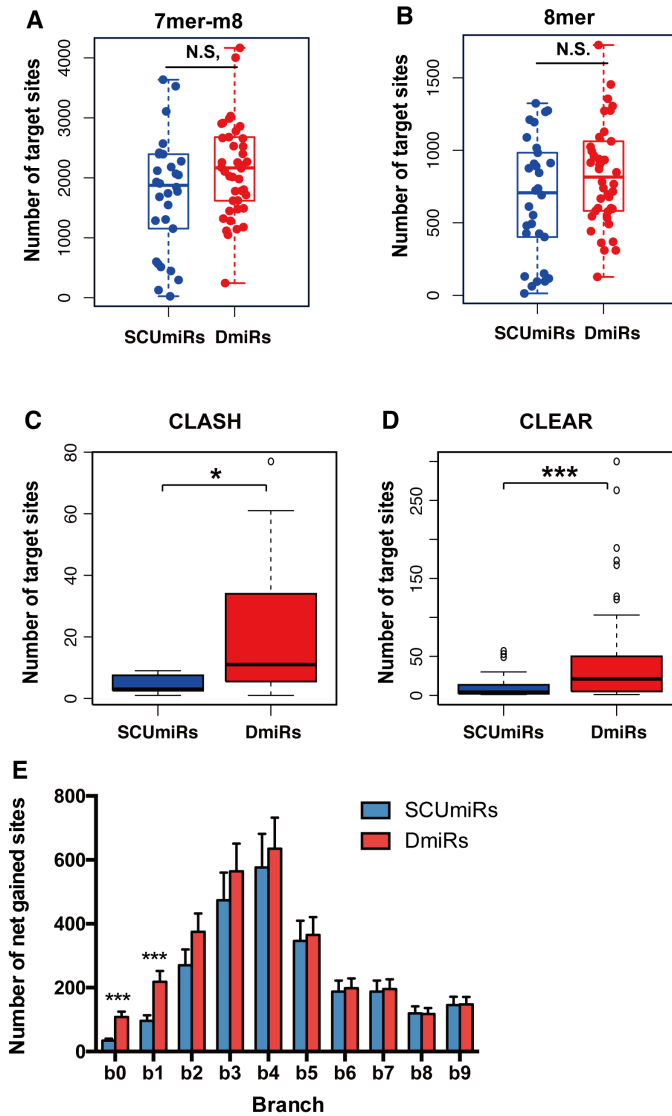


Figure S6. The number of canonical target sites for the broadly conserved SCUMiRs and homo-seed DmiR families.

(A-B) The distribution of type target sites; The boxplot of canonical target sites (7mer-m8, **A**; and 8mer, **B**) of the homo-seed DmiRs and SCUMiRs.

(C-D) The numbers of canonical target sites are significantly higher for the conserved homo-seed DmiRs than the SCUMiRs in the (C) CLASH and (D) CLEAR datasets.

(E) The average numbers of target sites that originated in the branches (b1-b9) and conserved in extant humans. For each branch, a WMW test was used to test whether there is a significant difference in the numbers of target sites for a homo-seed DmiR family and a SCUMiR (*, $P < 0.05$; ***, $P < 0.001$). The number of target sites in b0 is the target sites (*per seed*) that are ancient and conserved in all the 16 species. The bars represent the standard errors.

N.S., not significant; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

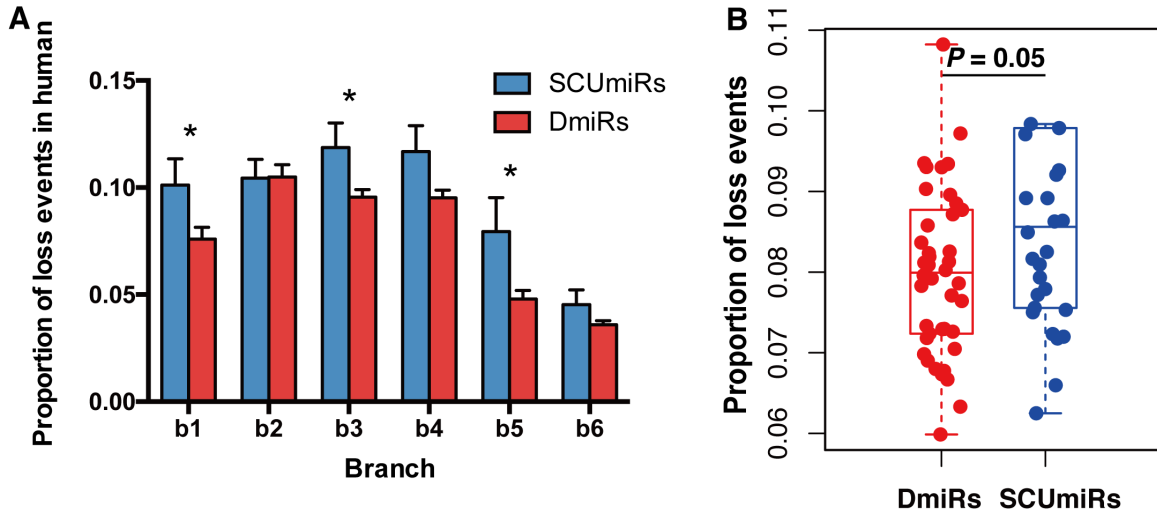


Figure S7. The proportion of target sites that were gained in the ancient branches but eventually lost in the offspring branches.

(A) The proportion of target sites gained in a branch [b1 to b6 as defined in (B)] but eventually lost in the offspring branches leading to extant humans. The proportion was calculated as the number of target sites that eventually got lost out of the total number of target sites originated in that branch. For each branch, a WMW test was used to test whether the proportion was statistically significantly different between SCUmiRs and homo-seed DmiR families (*, $P < 0.05$). The average proportion and the standard errors are given.

(B) Boxplot of the proportions of target sites that originated in branches b1-b6 (combined) but eventually lost in extant humans for the homo-seed DmiRs and SCUmiRs.

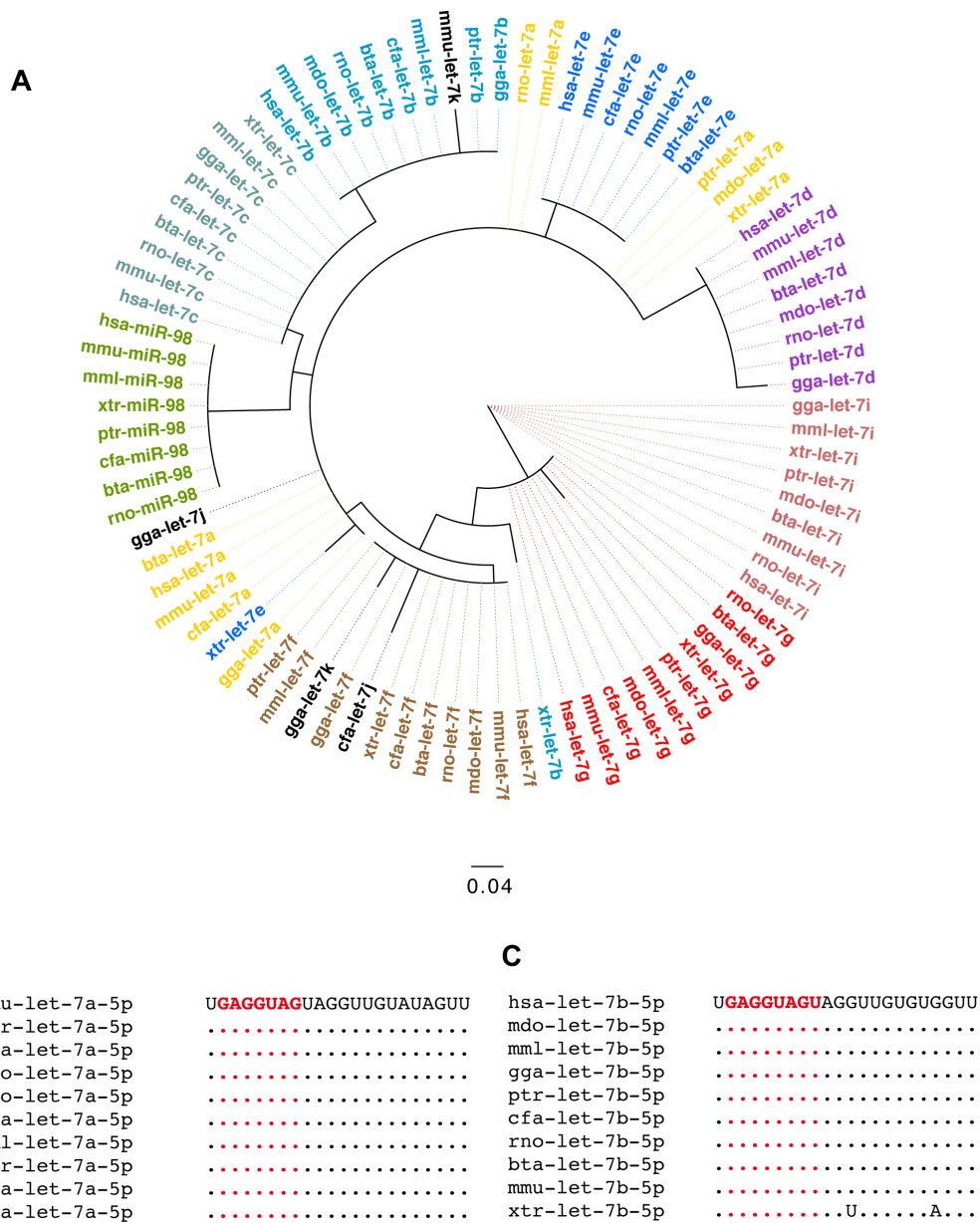


Figure S8. The duplicated miRNAs in the *let-7* family are broadly conserved in vertebrates.

(A) Phylogenetic tree of the vertebrate *let-7* family of miRNAs based on the mature sequences;

(B) Mature sequences alignment of *let-7a*;

(C) Mature sequences alignment of *let-7b*. (gga: chicken; xtr: frog; rno: rat; mmu: mouse; mdo: opossum; cfa: dog; bta: cow; mml: rhesus; ptr: chimpanzee; has: human).

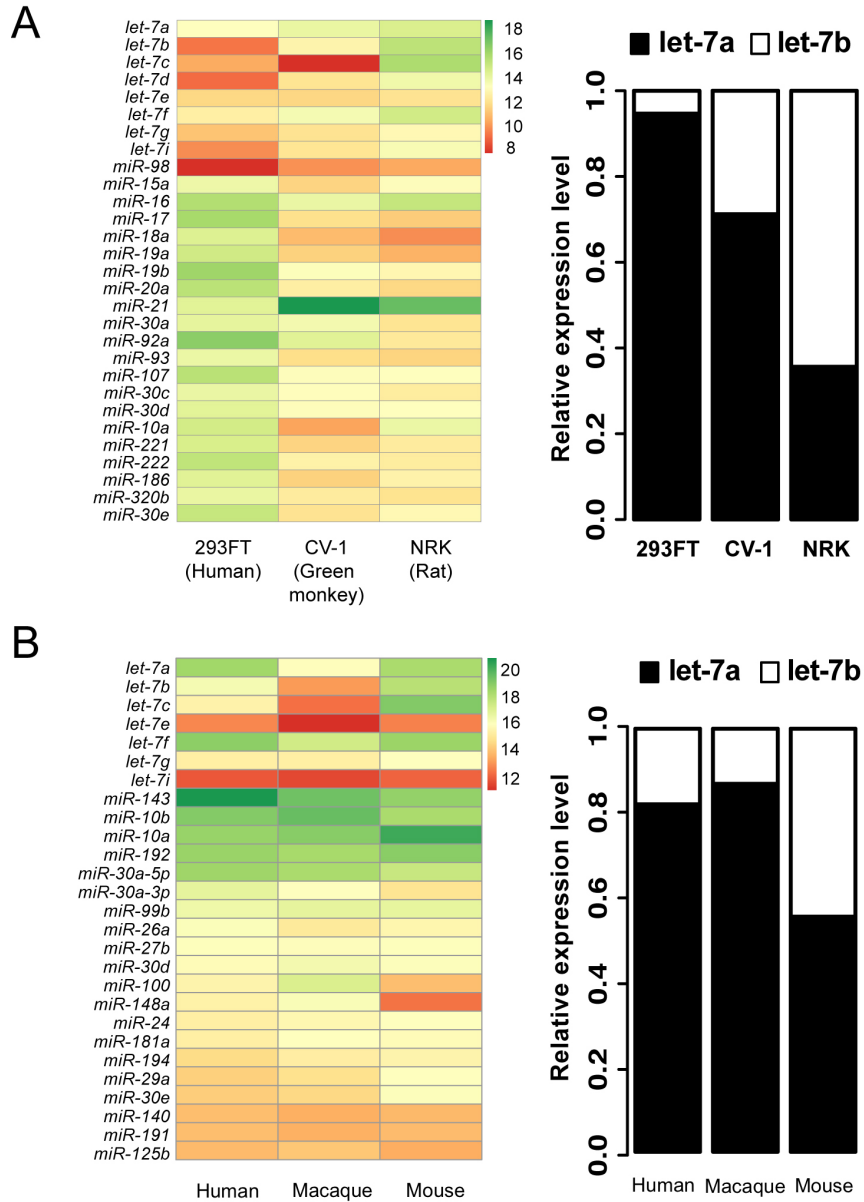


Figure S9. Expression divergence between *let-7a* and *let-7b* in tissues and cell lines across species.

(A) Expression profile of members of the *let-7* family and the top 20 most abundant miRNAs in the 293FT (human), CV-1 (green monkey) and NRK (rat) cell lines (left). The relative expression abundance of *let-7a* and *let-7b* in the three cells lines is presented in the right panel.

(B) Expression profile of *let-7* family members and the top 20 most abundant miRNAs in the human, macaque and mouse kidney (left). The relative expression abundance of *let-7a* and *let-7b* in the human, macaque and mouse kidney is presented in the right panel.

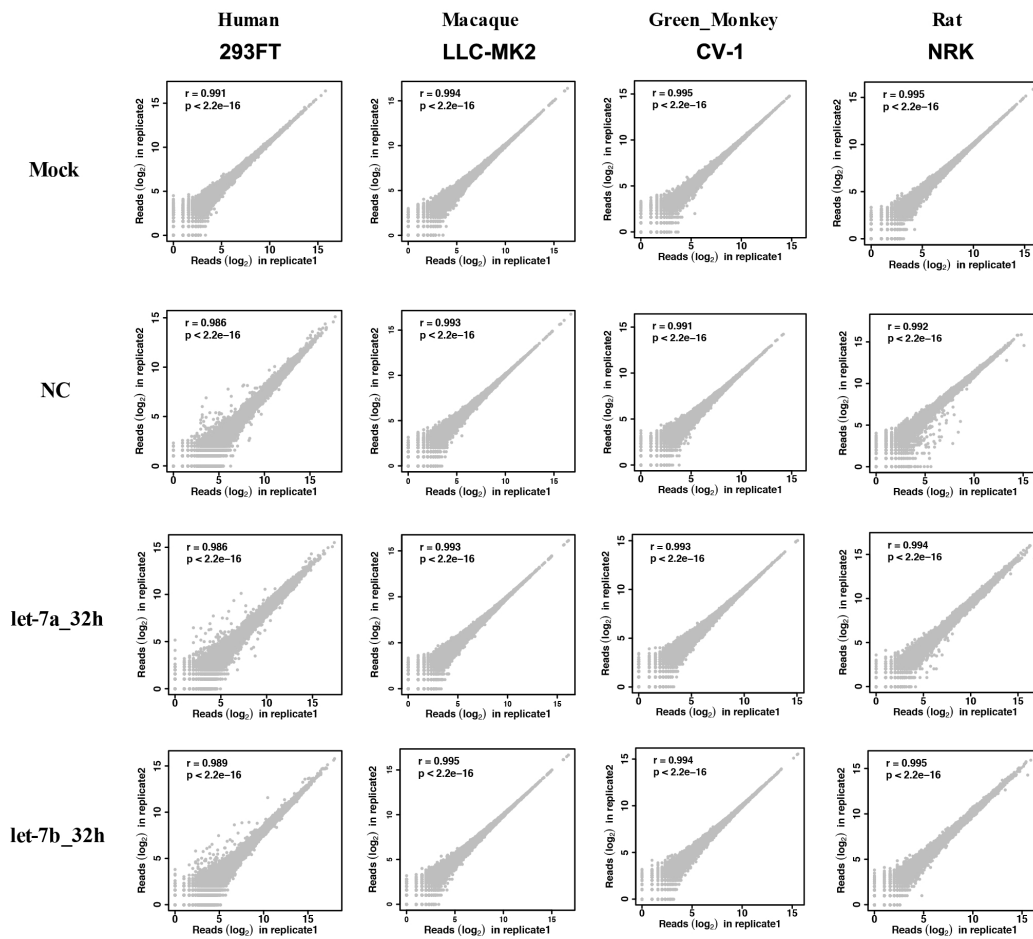


Figure S10. Scatter plots depicting correlations in gene expression between replicates under all tested conditions. The expression of all genes was well correlated between biological replicates (293FT and NRK) and technical replicates (LLC-MK2 and CV-1). “Mock” indicates cell lines treated with transfection reagents without any small RNA sequences; “NC” represents cell lines transfected with a small RNA duplex as the negative control; “*let-7a_32h*” and “*let-7b_32h*” represent cells transfected with *let-7a* or *let-7b*, respectively, for 32 h.

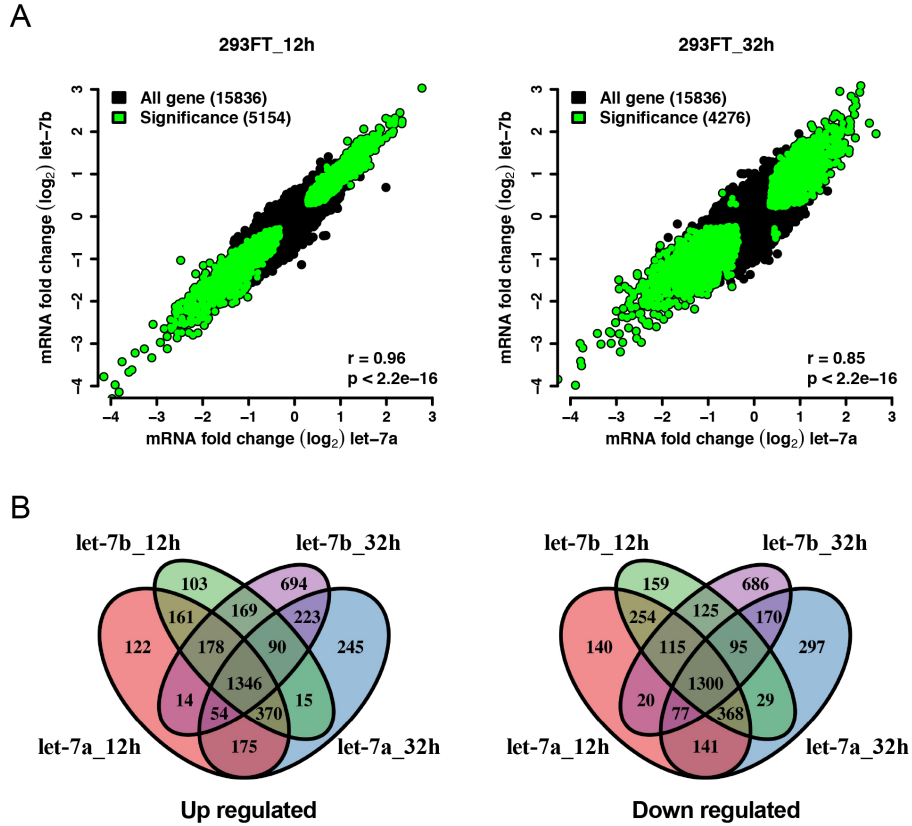


Figure S11. Transcriptome sequencing of *let-7a* and *let-7b* transfected human cell lines (293FT). (A) The fold change (\log_2) of mRNA abundance in 293FT cells transfected with *let-7a* relative to *let-7b* after 12 h or 32 h. Green represents genes that showed significant changes in mRNA levels (FDR of 0.05), and black indicates all genes that showed changes in mRNA levels. (B) Venn diagram showing the number of genes with significantly up-regulated or down-regulated mRNA expression that were common or unique after 293FT cells were transfected with *let-7a* or *let-7b* for 12 h or 32 h.

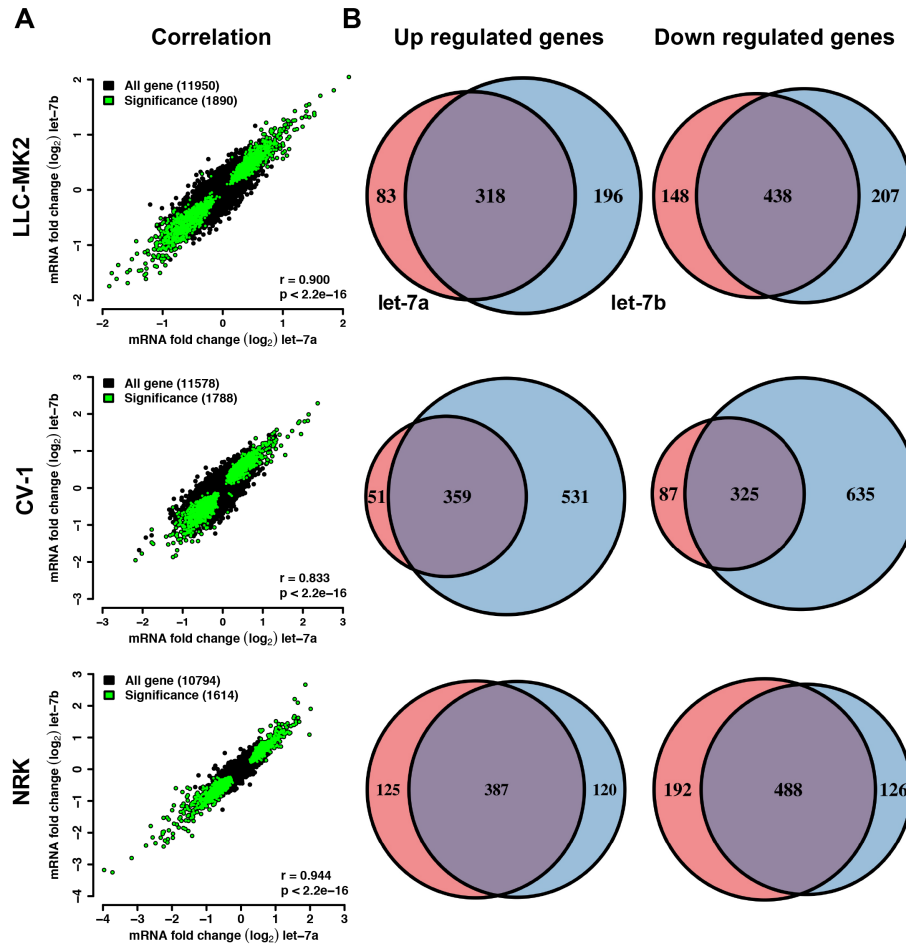


Figure S12. Transcriptome sequencing of *let-7a* and *let-7b* transfected macaque (LLC-MK2), green monkey (CV-1) and rat (NRK) cell lines. (A) The fold change (\log_2) of mRNA abundance in *let-7a*-transfected MK2 (macaque), CV-1 (green monkey) and NRK (rat) cell lines relative to *let-7b*-transfected cells after 32 h. (B) Venn diagram demonstrating the number of genes with significantly up-regulated or down-regulated mRNA expression that were common or unique after the cells were transfected with *let-7a* or *let-7b* for 32 h.

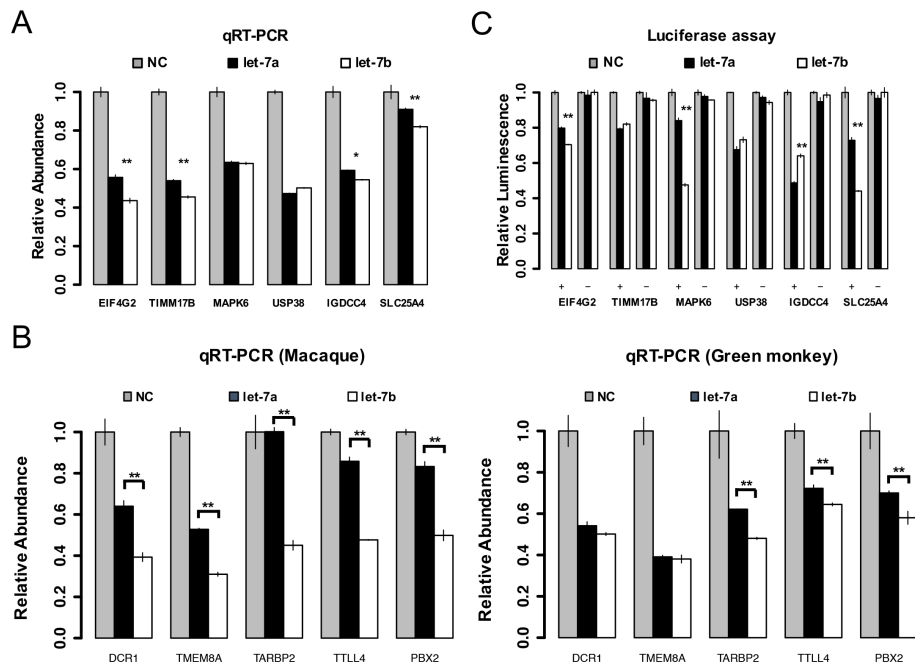


Figure S13. Experimental verification of *let-7a* and *let-7b* target repression by qRT-PCR and luciferase reporter assay.

(A) qRT-PCR results verified the down-regulation of target genes after transfection of human 293FT cells with *let-7a* (black) or *let-7b* (white). Statistically significant differences in the repression efficiency between *let-7a* and *let-7b* for each gene are indicated with asterisks (*, $P < 0.05$, **, $P < 0.01$, Kolmogorov-Smirnov test). Cells transfected with a negative control small RNA (NC) were used as controls (gray).

(B) qRT-PCR results verified the down-regulation of target genes in the *let-7a* (black) or *let-7b* (white) transfection experiments (32 h post-transfection) for macaque (left) and green monkey (right). Error bars represent the standard error among 3 replicates. Statistically significant differences between *let-7a* and *let-7b* are indicated by asterisks (**, $P < 0.01$, Kolmogorov-Smirnov test).

(C) Luciferase reporter assay results verified the repression of target genes of *let-7a* (black) and *let-7b* (white) in human 293FT cells. The y-axis shows the relative luminescence of the luciferase reporter gene fused to 3' UTR fragments with canonical target sites (+) relative to genes with mutant sites (-). Statistically significant differences in repression efficiency for the target sites between *let-7a* (black) and *let-7b* (white) are marked with asterisks (** $P < 0.01$, Kolmogorov-Smirnov test).

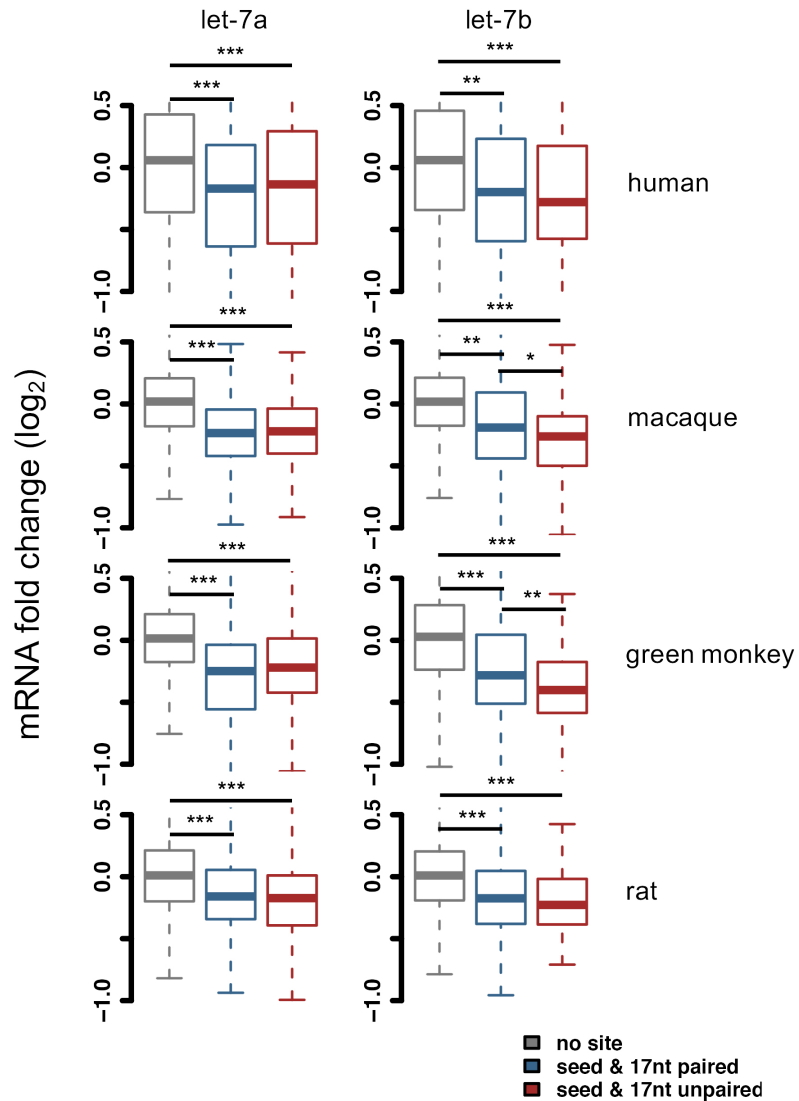


Figure S14. Changes in the mRNA abundance (y-axis) of the conserved canonical target genes (seed pairing) that are paired (seed & 17 nt paired) or not paired (seed & 17 nt unpaired) to position 17 of *let-7a* (left) or *let-7b* (right) in the cellular transfection experiments. The genes without any site complementary to the seed sequence of *let-7a/b* were used as controls (*, $P < 0.05$; **, $P < 0.01$, *, $P < 0.001$; Wilcoxon test).**

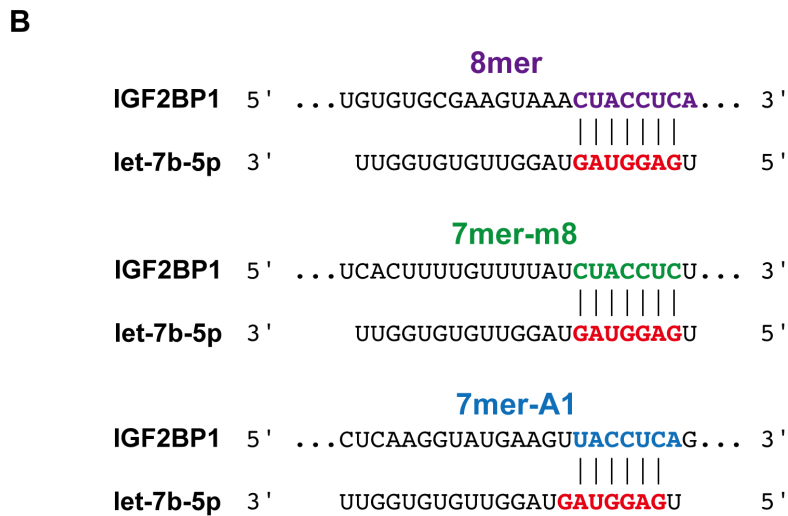
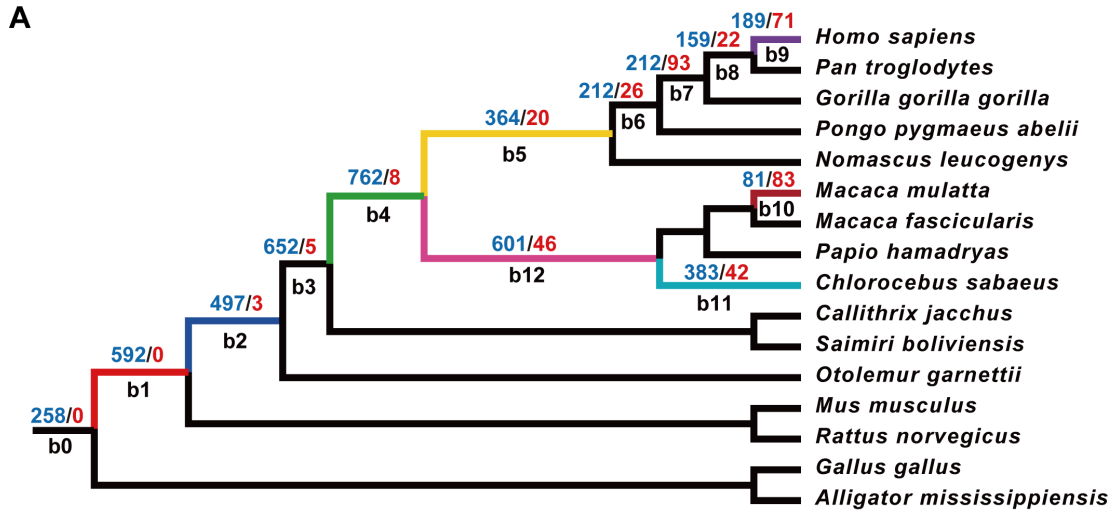


Figure S15. Birth and death of *let-7* canonical target sites during mammalian evolution.

(A) The gain and loss of *let-7a/b* canonical target sites in the branches leading to extant primates. The numbers of gain and loss events are in blue and red, respectively. All the three types of target sites that are complementary to the seed of *let-7* (8mer, 7mer-m8 and 7mer-A1) are presented.

(B) Examples show the definition of three types of canonical target site. IGF2BP1 is a target gene of *let-7* family, which harbors all the three types of target sites on its 3'UTR.

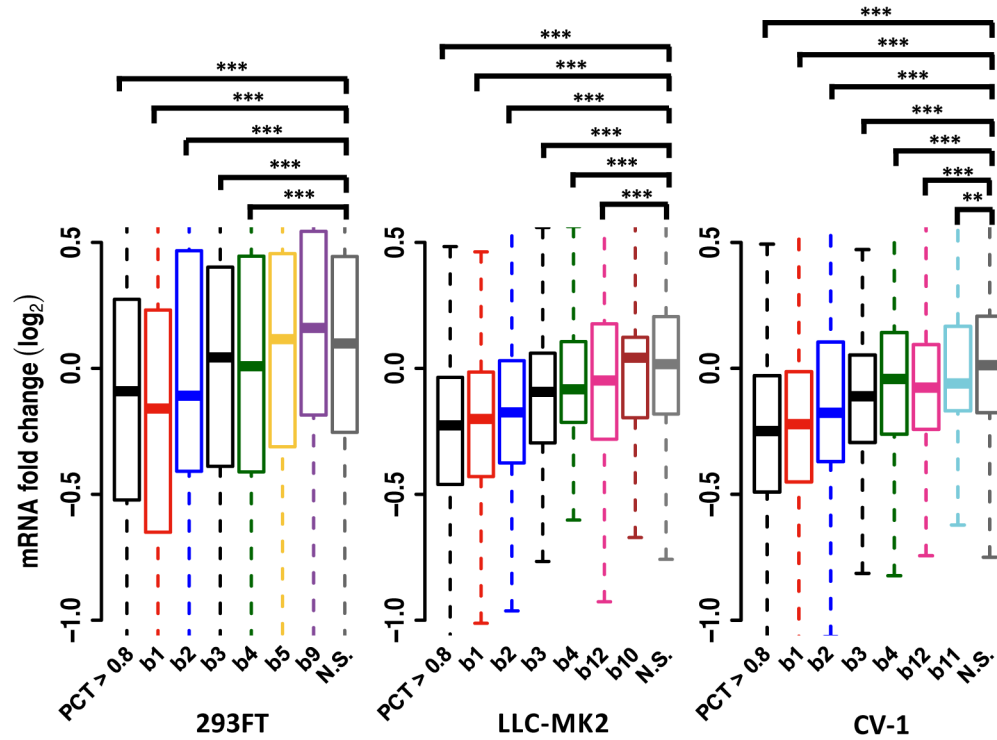


Figure S16. Changes in the mRNA abundance of genes with ancient or newly emerged target sites in human, macaque and green monkey cells transfected with *let-7a*. P_{cr} represents target genes of *let-7a* predicted by TargetScan ($P_{cr} > 0.8$). The genes with target sites originating in a branch and maintained thereafter were used in the analysis. If a gene had multiple target sites of different ages, the gene was assigned to the most ancient class. The genes without any site complementary to the seed sequence of *let-7alb* (N.S., no sites) were used as controls (*, $P < 0.05$; **, $P < 0.01$, ***, $P < 0.001$; Kolmogorov-Smirnov test).

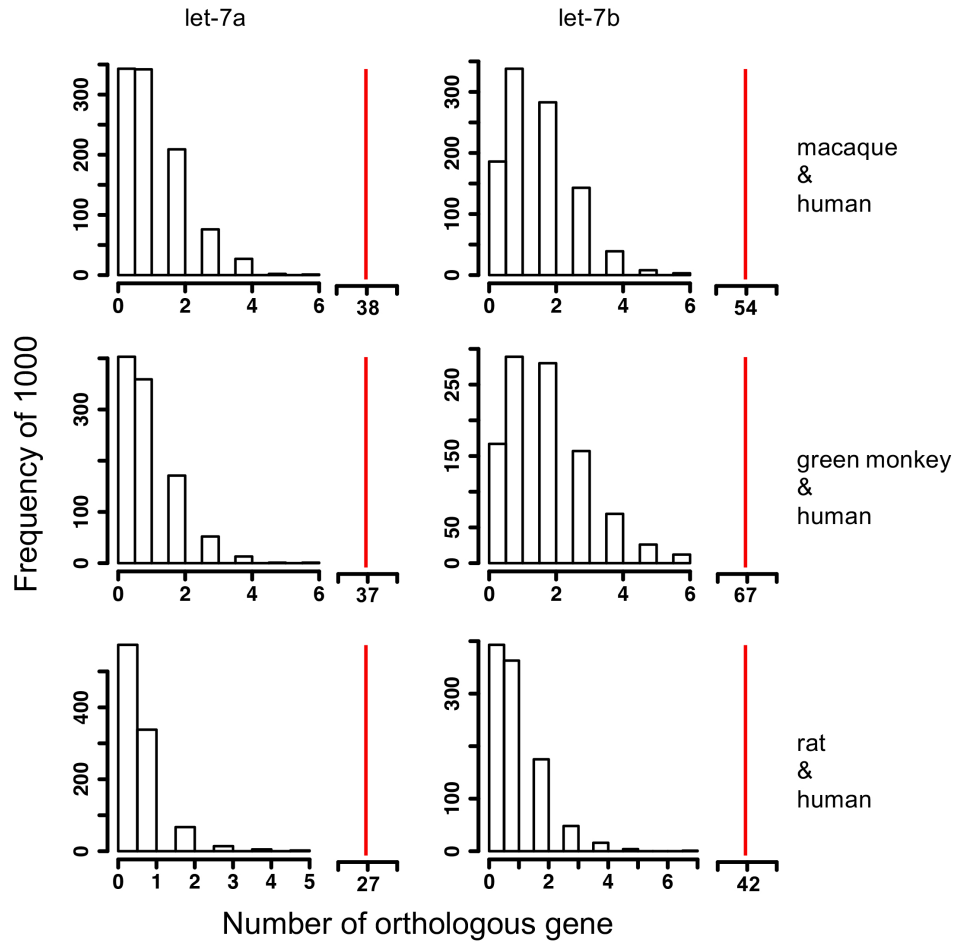


Figure S17. The observed numbers of the orthologous target genes of *let-7a/b* between humans and other mammalian species are significantly higher than the numbers obtained under the assumption of randomness. For each comparison, the distribution of the simulated numbers of target genes down-regulated in both humans and other species is shown in black, and the observed value is in red. The simulated numbers were obtained based on random sampling the same numbers of genes in the gene expressed in each species and counting the over-lapping genes. 1000 replicates were conducted in each simulation.

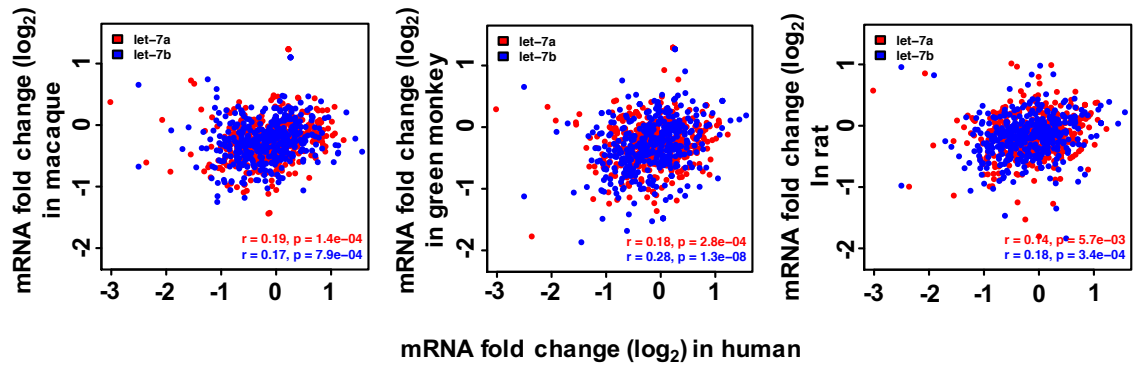


Figure S18. The mRNA expression changes for orthologous target genes of *let-7a/b* are weakly correlated between humans and other mammalian species in both the *let-7a* (red) and *let-7b* (blue) experiments. The three groups are human versus macaque, human versus green monkey, and human versus rat.

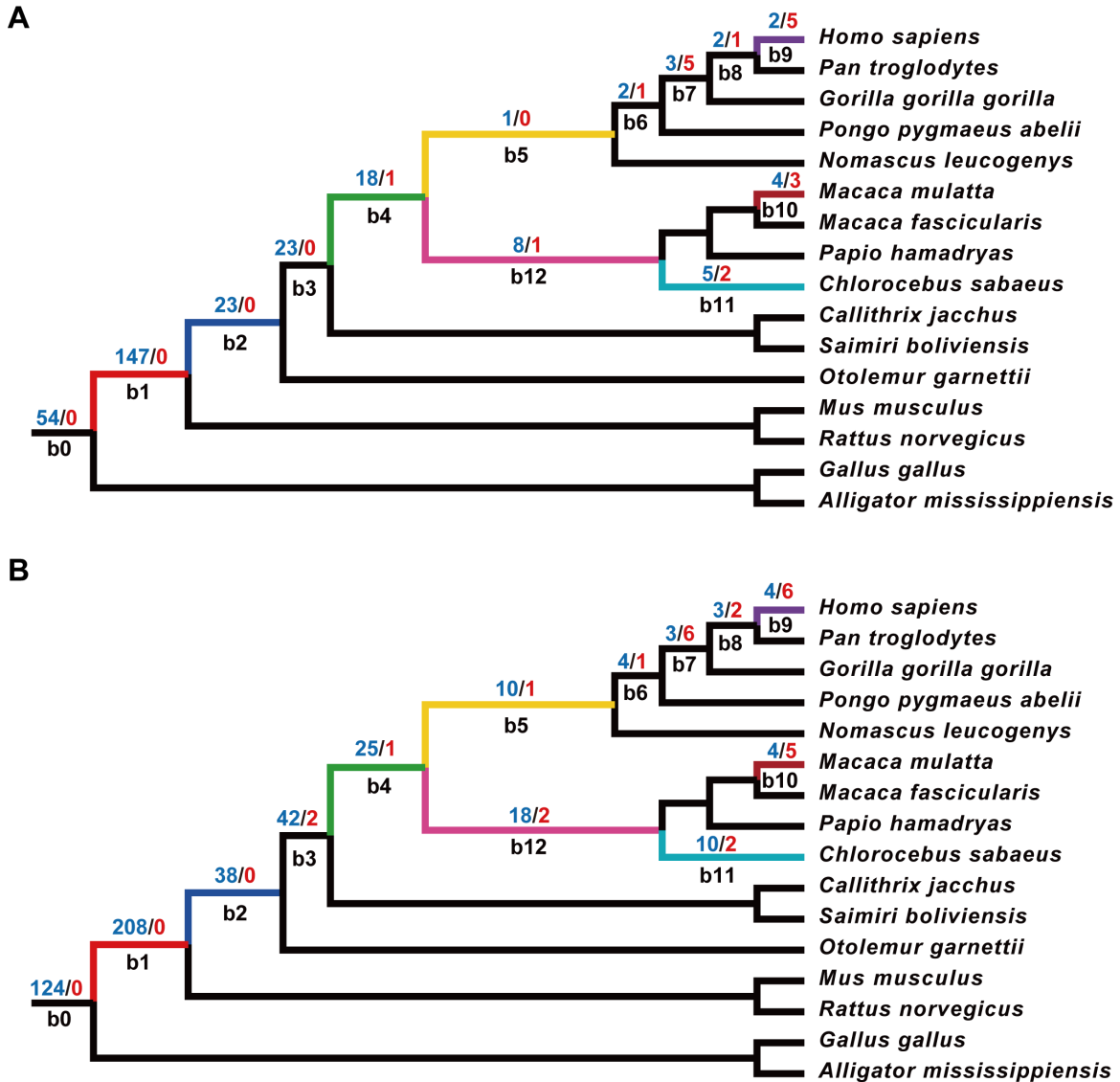


Figure S19. The gain and loss events of non-conserved target sites in the conserved target genes of *let-7*. Only the genes with at least one conserved target site with $P_{CT} > 0.8$ were considered.

(A) Target sites based on seed perfect pairing (8mer and 7mer-m8 in TargetScan);

(B) All canonical target sites (8mer, 7mer-m8 and 7mer-A1 in TargetScan). The numbers of gain and loss events in each branch are in blue and red, respectively.

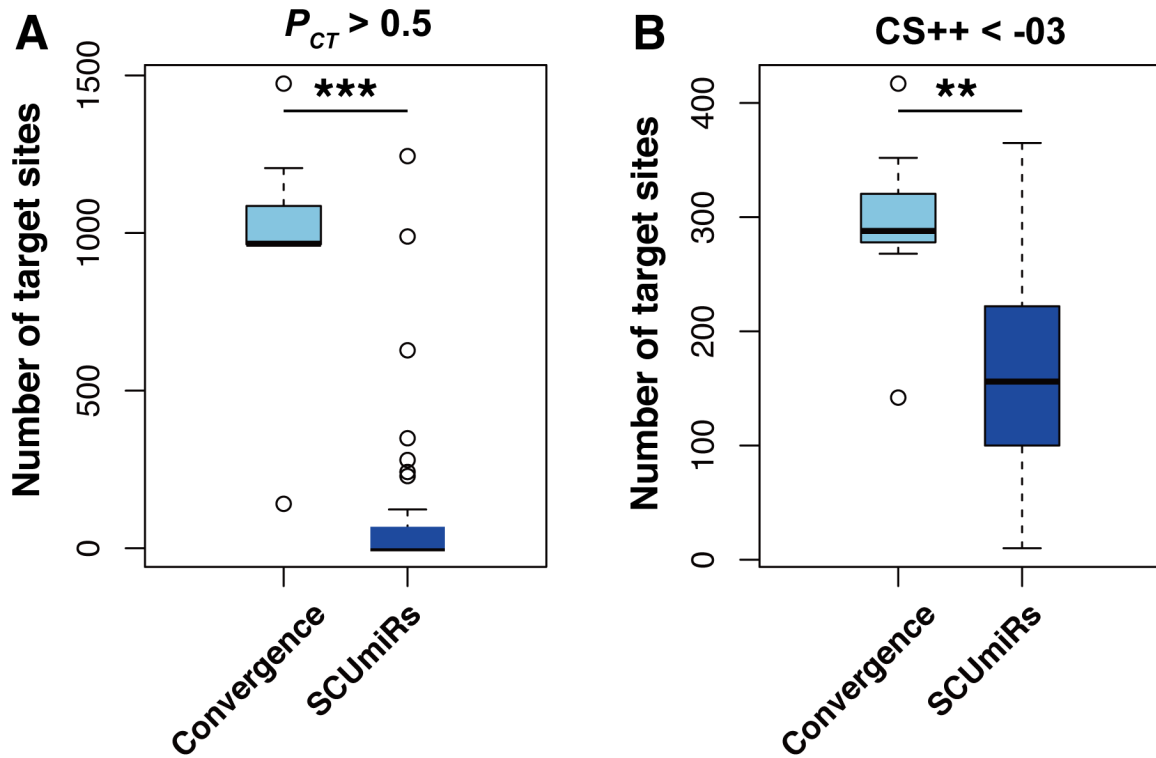


Figure S20. The numbers of target sites are higher for the broadly conserved Convergence miRNAs than the SCUmIRs (**, $P < 0.01$; ***, $P < 0.001$; WMW test).

(A) Boxplot of the numbers of conserved target sites (TargetScan $P_{ct} > 0.5$).

(B) Boxplot of the numbers of target sites with Context++ Score < -0.3 .

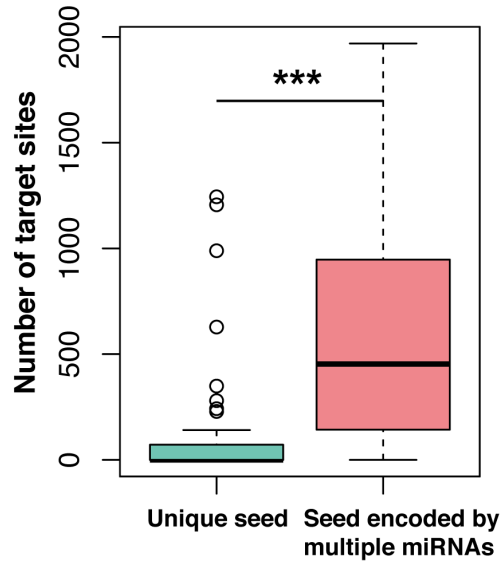


Figure S21. Seeds shared by multiple broadly conserved miRNAs pair higher numbers of conserved target sites ($P_{cr} > 0.5$) than those of the single-copy miRNAs. Only the seeds of the broadly conserved miRNAs were considered (***, $P < 0.001$, WMW test).

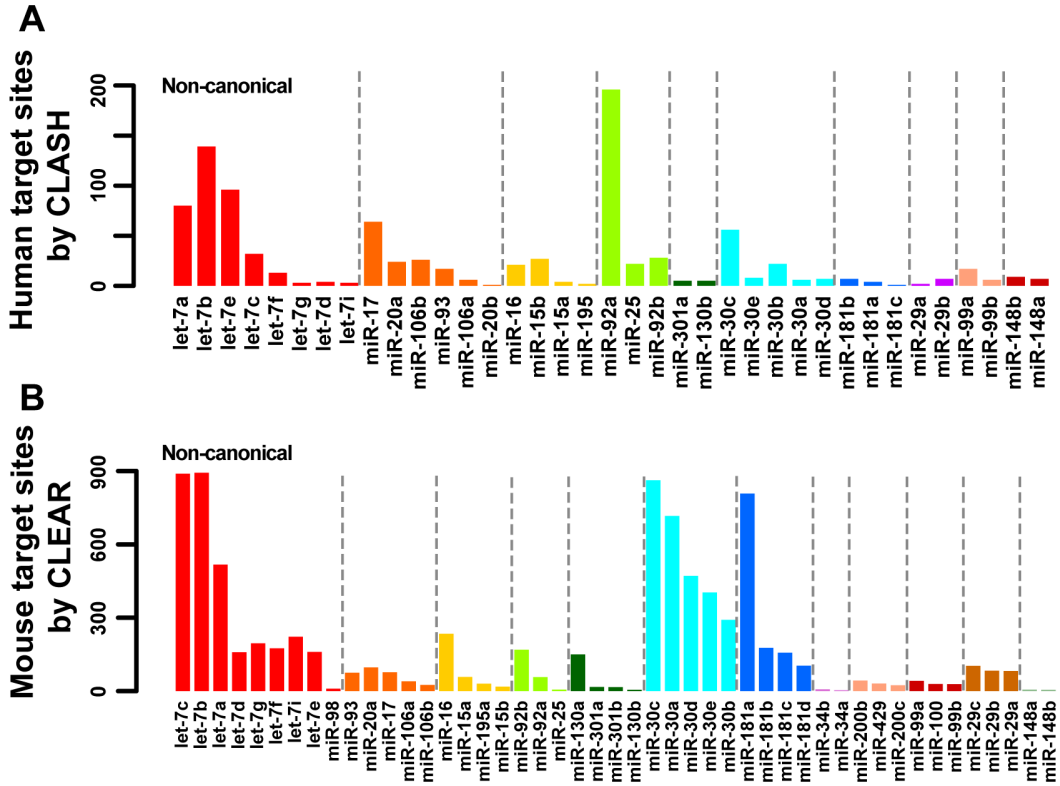


Figure S22. The numbers of non-canonical target sites bound by each miRNA member in ten representative miRNA families in the CLASH HEK-293T cell dataset (A) and the CLEAR mouse brain dataset (B).

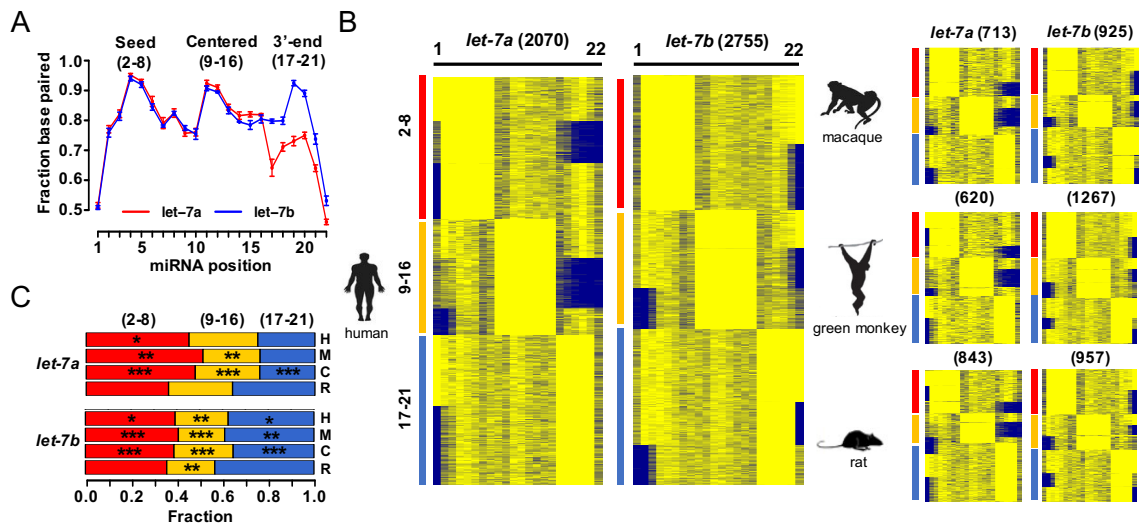


Figure S23. The putative non-canonical target sites in 3' UTRs recognized by *let-7a* or *let-7b*.

(A) The fraction of each nucleotide in *let-7a* and *let-7b* that is paired to the putative target sites out of all the possible targets in human 3' UTRs. RNAhybrid was used to predict the target sites with the default parameter settings. Perfect pairing between the *let-7a/b* seed sequence and target sites was not required in the analysis.

(B) The heatmaps of the putative target sites that are paired to the 5' end (position 2-8), center (9-16) and 3' end (17-21) of *let-7a* or *let-7b*. In each of the four species, the putative target sites that are associated with mRNA destabilization in each experiment are presented (detailed numbers are presented in parenthesis).

(C) The fraction of predicted target sites (5' end, center, or 3' end) of *let-7a* or *let-7b* in human (H), macaque (M), green monkey (G) and rat (R). For target sites of each category, Fisher's exact test was employed to test whether those target mRNAs were significantly enriched in the down-regulated gene sets in the corresponding transfection experiment (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$).