

Supplementary information:

Title:

Elevated expression of circulating miR876-5p is a specific response to severe EV71 infections

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Table S1 - Table S3.

Fig. S1 - Fig.S4

Table S1. Clinical features of 8 EV71-infected patients with distinct severities and 4 healthy control children undergoing serum global microRNAs array.

| Features | EV71 infected cases | | | | | | | | Control patient |
|---|-------------------------|---|--|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-----------------|
| | Severe infection | | | | Mild infection | | | | |
| | Case I | Case II | Case III | Case IV | Case V | Case VI | Case VII | Case VIII | |
| Gender | Male | Female | Male | Male | Male | Male | Male | Female | |
| Age (years) | 3.3 | 1.6 | 2.0 | 3.9 | 2.6 | 2.8 | 1.5 | 9.2 | 2.3 |
| Underlying condition | Previous healthy | Previous healthy | Previous healthy | Previous healthy | Previous healthy | Previous healthy | Previous healthy | Previous healthy | healthy |
| Duration of symptom before hospitalization (days) | 3 | 5 | 3 | 2 | 2 | 3 | 3 | 3 | 0 |
| Clinical diagnosis | HFMD with encephalitis | HFMD with brain stem encephalitis and cardio-pulmonary failure | HFMD with brain stem encephalitis and cardio-pulmonary failure | HFMD with encephalitis | HFMD | Herpangina | HFMD | HFMD | none |
| Outcome | Survival without sequel | Survival with respiratory failure on mechanical ventilation, and limb paralysis | Died | Survival without sequel | Survival without sequel | Survival without sequel | Survival without sequel | Survival without sequel | none |

Abbreviation: EV71, enterovirus 71; HFMD, hand-foot-and-mouth disease; VUR, vesicoureter reflux

Table S2. The list of up- and down-regulated expression of miRNAs detected from the blood serum of EV71-infected patient with mild symptom in comparison with healthy controls.

| Gene Name | Accession Number | Target Sequence (5' to 3') | Mild ^{2**} | Control ^{1**} | Severe ^{3**} | Mild v.s. Control* | Severe vs. Control* |
|-----------------------------------|------------------|----------------------------|---------------------|------------------------|-----------------------|-----------------------|------------------------|
| Up-Regulated⁴ | | | | | | | |
| hsa-miR-494 | MIMAT0002816 | UGAAACAUACACGGGAAACCUC | 9.33 | 6.30 | 6.25 | 3.03 | -0.05 |
| hsa-miR-29b-3p | MIMAT0000100 | UAGCACCAUUUGAAAUCAGUGUU | 8.00 | 5.40 | 5.87 | 2.60 | 0.47 |
| hsa-miR-30e-5p | MIMAT0000692 | UGUAAACAUCUUGACUGGAAG | 10.57 | 8.34 | 9.11 | 2.24 | 0.78 |
| hsa-miR-19a-3p | MIMAT0000073 | UGUGCAAAUCUAUGCAAAACUGA | 9.25 | 7.21 | 7.73 | 2.04 | 0.52 |
| hsa-miR-27b-3p | MIMAT0000419 | UUCACAGUGGCUAAGUUCUGC | 6.57 | 4.60 | 5.21 | 1.97 | 0.61 |
| hsa-miR-19b-3p | MIMAT0000074 | UGUGCAAAUCCAUGCAAAACUGA | 11.66 | 9.83 | 10.49 | 1.82 | 0.65 |
| hsa-miR-590-5p | MIMAT0003258 | GAGCUUUAUCAUAAAAGUGCAG | 7.00 | 5.28 | 5.29 | 1.73 | 0.01 |
| hsa-miR-32-5p | MIMAT0000090 | UAUUGCACAUUACUAAGUUGCA | 6.72 | 5.03 | 5.05 | 1.69 | 0.02 |
| hsa-miR-21-5p | MIMAT0000076 | UAGCUUAUCAGACUGAUGUUGA | 11.49 | 9.91 | 10.22 | 1.59 | 0.32 |
| hsa-miR-302b-3p | MIMAT0000715 | UAAGUGCUUCAUGUUUUAGUAG | 9.71 | 8.22 | 8.66 | 1.50 | 0.44 |
| hsa-miR-199a-5p | MIMAT0000231 | CCCAGUGUUCAGACUACCUGUUC | 6.39 | 4.92 | 4.42 | 1.47 | -0.50 |
| hsa-miR-26b-5p | MIMAT0000083 | UUCAAGUAAUUCAGGAUAGGU | 13.36 | 11.89 | 12.30 | 1.47 | 0.41 |
| hsa-miR-142-3p | MIMAT0000434 | UGUAGUGUUUCCUACUUUAUGGA | 11.69 | 10.25 | 10.48 | 1.43 | 0.23 |
| hsa-miR-146a-5p | MIMAT0000449 | UGAGAACUGAAUCCAUGGGUU | 7.86 | 6.84 | 6.17 | 1.02 | -0.67 |
| Down-Regulated⁵ | | | | | | | |
| hsa-miR-137 | MIMAT0000429 | UUUUGCUUUAAGAAUACGCGUAG | 2.97 | 3.98 | 4.36 | -1.00 | 0.38 |
| hsa-miR-374c-5p | MIMAT0018443 | AUAAUACAACCUGCUAAGUGCU | 2.39 | 3.44 | 3.55 | -1.06 | 0.10 |
| hsa-miR-564 | MIMAT0003228 | AGGCACGGUGUCAGCAGGC | 1.80 | 2.86 | 3.66 | -1.06 | 0.80 |
| hsa-miR-1298 | MIMAT0005800 | UUCAUUCGGCUGUCCAGAUGUA | 1.80 | 2.86 | 3.29 | -1.06 | 0.43 |

| | | | | | | | |
|-----------------|--------------|----------------------------|------|------|------|-------|-------|
| hsa-miR-1272 | MIMAT0005925 | GAUGAUGAUGGCAGCAAAUUCUGAAA | 1.80 | 2.86 | 2.96 | -1.06 | 0.10 |
| hsa-miR-2114-5p | MIMAT0011156 | UAGUCCCUCCUUGAAGCGGUC | 2.97 | 4.08 | 4.36 | -1.11 | 0.27 |
| hsa-miR-613 | MIMAT0003281 | AGGAAUGUCCUUCUUUGCC | 2.61 | 3.73 | 3.77 | -1.13 | 0.04 |
| hsa-miR-1469 | MIMAT0007347 | CUCGGCGCGGGCGCGGCUC | 2.12 | 3.28 | 3.55 | -1.15 | 0.27 |
| hsa-miR-1203 | MIMAT0005866 | CCCGGAGCCAGGAUGCAGCUC | 2.12 | 3.28 | 3.29 | -1.15 | 0.01 |
| hsa-miR-599 | MIMAT0003267 | GUUGUGUCAGUUUAUCAAAC | 2.12 | 3.28 | 3.29 | -1.15 | 0.01 |
| hsa-miR-553 | MIMAT0003216 | AAAACGGUGAGAUUUUGUUUU | 2.12 | 3.28 | 3.13 | -1.15 | -0.14 |
| hsa-miR-3187-3p | MIMAT0015069 | UUGGCCAUGGGGCGCGCGG | 2.80 | 3.98 | 4.13 | -1.17 | 0.16 |
| hsa-miR-924 | MIMAT0004974 | AGAGUCUUGUGAUGUCUUGC | 2.39 | 3.60 | 3.96 | -1.21 | 0.37 |
| hsa-miR-1179 | MIMAT0005824 | AAGCAUUCUUCAUUGGUUGG | 2.39 | 3.60 | 3.87 | -1.21 | 0.27 |
| hsa-miR-193a-3p | MIMAT0000459 | AACUGGCCUACAAAGUCCAGU | 2.39 | 3.60 | 3.66 | -1.21 | 0.07 |
| hsa-miR-1 | MIMAT0000416 | UGGAAUGUAAAGAAGUAUGUAU | 2.39 | 3.60 | 3.55 | -1.21 | -0.05 |
| hsa-miR-1267 | MIMAT0005921 | CCUGUUGAAGUGAAUCCCA | 2.39 | 3.60 | 3.55 | -1.21 | -0.05 |
| hsa-miR-634 | MIMAT0003304 | AACCAGCACCCAACUUUGGAC | 3.39 | 4.60 | 5.01 | -1.21 | 0.41 |
| hsa-miR-577 | MIMAT0003242 | UAGAUAAAAUAUUGGUACCUG | 3.12 | 4.36 | 4.13 | -1.24 | -0.23 |
| hsa-miR-1180 | MIMAT0005825 | UUUCCGGCUCGCGUGGGUGUGU | 5.47 | 6.72 | 6.89 | -1.25 | 0.18 |
| hsa-miR-412 | MIMAT0002170 | ACUUCACCGGUCCACUAGCCGU | 2.61 | 3.86 | 4.05 | -1.25 | 0.19 |
| hsa-miR-491-5p | MIMAT0002807 | AGUGGGAACCCUCCAUGAGG | 2.61 | 3.86 | 3.96 | -1.25 | 0.10 |
| hsa-miR-297 | MIMAT0004450 | AUGUAUGUGUGCAUGUGCAUG | 2.80 | 4.08 | 3.87 | -1.28 | -0.21 |
| hsa-miR-3180 | MIMAT0018178 | UGGGGCGGAGCUUCCGGAG | 1.80 | 3.08 | 2.96 | -1.28 | -0.12 |
| hsa-miR-638 | MIMAT0003308 | AGGGAUCGCGGGCGGGUGGCGCCU | 3.71 | 5.03 | 5.13 | -1.32 | 0.10 |
| hsa-miR-512-5p | MIMAT0002822 | CACUCAGCCUUGAGGGCACUUUC | 2.12 | 3.44 | 3.42 | -1.32 | -0.02 |
| hsa-miR-4741 | MIMAT0019871 | CGGGCUGUCCGGAGGGGUCGGCU | 3.89 | 5.23 | 5.13 | -1.34 | -0.10 |
| hsa-miR-3934 | MIMAT0018349 | UCAGGUGUGAAACUGAGGCAG | 2.39 | 3.73 | 3.77 | -1.35 | 0.04 |
| hsa-miR-557 | MIMAT0003221 | GUUUGCACGGGUGGGCCUUGUCU | 2.39 | 3.73 | 3.77 | -1.35 | 0.04 |

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|------------------|--------------|--------------------------|------|------|------|-------|-------|
| hsa-miR-515-5p | MIMAT0002826 | UUCUCCAAAAGAAAGCACUUUCUG | 2.39 | 3.73 | 3.42 | -1.35 | -0.31 |
| hsa-miR-892a | MIMAT0004907 | CACUGUGUCCUUUCUGCGUAG | 2.39 | 3.73 | 3.42 | -1.35 | -0.31 |
| hsa-miR-4448 | MIMAT0018967 | GGCUCCUUGGUCUAGGGGUA | 2.61 | 3.98 | 3.66 | -1.37 | -0.31 |
| hsa-miR-2682-5p | MIMAT0013517 | CAGGCAGUGACUGUUCAGAGUC | 3.61 | 4.98 | 4.66 | -1.37 | -0.31 |
| hsa-miR-647 | MIMAT0003317 | GUGGCUGCACUCACUUCUUC | 2.80 | 4.18 | 3.96 | -1.38 | -0.22 |
| hsa-miR-371a-3p | MIMAT0000723 | AAGUGCCGCCAUCUUUUGAGUGU | 2.97 | 4.36 | 4.05 | -1.39 | -0.31 |
| hsa-miR-761 | MIMAT0010364 | GCAGCAGGGUGAAACUGACACA | 3.61 | 5.03 | 4.82 | -1.42 | -0.21 |
| hsa-miR-548an | MIMAT0019079 | AAAAGGCAUUGUGUUUUUG | 2.39 | 3.86 | 3.77 | -1.47 | -0.09 |
| hsa-miR-1273c | MIMAT0015017 | GGCGACAAAACGAGACCCUGUC | 2.39 | 3.86 | 3.42 | -1.47 | -0.44 |
| hsa-miR-744-5p | MIMAT0004945 | UGC GGGCUAGGGCUAACAGCA | 2.80 | 4.28 | 4.13 | -1.47 | -0.14 |
| hsa-miR-487a | MIMAT0002178 | AAUCAUACAGGGACAUCAGUU | 2.80 | 4.28 | 4.05 | -1.47 | -0.22 |
| hsa-miR-584-5p | MIMAT0003249 | UUAUGGUUUGCCUGGGACUGAG | 2.97 | 4.44 | 4.42 | -1.47 | -0.02 |
| hsa-miR-1278 | MIMAT0005936 | UAGUACUGUGCAUAUCAUCAU | 3.26 | 4.73 | 4.29 | -1.47 | -0.45 |
| hsa-miR-626 | MIMAT0003295 | AGCUGUCUGAAAUGUCUU | 3.50 | 4.98 | 4.92 | -1.47 | -0.06 |
| hsa-miR-217 | MIMAT0000274 | UACUGCAUCAGGAACUGAUUGGA | 1.80 | 3.28 | 3.13 | -1.48 | -0.14 |
| hsa-miR-497-5p | MIMAT0002820 | CAGCAGCACACUGUGUUUGU | 2.12 | 3.60 | 3.29 | -1.48 | -0.31 |
| hsa-miR-548ag | MIMAT0018969 | AAAGGUAAUUGUGUUUCUGC | 3.26 | 4.80 | 4.49 | -1.54 | -0.31 |
| hsa-miR-182-5p | MIMAT0000259 | UUUGGCAAUGGUAGAACUCACACU | 6.79 | 8.35 | 8.05 | -1.56 | -0.31 |
| hsa-miR-640 | MIMAT0003310 | AUGAUCCAGGAACCGCCUCU | 2.61 | 4.18 | 4.29 | -1.57 | 0.10 |
| hsa-miR-520a-5p | MIMAT0002833 | CUCCAGAGGGAAGUACUUUCU | 2.61 | 4.18 | 3.87 | -1.57 | -0.31 |
| hsa-miR-3154 | MIMAT0015028 | CAGAAGGGGAGUUGGGAGCAGA | 2.12 | 3.73 | 3.42 | -1.61 | -0.31 |
| hsa-miR-1468 | MIMAT0006789 | CUCCGUUUGCCUGUUUCGUG | 2.12 | 3.73 | 3.29 | -1.61 | -0.45 |
| hsa-miR-504 | MIMAT0002875 | AGACCCUGGUCUGCACUCAUC | 2.80 | 4.44 | 4.36 | -1.64 | -0.09 |
| hsa-miR-1245b-3p | MIMAT0019951 | UCAGAUGAUCUAAAGGCCUAUA | 1.80 | 3.44 | 3.55 | -1.65 | 0.10 |
| hsa-miR-499b-3p | MIMAT0019898 | AACAUCACUGCAAGUCUUAACA | 1.80 | 3.44 | 3.55 | -1.65 | 0.10 |

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|------------------|--------------|-------------------------|-------|-------|-------|-------|-------|
| hsa-miR-518f-3p | MIMAT0002842 | GAAAGCGCUUCUCUUUAGAGG | 1.80 | 3.44 | 3.13 | -1.65 | -0.31 |
| hsa-miR-611 | MIMAT0003279 | GCGAGGACCCUCGGGGUCUGAC | 2.39 | 4.08 | 3.55 | -1.70 | -0.53 |
| hsa-miR-767-3p | MIMAT0003883 | UCUGCUCAUACCCCAUGGUUUCU | 1.38 | 3.08 | 2.96 | -1.70 | -0.12 |
| hsa-miR-369-5p | MIMAT0001621 | AGAUCGACCGUGUUUAUUCGC | 1.38 | 3.08 | 2.77 | -1.70 | -0.31 |
| hsa-miR-1268a | MIMAT0005922 | CGGGCGUGGUGGUGGGGG | 3.61 | 5.32 | 4.92 | -1.71 | -0.40 |
| hsa-miR-922 | MIMAT0004972 | GCAGCAGAGAAUAGGACUACGUC | 3.26 | 4.98 | 4.49 | -1.72 | -0.49 |
| hsa-miR-329 | MIMAT0001629 | AACACACCGGUUAACCUCUUU | 2.80 | 4.52 | 4.21 | -1.72 | -0.31 |
| hsa-miR-625-5p | MIMAT0003294 | AGGGGAAAGUUCUAUAGUCC | 3.12 | 4.86 | 4.29 | -1.74 | -0.57 |
| hsa-miR-216a | MIMAT0000273 | UAAUCUCAGCUGGCAACUGUGA | 2.61 | 4.36 | 4.05 | -1.75 | -0.31 |
| hsa-miR-2053 | MIMAT0009978 | GUGUUAAUAAAACCUCUAUUUAC | 2.61 | 4.36 | 3.87 | -1.75 | -0.49 |
| hsa-miR-588 | MIMAT0003255 | UUGGCCACAAUGGGUUAGAAC | 2.61 | 4.36 | 3.66 | -1.75 | -0.70 |
| hsa-miR-1204 | MIMAT0005868 | UCGUGGCCUGGUCUCCAUAU | 2.39 | 4.18 | 3.77 | -1.80 | -0.41 |
| hsa-miR-518d-3p | MIMAT0002864 | CAAAGCGCUUCCCUUUGGAGC | 2.39 | 4.18 | 3.42 | -1.80 | -0.76 |
| hsa-miR-124-3p | MIMAT0000422 | UAAGGCACGCGGUGAAUGCC | 1.80 | 3.60 | 3.13 | -1.80 | -0.46 |
| hsa-miR-509-3-5p | MIMAT0004975 | UACUGCAGACGUGGCAAUCAUG | 0.80 | 2.60 | 2.29 | -1.80 | -0.31 |
| hsa-miR-516a-3p | MIMAT0006778 | UGCUUCCUUUCAGAGGGU | 2.97 | 4.80 | 4.13 | -1.83 | -0.66 |
| hsa-miR-491-3p | MIMAT0004765 | CUUAUGCAAGAUUCCCUUCUAC | 2.12 | 3.98 | 3.29 | -1.85 | -0.69 |
| hsa-miR-450b-5p | MIMAT0004909 | UUUUGCAAUAUGUCCUGAAUA | 2.80 | 4.67 | 4.49 | -1.87 | -0.18 |
| hsa-miR-1287 | MIMAT0005878 | UGCUGGAUCAGUGGUUCGAGUC | 2.80 | 4.67 | 4.42 | -1.87 | -0.24 |
| hsa-miR-548m | MIMAT0005917 | CAAAGGUAAUUGUGGUUUUUG | 2.39 | 4.28 | 3.66 | -1.89 | -0.61 |
| hsa-miR-499b-5p | MIMAT0019897 | ACAGACUUGCUGUGAUGUUCA | 2.39 | 4.28 | 3.55 | -1.89 | -0.73 |
| hsa-miR-518e-3p | MIMAT0002861 | AAAGCGCUUCCCUUCAGAGUG | 1.38 | 3.28 | 2.96 | -1.89 | -0.31 |
| hsa-miR-203 | MIMAT0000264 | GUGAAAUGUUUAGGACCACUAG | 2.61 | 4.52 | 3.66 | -1.91 | -0.86 |
| hsa-miR-630 | MIMAT0003299 | AGUAUUCUGUACCAGGGAAGGU | 12.47 | 14.39 | 13.81 | -1.92 | -0.58 |
| hsa-miR-1227 | MIMAT0005580 | CGUGCCACCCUUUCCCCAG | 1.80 | 3.73 | 3.13 | -1.94 | -0.60 |

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|------------------|--------------|-------------------------|-------|------|------|-------|-------|
| hsa-miR-1236 | MIMAT0005591 | CCUCUUCUUUGUCUCUCCAG | 2.12 | 4.08 | 3.55 | -1.96 | -0.53 |
| hsa-miR-1265 | MIMAT0005918 | CAGGAUGUGGUCAAGUGUUGUU | 2.39 | 4.36 | 3.87 | -1.98 | -0.49 |
| hsa-miR-585 | MIMAT0003250 | UGGGCGUAUCUGUAUGCUA | 2.39 | 4.36 | 3.77 | -1.98 | -0.59 |
| hsa-miR-559 | MIMAT0003223 | UAAAGUAAAUUGCACCAAAA | 2.12 | 4.18 | 3.55 | -2.06 | -0.63 |
| hsa-miR-1225-3p | MIMAT0005573 | UGAGCCCCUGUGCCGCCCCAG | 1.80 | 3.86 | 3.13 | -2.06 | -0.73 |
| hsa-miR-2115-5p | MIMAT0011158 | AGCUUCCAUGACUCCUGAUGGA | 1.80 | 3.86 | 2.96 | -2.06 | -0.90 |
| hsa-miR-548am-3p | MIMAT0019076 | CAAAAACUGCAGUUACUUUUGU | 1.80 | 3.98 | 3.87 | -2.18 | -0.10 |
| hsa-miR-323a-5p | MIMAT0004696 | AGGUGGUCCGUGGCGGUUCGC | 1.80 | 3.98 | 3.42 | -2.18 | -0.55 |
| hsa-miR-654-3p | MIMAT0004814 | UAUGUCUGCUGACCAUCACCUU | 1.80 | 3.98 | 3.42 | -2.18 | -0.55 |
| hsa-miR-302e | MIMAT0005931 | UAAGUGCUUCCAUGCUU | 2.12 | 4.36 | 3.66 | -2.24 | -0.70 |
| hsa-miR-3175 | MIMAT0015052 | CGGGGAGAGAACGCAGUGACGU | 0.80 | 3.08 | 3.42 | -2.28 | 0.34 |
| hsa-miR-455-5p | MIMAT0003150 | UAUGUGCCUUUGGACUACAUCG | 0.80 | 3.08 | 2.77 | -2.28 | -0.31 |
| hsa-miR-193a-5p | MIMAT0004614 | UGGGUCUUUGCGGGCGAGAUGA | 2.61 | 4.92 | 4.29 | -2.31 | -0.63 |
| hsa-miR-450b-3p | MIMAT0004910 | UUGGGAUCAUUUUGCAUCCAUA | 1.38 | 3.73 | 3.42 | -2.35 | -0.31 |
| hsa-miR-1226-3p | MIMAT0005577 | UCACCAGCCCUGUGUCCCUAG | 2.61 | 5.08 | 4.36 | -2.47 | -0.73 |
| hsa-miR-1202 | MIMAT0005865 | GUGCCAGCUGCAGUGGGGGAG | 2.12 | 4.60 | 3.77 | -2.48 | -0.83 |
| hsa-miR-3136-5p | MIMAT0015003 | CUGACUGAAUAGGUAGGGUCAUU | 0.80 | 3.28 | 3.29 | -2.48 | 0.01 |
| hsa-miR-4485 | MIMAT0019019 | UAACGGCCGCGGUACCCUAA | -0.20 | 2.28 | 2.96 | -2.48 | 0.69 |
| hsa-miR-136-5p | MIMAT0000448 | ACUCCAUUUGUUUGAUGAUGGA | 0.80 | 3.44 | 2.77 | -2.65 | -0.67 |
| hsa-miR-502-3p | MIMAT0004775 | AAUGCACCUGGGCAAGGAUUCA | 0.80 | 3.44 | 2.77 | -2.65 | -0.67 |
| hsa-miR-614 | MIMAT0003282 | GAACGCCUGUUCUUGCCAGGUGG | 0.80 | 3.73 | 4.05 | -2.94 | 0.32 |
| hsa-miR-338-5p | MIMAT0004701 | AACAAUAUCCUGGUGCUGAGUG | -0.20 | 2.86 | 2.77 | -3.06 | -0.09 |
| hsa-miR-606 | MIMAT0003274 | AAACUACUGAAAAUCAAGAU | -0.20 | 3.08 | 3.13 | -3.28 | 0.05 |
| hsa-miR-551a | MIMAT0003214 | GCGACCCACUCUUGGUUCCA | 0.80 | 4.36 | 3.96 | -3.56 | -0.40 |

Footnotes:

* Values represent \log_2 fold change of significantly up- or down-regulated miRNAs in EV71-infected mild symptom (n=4) and severe symptom (n=4) subjects from healthy control (n=4).

1. The blood serums were obtained from healthy children.
2. The blood serums were obtained from EV71-infected children with mild symptom.
3. The blood serums were obtained from EV71-infected children with severe symptom.
4. The up-regulated is defined as the expression level of miRNA is more or equal 2 folds detected in EV71-infected mild symptom in comparison with healthy control group.
5. The down-regulated is defined as the expression level of miRNA is less 2 folds detected in EV71-infected mild symptom in comparison with healthy control group

Table S3. The list of up- and down-regulated expression of miRNAs detected from the blood serum of EV71-infected patient with severe symptom in comparison with healthy controls.

| Gene Name | Accession Number | Target Sequence (5' to 3') | Mild ^{2,*} | Control ^{1,*} | Severe ^{3,*} | Severe vs. Control* | Mild vs. Control* |
|---------------------------------|------------------|----------------------------|---------------------|------------------------|-----------------------|---------------------|-------------------|
| Up-Regulated⁴ | | | | | | | |
| hsa-miR-876-5p | MIMAT0000269 | UACAGUCUCCAGUCACGGCC | 4.50 | 4.36 | 7.61 | 3.25 | 0.14 |
| hsa-miR-30c-5p | MIMAT0000244 | UGUAAACAUCUACACUCUCAGC | 8.20 | 7.34 | 9.09 | 1.75 | 0.86 |
| hsa-miR-580 | MIMAT0003245 | UUGAGAAUGAUGAAUCAUUAGG | 3.50 | 2.60 | 4.21 | 1.61 | 0.90 |
| hsa-miR-454-3p | MIMAT0003885 | UAGUGCAAUAUUGCUUAUAGGGU | 8.72 | 7.79 | 9.40 | 1.61 | 0.93 |
| hsa-miR-296-5p | MIMAT0000690 | AGGGCCCCCUCAAUCCUGU | 6.90 | 6.52 | 8.11 | 1.59 | 0.38 |
| hsa-miR-1271-5p | MIMAT0005796 | CUUGGCACCUAGCAAGCACUCA | 2.12 | 2.60 | 4.13 | 1.54 | -0.48 |
| hsa-let-7b-5p | MIMAT0000063 | UGAGGUAGUAGGUUGUGUGGUU | 13.07 | 12.75 | 14.26 | 1.51 | 0.31 |
| hsa-miR-15b-5p | MIMAT0000417 | UAGCAGCACAUCAUGGUUUACA | 14.17 | 13.60 | 15.05 | 1.45 | 0.57 |
| hsa-miR-339-5p | MIMAT0000764 | UCCUGUCCUCCAGGAGCUCACG | 4.19 | 3.44 | 4.87 | 1.43 | 0.75 |
| hsa-miR-369-3p | MIMAT0000721 | AAUAAUCAUGGUUGAUUUUU | 2.80 | 1.86 | 3.29 | 1.43 | 0.94 |
| hsa-miR-513c-5p | MIMAT0005789 | UUCUCAAGGAGGUGUCGUUUAU | 2.61 | 1.86 | 3.29 | 1.43 | 0.75 |
| hsa-let-7c | MIMAT0000064 | UGAGGUAGUAGGUUGUAUGGUU | 9.88 | 9.72 | 11.11 | 1.39 | 0.16 |
| hsa-miR-331-3p | MIMAT0000760 | GCCCCUGGGCCUAUCCUAGAA | 5.78 | 5.13 | 6.52 | 1.39 | 0.64 |
| hsa-miR-652-3p | MIMAT0003322 | AAUGGCGCCACUAGGGUUGUG | 8.77 | 8.24 | 9.52 | 1.28 | 0.53 |
| hsa-miR-92a-3p | MIMAT0000092 | UAUUGCACUUGUCCGGCCUGU | 11.30 | 10.83 | 12.10 | 1.28 | 0.47 |
| hsa-miR-1539 | MIMAT0007401 | UCCUGCGCGUCCAGAUGCCC | 2.80 | 2.28 | 3.55 | 1.27 | 0.53 |
| hsa-miR-4508 | MIMAT0019045 | GCGGGCUGGGCGCGCG | 7.33 | 6.38 | 7.61 | 1.22 | 0.95 |
| hsa-let-7f-5p | MIMAT0000067 | UGAGGUAGUAGAUUGUAUAGUU | 9.57 | 8.86 | 10.07 | 1.21 | 0.71 |
| hsa-miR-3195 | MIMAT0015079 | CGCGCCGGGCCCGGGUU | 7.31 | 6.99 | 8.18 | 1.19 | 0.32 |
| hsa-miR-552 | MIMAT0003215 | AACAGGUGACUGGUAGACAA | 3.26 | 2.60 | 3.77 | 1.17 | 0.66 |

| | | | | | | | |
|-----------------------------------|--------------|-------------------------|-------|-------|-------|-------|-------|
| hsa-miR-424-5p | MIMAT0001341 | CAGCAGCAAUUC AUGUUUGAA | 3.39 | 3.44 | 4.61 | 1.16 | -0.06 |
| hsa-let-7a-5p | MIMAT0000062 | UGAGGUAGUAGGUUGUAUAGUU | 12.52 | 12.40 | 13.56 | 1.15 | 0.12 |
| hsa-miR-26a-5p | MIMAT0000082 | UUCAAGUAAUCCAGGAUAGGCU | 11.07 | 10.13 | 11.28 | 1.15 | 0.95 |
| hsa-miR-660-5p | MIMAT0003338 | UACCCAUUGCAUAUCGGAGUUG | 9.57 | 8.73 | 9.87 | 1.14 | 0.83 |
| hsa-miR-3144-5p | MIMAT0015014 | AGGGGACCAAAGAGAUUAUAG | 3.12 | 2.86 | 3.96 | 1.10 | 0.26 |
| hsa-let-7e-5p | MIMAT0000066 | UGAGGUAGGAGGUUGUAUAGUU | 7.39 | 6.68 | 7.76 | 1.08 | 0.71 |
| hsa-miR-107 | MIMAT0000104 | AGCAGCAUUGUACAGGGCUAUC | 9.99 | 9.25 | 10.26 | 1.01 | 0.74 |
| hsa-miR-3196 | MIMAT0015080 | CGGGGCGGCAGGGGCCUC | 3.12 | 2.86 | 3.87 | 1.01 | 0.26 |
| hsa-miR-550a-5p | MIMAT0004800 | AGUGCCUGAGGGAGUAAGAGCCC | 2.12 | 2.86 | 3.87 | 1.01 | -0.74 |
| hsa-miR-490-3p | MIMAT0002806 | CAACCUGGAGGACUCCAUGCUG | 2.39 | 2.28 | 3.29 | 1.01 | 0.11 |
| Down-Regulated⁵ | | | | | | | |
| hsa-miR-629-5p | MIMAT0004810 | UGGGUUUACGUUGGGAGAACU | 6.47 | 7.36 | 6.34 | -1.02 | -0.89 |
| hsa-miR-876-5p | MIMAT0004924 | UGGAUUUCUUUGUGAAUCACCA | 3.12 | 2.60 | 1.55 | -1.05 | 0.53 |
| hsa-miR-9-5p | MIMAT0000441 | UCUUUGGUUAUCUAGCUGUAUGA | 3.61 | 4.18 | 3.13 | -1.05 | -0.57 |
| hsa-miR-502-5p | MIMAT0002873 | AUCCUUGCUAUCUGGGUGCUA | 3.12 | 3.60 | 2.55 | -1.05 | -0.47 |
| hsa-miR-889 | MIMAT0004921 | UUAAUAUCGGACAACCAUUGU | 2.80 | 3.60 | 2.55 | -1.05 | -0.80 |
| hsa-miR-920 | MIMAT0004970 | GGGGAGCUGUGGAAGCAGUA | 2.97 | 3.86 | 2.77 | -1.09 | -0.89 |
| hsa-miR-517a-3p | MIMAT0002852 | AUCGUGCAUCCUUUAGAGUGU | 3.71 | 4.52 | 3.42 | -1.10 | -0.82 |
| hsa-miR-342-3p | MIMAT0000753 | UCUCACACAGAAAUCGCACCCGU | 9.57 | 9.26 | 8.11 | -1.14 | 0.31 |
| hsa-miR-873-5p | MIMAT0004953 | GCAGGAACUUGUGAGUCUCCU | 3.39 | 3.44 | 2.29 | -1.16 | -0.06 |
| hsa-miR-146b-3p | MIMAT0004766 | UGCCUGUGGACUCAGUUCUGG | 3.80 | 4.44 | 3.29 | -1.16 | -0.64 |
| hsa-miR-1262 | MIMAT0005914 | AUGGGUGAAUUUGUAGAAGGAU | 4.05 | 4.60 | 3.42 | -1.17 | -0.55 |
| hsa-miR-936 | MIMAT0004979 | ACAGUAGAGGGAGGAAUCGCAG | 3.50 | 4.36 | 3.13 | -1.23 | -0.86 |
| hsa-miR-3182 | MIMAT0015062 | GCUUCUGUAGUGUAGUC | 3.50 | 4.44 | 3.13 | -1.31 | -0.94 |

| | | | | | | | |
|---------------------------------|--------------|-------------------------|-------|-------|------|-------|-------|
| hsa-miR-199a-3p+hsa-miR-199b-3p | MIMAT0000232 | ACAGUAGUCUGCACAUUGGUUA | 6.81 | 6.40 | 5.09 | -1.31 | 0.41 |
| hsa-miR-1181 | MIMAT0005826 | CCGUCGCCGCCACCCGAGCCG | 4.44 | 4.86 | 3.55 | -1.31 | -0.42 |
| hsa-miR-3127-5p | MIMAT0014990 | AUCAGGGCUUGUGGAAUGGGAAG | 2.97 | 3.86 | 2.55 | -1.31 | -0.89 |
| hsa-miR-769-3p | MIMAT0003887 | CUGGGAUCUCCGGGGUCUUGGUU | 3.97 | 4.36 | 2.96 | -1.40 | -0.39 |
| hsa-miR-219-2-3p | MIMAT0004675 | AGAAUUGUGGCUGGACAUCUGU | 3.71 | 4.36 | 2.96 | -1.40 | -0.66 |
| hsa-miR-125a-5p | MIMAT0000443 | UCCCUAGACCCUUUAACCUUGA | 4.56 | 4.18 | 2.77 | -1.41 | 0.37 |
| hsa-miR-2054 | MIMAT0009979 | CUGUAAUUAUUUUUUUUUUUU | 2.80 | 3.44 | 1.96 | -1.48 | -0.64 |
| hsa-miR-361-5p | MIMAT0000703 | UUUUCAGAAUCUCCAGGGGUAC | 6.46 | 7.42 | 5.85 | -1.58 | -0.97 |
| hsa-miR-337-5p | MIMAT0004695 | GAACGGCUUCAUACAGGAGUU | 3.89 | 4.73 | 3.13 | -1.60 | -0.85 |
| hsa-miR-675-5p | MIMAT0004284 | UGGUGCGGAGAGGGCCACAGUG | 2.39 | 3.28 | 1.55 | -1.72 | -0.89 |
| hsa-miR-346 | MIMAT0000773 | UGUCUGCCCGCAUGCCUGCCUCU | 3.71 | 4.08 | 2.29 | -1.80 | -0.38 |
| hsa-miR-758 | MIMAT0003879 | UUUGUGACCUUGUCCACUAACC | 3.12 | 3.44 | 1.55 | -1.89 | -0.32 |
| hsa-miR-27a-3p | MIMAT0000084 | UUCACAGUGGCUAAGUCCGC | 4.89 | 5.03 | 3.13 | -1.90 | -0.14 |
| hsa-miR-221-3p | MIMAT0000278 | AGCUACAUGUCUGCGGUUUC | 7.37 | 6.70 | 4.77 | -1.93 | 0.67 |
| hsa-miR-1973 | MIMAT0009448 | ACCGUGCAAAGGUAGCAUA | 5.84 | 6.65 | 4.55 | -2.10 | -0.81 |
| hsa-miR-1910 | MIMAT0007884 | CCAGUCCUGUGCCUGCCGCCU | 2.97 | 3.08 | 0.96 | -2.12 | -0.11 |
| hsa-miR-150-5p | MIMAT0000451 | UCUCCCAACCCUUGUACCAGUG | 10.85 | 10.97 | 6.64 | -4.34 | -0.12 |

Footnotes:

* Values represent fold change (\log_2) of significantly up- or down-regulated miRNAs in EV71-infected mild symptom (n=4) and severe symptom (n=4) subjects from healthy control (n=4).

1. The blood serums were obtained from healthy children.
2. The blood serums were obtained from EV71-infected children with mild symptom.
3. The blood serums were obtained from EV71-infected children with severe symptom.

4. The up-regulated is defined as the expression level of miRNA is more or equal 2 folds detected in EV71-infected severe symptom in comparison with healthy control group.
5. The down-regulated is defined as the expression level of miRNA is less 2 folds detected in EV71-infected severe symptom in comparison with healthy control group

Fig. S1. MicroRNA-mediated regulation of target genes in response to EV71 infection mild symptom. KEGG pathway analysis was performed on cellular genes identified as important for EV71 progressive disease. The red stars were located near the targeted genes of miR-494.

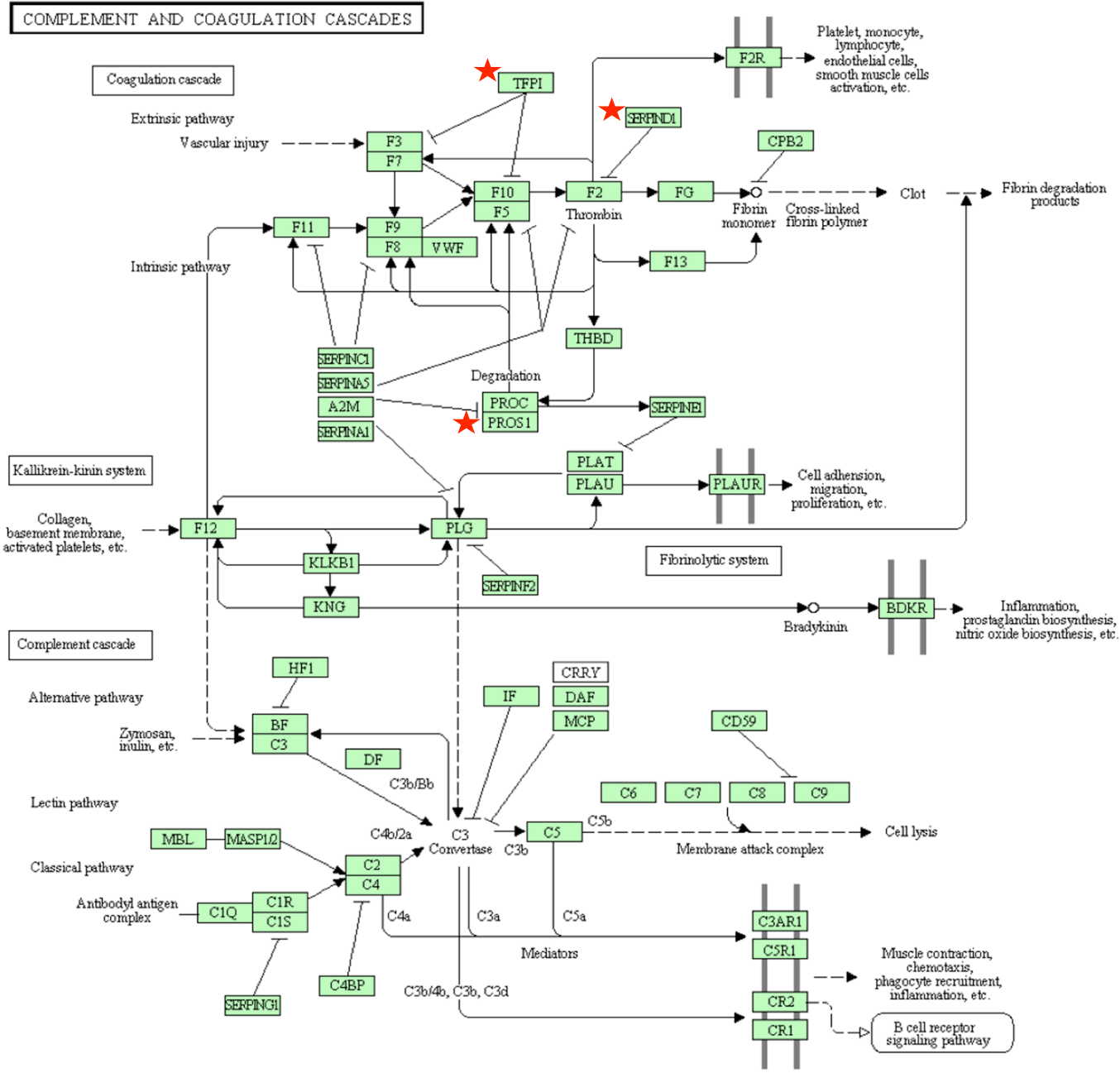
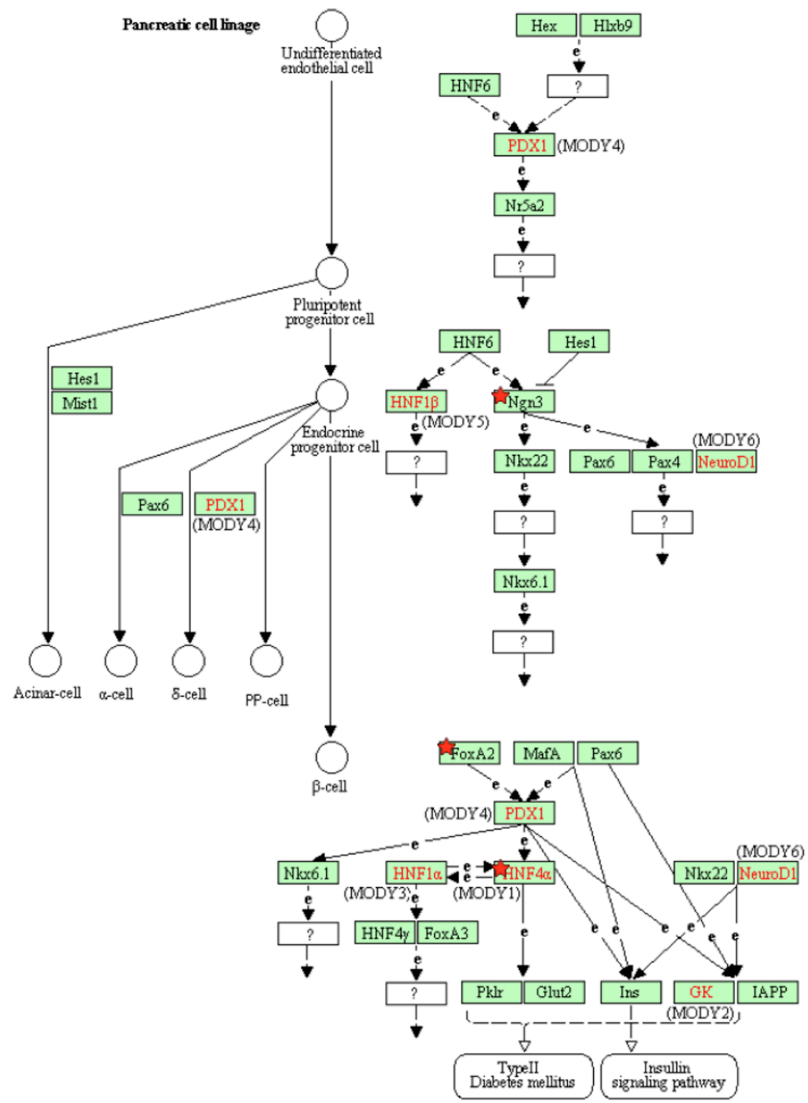


Fig. S2. MicroRNA-mediated regulation of target genes in response to EV71 infection mild symptom. KEGG pathway analysis was performed on cellular genes identified as important for EV71 progressive disease. The red stars were located near the targeted genes of miR-551a.

MATURITY ONSET DIABETES OF THE YOUNG



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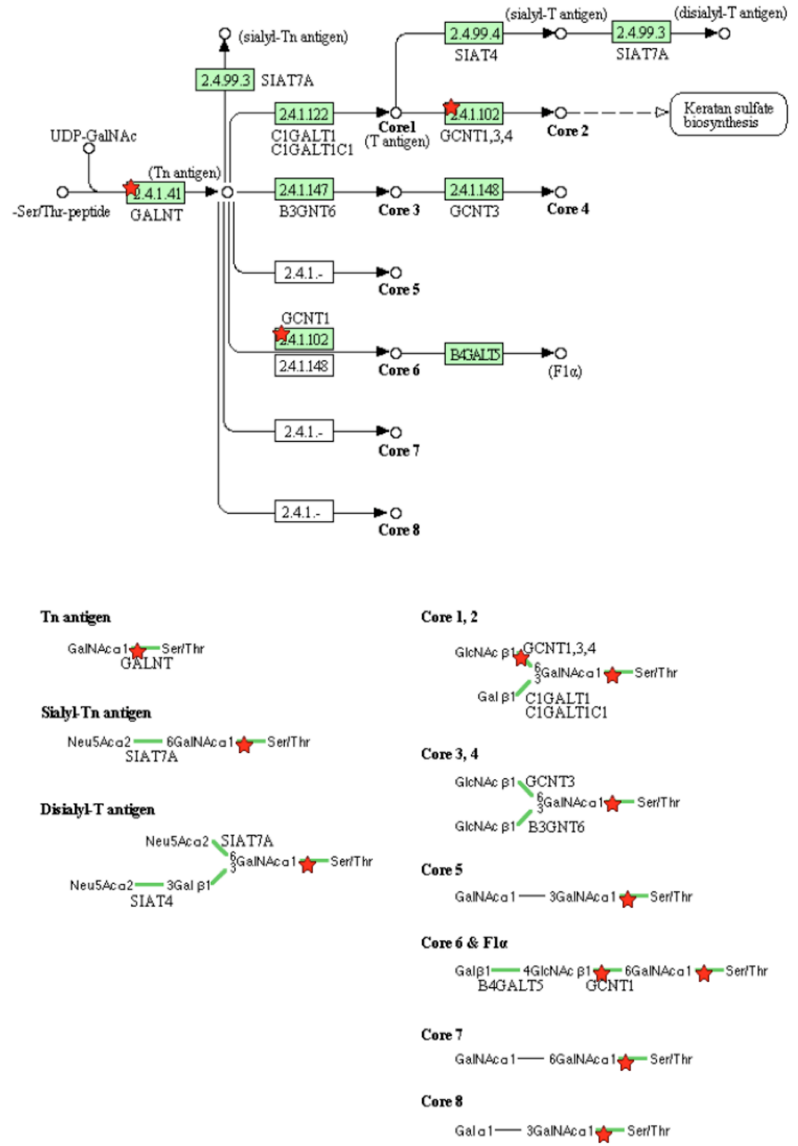


Fig. S3. MicroRNA-mediated regulation of target genes in response to EV71 infection mild symptom. KEGG pathway analysis was performed on cellular genes identified as important for EV71 progressive disease. The red stars were located near the targeted genes of miR-876-5p.

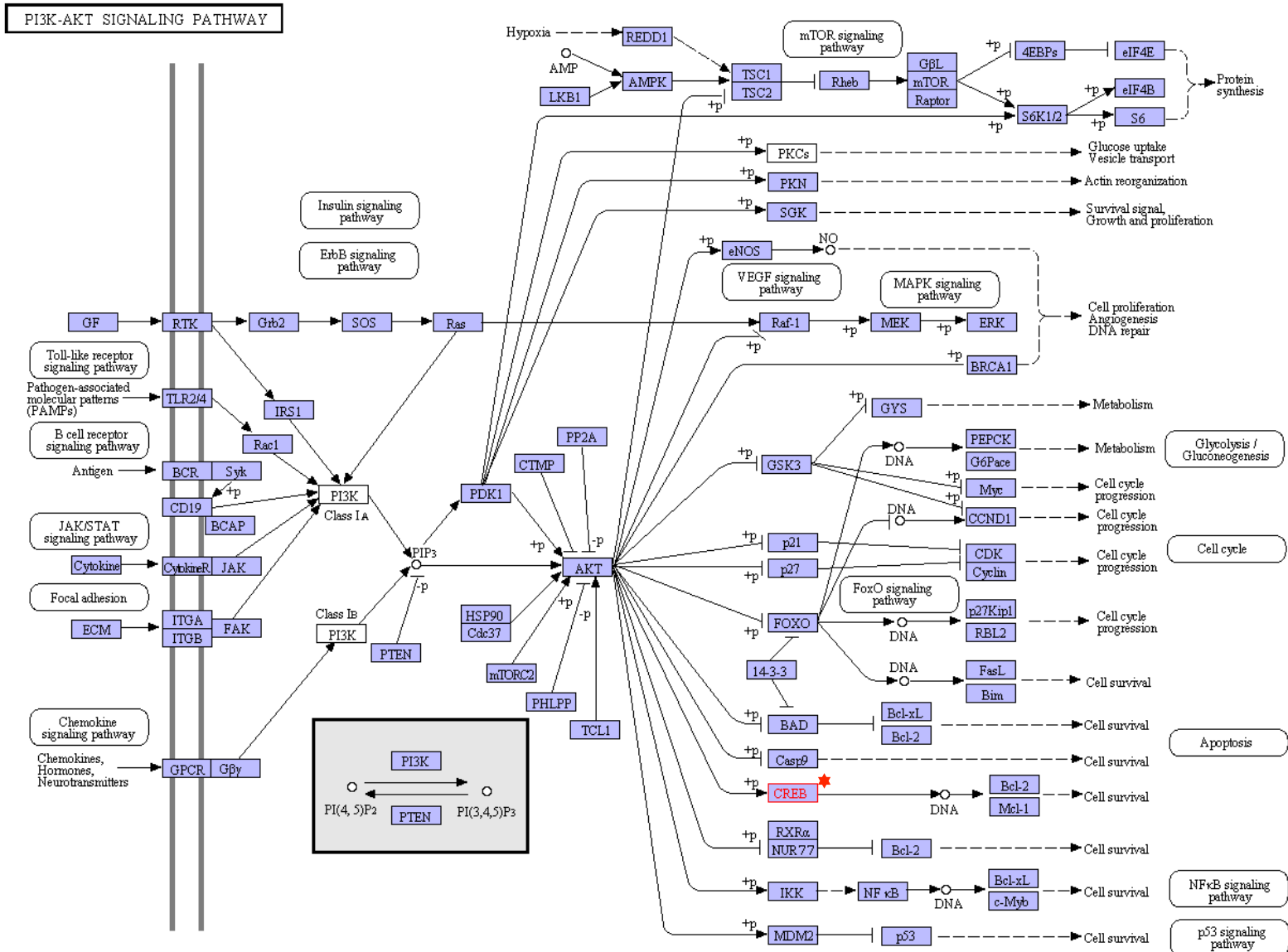


Fig. S4. MicroRNA-mediated regulation of target genes in response to EV71 infection mild symptom. KEGG pathway analysis was performed on cellular genes identified as important for EV71 progressive disease. The red stars were located near the targeted genes of miR-150-5p.

