# Supplementary Materials: Differential MicroRNA Expression Profile in Myxomatous Mitral Valve Prolapse and Fibroelastic Deficiency Valves

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**Table S1.** Detailed characterization of individual patients with myxomatous mitral valve prolase (MMVP) and fibroelastic deficiency (FED).

| Case | Prolapsed Segment(s) | Flail Segment | Segment with Ruptured Chord | Myxomatous, or Redundant Mitral Leaflets | AML Length, mm | AML Thickness, mm | PML Length, mm | PML Thickness, mm |
|---|---|---|---|---|---|---|---|---|
| MMVP1 | A2 A3 P1 P2 P3 | P2 | P2 | yes | 30 | 4 | 24 | 4.8 |
| MMVP2 | A2 A3 P1 P2 P3 | none | none | yes | 30 | 4 | 13 | 1.8 |
| MMVP3 | A1 A2 A3 P3 | none | none | yes | 46 | 6 | 16 | 6 |
| MMVP4 | none | P1 P2 | P2 | yes | 29 | 5 | 23 | 6 |
| MMVP5 | A2 A3 P2 P3 | none | none | yes | 31 | 5.1 | 20 | 4.8 |
| MMVP6 | P2 | none | none | yes | 32 | 3.3 | 26 | 3.6 |
| MMVP7 | A2 A3 P1 P2 P3 | none | none | yes | 33 | 6.8 | 22 | 4 |
| MMVP8 | A2 A3 | none | none | yes | 34 | 5.5 | 14 | 5 |
| MMVP9 | P3 A3 A2 | P2 | P2 | yes | 28 | 4.6 | 31 | 5.2 |
| MMVP10 | P1 P2 P3 A2 A3 | none | no | yes | 26 | 2.5 | 22 | 3.7 |
| FED1 | none | P3 | P3 | no | 28 | 2.9 | 16 | 3.2 |
| FED2 | P3 | P2 | P2 | no | 22 | 2.7 | 17 | 1.9 |
| FED3 | A2 | P2 | none | no | 26 | 3.1 | 22 | 5 |
| FED4 | none | P2 | P2 | no | 23 | 3.1 | 19 | 3.1 |
| FED5 | P2 | P3 | P3 | no | - | - | - | - |
| FED6 | none | P2 | P2 | no | 19 | 2.7 | 20 | 4 |
| FED7 | P3 | P2 | P2 | no | 20 | 2.5 | 16 | 4.7 |
| FED8 | none | C2 | C2 | no | 26 | 3.6 | 17 | 3.6 |
| FED9 | A3 P3 | A2 | A2 | no | 24 | 2.6 | 10 | 1.4 |
| FED10 | none | P2 | P2 | no | 23 | 2.5 | 27 | 5.1 |

A (1, 2 or 3), anterior leaflet segment affected, AML, anterior mitral leaflet; P (1, 2 or 3), posterior leaflet scallop; PML, posterior mitral leaflet. For patient FED5, leaflet measurements were omitted as the original echocardiogram was no longer available.

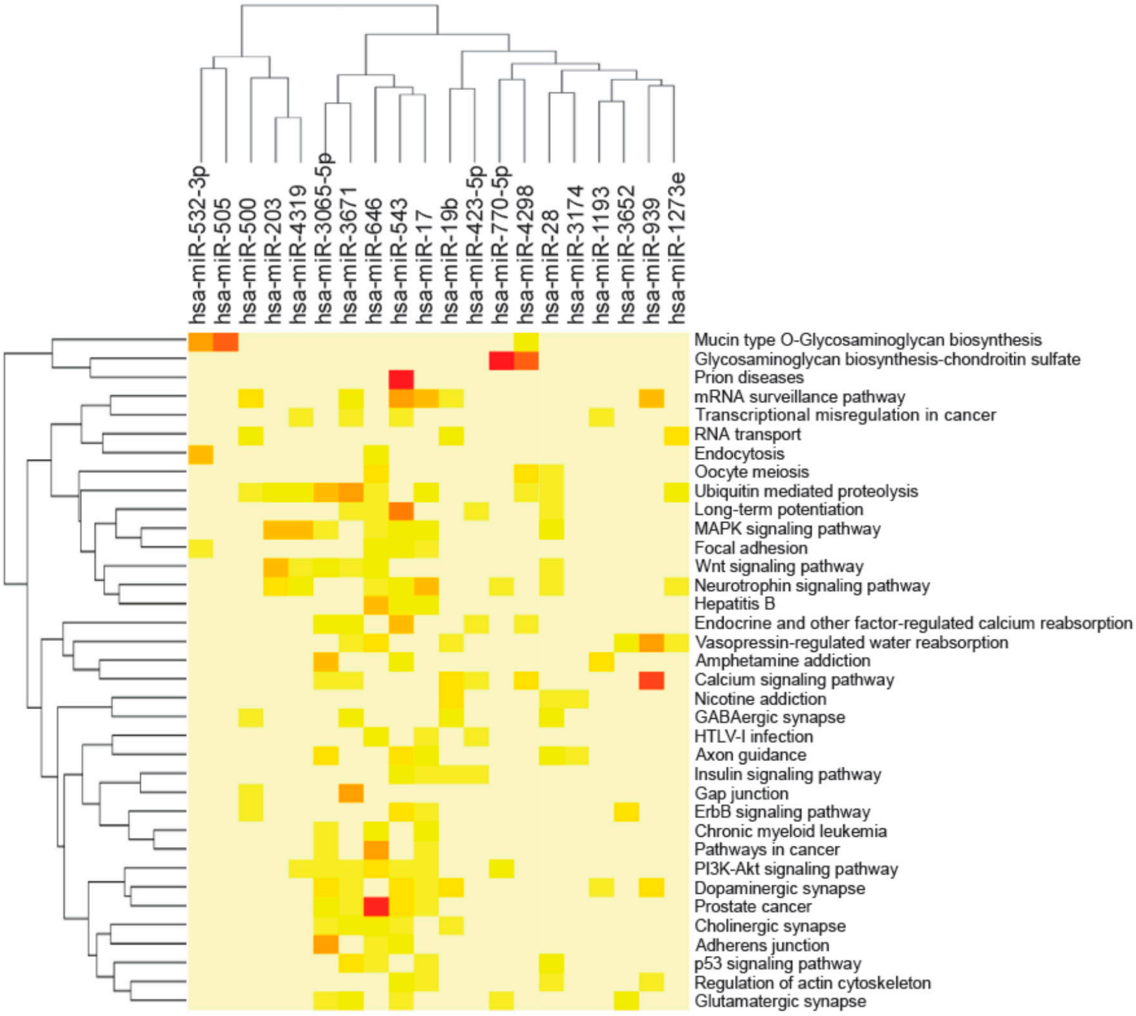


**Figure S1.** Heat map of microRNAs versus predicted pathways. Hierarchical clustering of predicted pathway and microRNAs that differentially expressed in MMVP and FED cohorts. The darker color clocks represent lower *p* values (cut-off, $p < 0.05$; Fisher's method).

**Table S2.** The Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway predication.

| KEGG Pathway (Pathway Union) | *p*-Value | #Genes | #miRNAs |
|---|---|---|---|
| Ubiquitin mediated proteolysis | $2.15 \times 10^{-12}$ | 59 | 10 |
| Transcriptional misregulation in cancer | $3.27 \times 10^{-12}$ | 53 | 6 |
| MAPK signaling pathway | $4.05 \times 10^{-10}$ | 69 | 7 |
| Neurotrophin signaling pathway | $1.54 \times 10^{-9}$ | 36 | 8 |
| Dopaminergic synapse | $3.15 \times 10^{-8}$ | 46 | 7 |
| Calcium signaling pathway | $8.13 \times 10^{-8}$ | 53 | 6 |
| Prostate cancer | $1.24 \times 10^{-7}$ | 35 | 5 |
| Wnt signaling pathway | $4.08 \times 10^{-7}$ | 41 | 6 |
| Glycosaminoglycan biosynthesis—chondroitin sulfate | $1.60 \times 10^{-6}$ | 2 | 2 |
| Long-term potentiation | $5.18 \times 10^{-6}$ | 25 | 5 |
| Mucin type O-Glycan biosynthesis | $1.08 \times 10^{-5}$ | 5 | 3 |
| Vasopressin-regulated water reabsorption | $4.82 \times 10^{-5}$ | 14 | 6 |
| PI3K-Akt signaling pathway | 0.0001 | 99 | 7 |
| Axon guidance | 0.0001 | 37 | 5 |
| Amphetamine addiction | 0.0003 | 22 | 3 |

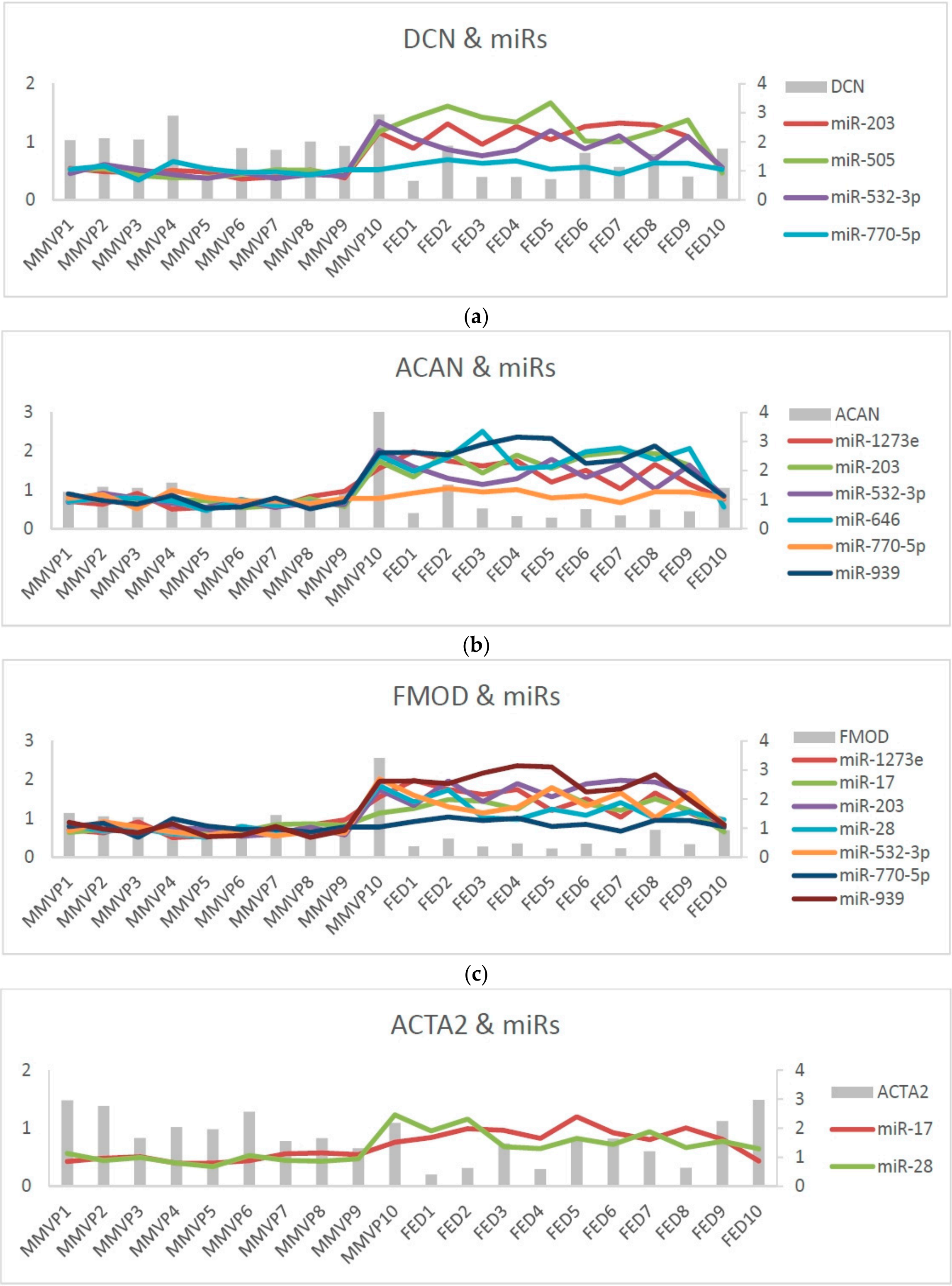
**Table S2.** *Cont.*

| **KEGG Pathway (Pathway Union)** | ***p*-Value** | **#Genes** | **#miRNAs** |
|---|---|---|---|
| Glutamatergic synapse | 0.0004 | 34 | 5 |
| Prion diseases | 0.0004 | 3 | 1 |
| ErbB signaling pathway | 0.0007 | 24 | 4 |
| Endocrine and other factor-regulated calcium reabsorption | 0.0007 | 18 | 5 |
| Regulation of actin cytoskeleton | 0.0013 | 44 | 4 |
| Focal adhesion | 0.0017 | 43 | 4 |
| Gap junction | 0.0023 | 16 | 2 |
| Hepatitis B | 0.0024 | 32 | 3 |
| Oocyte meiosis | 0.0044 | 17 | 3 |
| Endocytosis | 0.0052 | 24 | 2 |
| Insulin signaling pathway | 0.0059 | 27 | 4 |
| RNA transport | 0.0101 | 15 | 3 |
| mRNA surveillance pathway | 0.0125 | 25 | 4 |
| GABAergic synapse | 0.0142 | 18 | 4 |
| Cholinergic synapse | 0.0170 | 30 | 5 |
| Nicotine addiction | 0.0196 | 6 | 3 |
| p53 signaling pathway | 0.0229 | 18 | 4 |
| Pathways in cancer | 0.0251 | 53 | 3 |
| HTLV-I infection | 0.0328 | 33 | 3 |
| Adherens junction | 0.0342 | 25 | 3 |
| Chronic myeloid leukemia | 0.0493 | 14 | 3 |
| **KEGG Pathway (Gene Union)** | | | |
| Ubiquitin mediated proteolysis | $1.48 \times 10^{-23}$ | 65 | 18 |
| Prostate cancer | $1.19 \times 10^{-16}$ | 42 | 16 |
| Calcium signaling pathway | $8.66 \times 10^{-16}$ | 75 | 18 |
| ErbB signaling pathway | $1.96 \times 10^{-15}$ | 41 | 17 |
| Transcriptional misregulation in cancer | $4.71 \times 10^{-14}$ | 75 | 19 |
| Long-term potentiation | $1.32 \times 10^{-13}$ | 33 | 19 |
| MAPK signaling pathway | $3.90 \times 10^{-13}$ | 100 | 19 |
| Endocrine and other factor-regulated calcium reabsorption | $1.28 \times 10^{-12}$ | 23 | 14 |
| Dopaminergic synapse | $1.84 \times 10^{-12}$ | 55 | 19 |
| Glutamatergic synapse | $2.53 \times 10^{-11}$ | 50 | 18 |
| PI3K-Akt signaling pathway | $3.96 \times 10^{-11}$ | 120 | 19 |
| Endocytosis | $4.68 \times 10^{-11}$ | 78 | 18 |
| Insulin signaling pathway | $7.77 \times 10^{-11}$ | 55 | 18 |
| Gap junction | $2.00 \times 10^{-10}$ | 37 | 16 |
| Regulation of actin cytoskeleton | $2.93 \times 10^{-10}$ | 82 | 19 |
| Neurotrophin signaling pathway | $3.76 \times 10^{-10}$ | 50 | 20 |
| Wnt signaling pathway | $9.20 \times 10^{-10}$ | 62 | 19 |
| Focal adhesion | $1.11 \times 10^{-9}$ | 75 | 19 |
| mTOR signaling pathway | $3.46 \times 10^{-9}$ | 29 | 15 |
| Axon guidance | $4.67 \times 10^{-9}$ | 56 | 19 |
| mRNA surveillance pathway | $2.62 \times 10^{-8}$ | 38 | 17 |
| p53 signaling pathway | $2.26 \times 10^{-7}$ | 29 | 18 |
| Melanogenesis | $3.64 \times 10^{-7}$ | 40 | 17 |
| GnRH signaling pathway | $5.03 \times 10^{-7}$ | 36 | 18 |
| TGF-beta signaling pathway | $2.71 \times 10^{-6}$ | 35 | 14 |
| Fc gamma R-mediated phagocytosis | $4.65 \times 10^{-6}$ | 36 | 18 |

**Table S2.** *Cont.*

| KEGG Pathway (Gene Union) | $p$-Value | #Genes | #miRNAs |
|---|---|---|---|
| Retrograde endocannabinoid signaling | $1.14 \times 10^{-5}$ | 44 | 17 |
| Type II diabetes mellitus | $1.14 \times 10^{-5}$ | 21 | 13 |
| Prion diseases | $1.61 \times 10^{-5}$ | 10 | 7 |
| Aldosterone-regulated sodium reabsorption | $1.84 \times 10^{-5}$ | 17 | 12 |
| Dilated cardiomyopathy | $2.51 \times 10^{-5}$ | 35 | 14 |
| Endometrial cancer | $4.33 \times 10^{-5}$ | 21 | 12 |
| Cholinergic synapse | $4.51 \times 10^{-5}$ | 45 | 17 |
| Melanoma | $8.49 \times 10^{-5}$ | 28 | 15 |
| Glycosylphosphatidylinositol(GPI)-anchor biosynthesis | 0.0001 | 11 | 10 |
| Protein processing in endoplasmic reticulum | 0.0001 | 61 | 19 |
| Chronic myeloid leukemia | 0.0001 | 28 | 15 |
| RNA transport | 0.0002 | 54 | 20 |
| B cell receptor signaling pathway | 0.0003 | 28 | 16 |
| Colorectal cancer | 0.0003 | 25 | 11 |
| Small cell lung cancer | 0.0004 | 31 | 14 |
| HTLV-I infection | 0.0004 | 87 | 20 |
| Long-term depression | 0.0005 | 27 | 12 |
| Inositol phosphate metabolism | 0.0005 | 25 | 15 |
| Hypertrophic cardiomyopathy (HCM) | 0.0006 | 31 | 13 |
| Adherens junction | 0.0006 | 33 | 15 |
| Taurine and hypotaurine metabolism | 0.0008 | 5 | 6 |
| Gastric acid secretion | 0.0008 | 28 | 15 |
| T cell receptor signaling pathway | 0.0008 | 38 | 16 |
| GABAergic synapse | 0.0008 | 39 | 17 |
| Pathways in cancer | 0.0010 | 112 | 19 |
| Nicotine addiction | 0.0014 | 19 | 13 |
| Hepatitis C | 0.0014 | 45 | 17 |
| RNA degradation | 0.0015 | 27 | 17 |
| Glioma | 0.0016 | 29 | 14 |
| Phosphatidylinositol signaling system | 0.0030 | 34 | 16 |
| Adipocytokine signaling pathway | 0.0033 | 25 | 14 |
| Oocyte meiosis | 0.0033 | 45 | 18 |
| Hepatitis B | 0.0061 | 52 | 20 |
| Vasopressin-regulated water reabsorption | 0.0061 | 16 | 12 |
| HIF-1 signaling pathway | 0.0067 | 37 | 15 |
| Non-small cell lung cancer | 0.0079 | 21 | 11 |
| Salivary secretion | 0.0081 | 30 | 17 |
| VEGF signaling pathway | 0.0104 | 23 | 17 |
| Osteoclast differentiation | 0.0161 | 42 | 17 |
| Jak-STAT signaling pathway | 0.0179 | 48 | 19 |
| Basal transcription factors | 0.0185 | 16 | 9 |
| Amphetamine addiction | 0.0185 | 29 | 16 |
| Circadian rhythm | 0.0199 | 13 | 10 |
| Maturity onset diabetes of the young | 0.0228 | 10 | 6 |
| Pancreatic cancer | 0.0305 | 26 | 14 |
| Acute myeloid leukemia | 0.0311 | 19 | 12 |
| Chemokine signaling pathway | 0.0337 | 57 | 18 |

The DNA intelligent Analysis (DIANA) miRPath v.2.0, a web-based microRNA-targeted pathway analysis algorithm was used to generate the list.



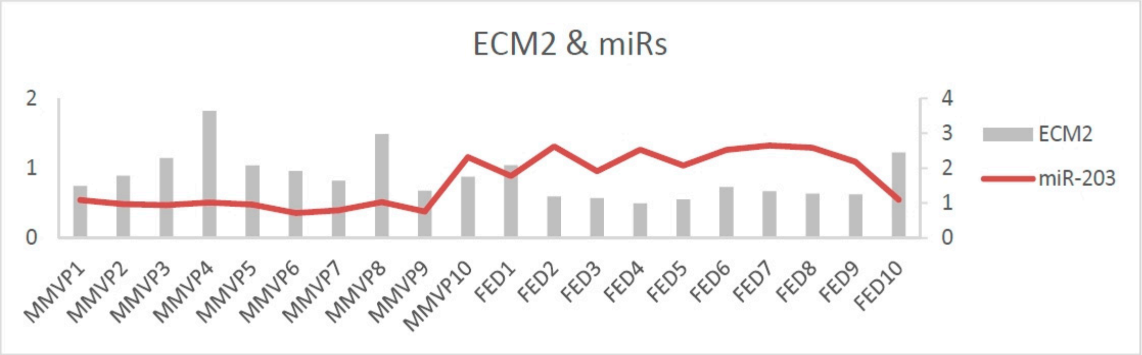
(**a**)

(**b**)

(**c**)

(**d**)

**Figure S2.** *Cont.*



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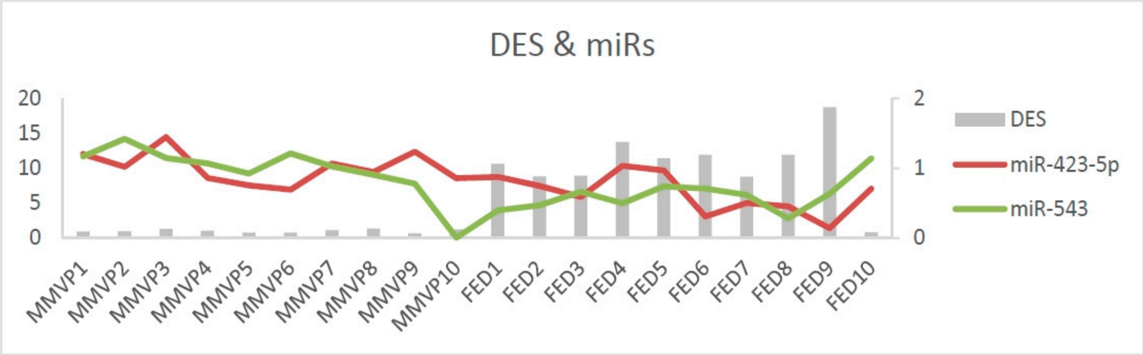

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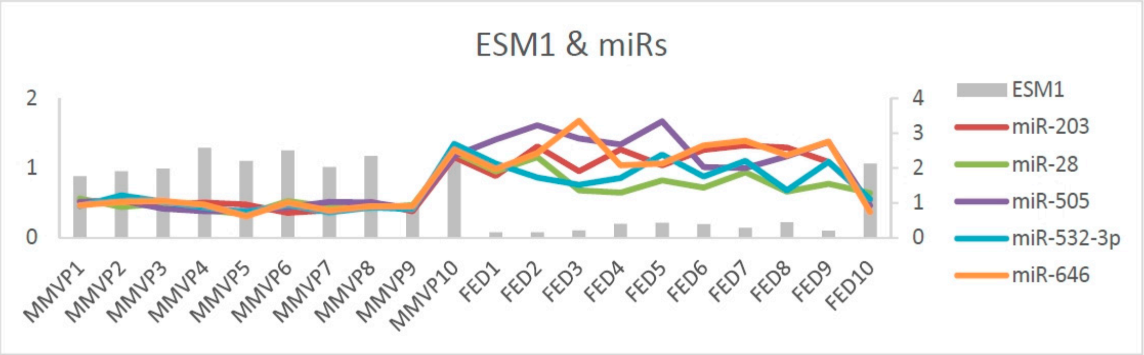
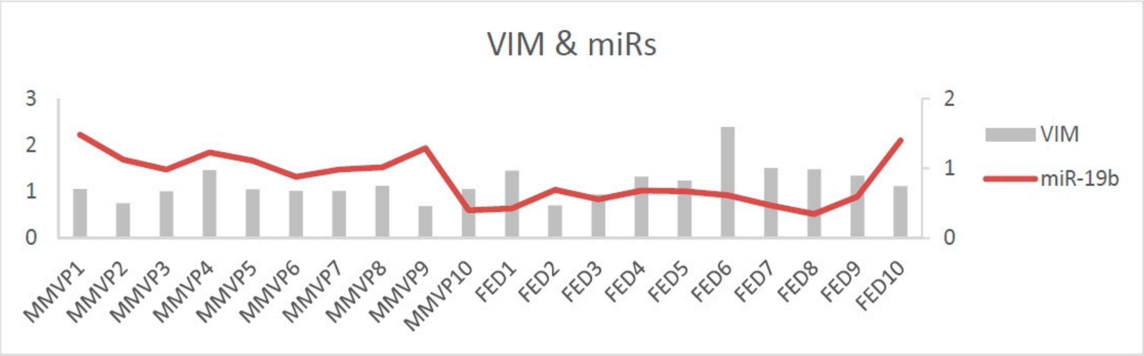


(**g**)



(**h**)

**Figure S2.** Relative expression patterns between microRNAs and putative target genes of individual patients. Data presented are means of gene expression levels relative to the average values of MMVP samples. Primary axis (**left**) indicate the relative expression levels of the predicated target genes (gray columns); whereas, secondary axis (**right**) indicate the relative expression levels of microRNAs (colored lines). (**a**) DCN; (**b**) ACAN; (**c**) FMOD; (**d**) ACTA2; (**e**) ECM2; (**f**) DES; (**g**) ESM1; (**h**) VIM.