

Small extracellular vesicle microRNAs as epigenetic regulators in the development of psychological resilience

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Background

Small extracellular vesicle (sEV) orchestrate central nervous system (CNS) homeostasis that regulate human behaviour via stress response neurons through transcellular communication. MicroRNAs (miRNAs) multiple biological function toward to homeostasis, and considered as neuropsychological biomarkers. It is important to clarify the neuropsychological-related miRNAs expression levels of sEV in psychological resilience individuals. Hence, the set of brain and circulating-enriched aberrant miRNAs might be served as a neuropsychological biomarker for individuals with different resilience.

Hypothesis & Specific Aims

Hypothesis

The set of brain and circulating-enriched aberrant miRNAs might be served as a neuropsychological biomarker for individuals with different resilience.

Specific Aims

Aim 1: To compare the expression difference of small extracellular vesicle miRNAs by genome-wide profiling between low and high resilience.

Aim 2: To assess the small extracellular vesicle contained miRNAs expression panel from low and high resilience.

Aim 3: To identify candidate small extracellular vesicle miRNAs target genes involved in niacin signaling pathway in low resilience.

Methods

We collected blood samples of high and low resilience individuals (n = 8) for sEV miRNAs genome-wide profiling, and will further validate in larger sample size (n = 40). We examined the neuropsychological-related miRNAs expression levels between high and low resilience via genome-wide profiling of sEV, then further validated the expression level of candidate miRNAs.

Extracellular vesicles isolation and analysis

For the extracellular vesicles isolation, we using ExoQuick extracellular vesicles precipitation solution protocol, and further using TRIre for the homogenization. The extracellular vesicles RNA extraction with Direct-zol™ RNA MiniPrep Kit from plasma exosome samples according to the manufacturer's instructions.

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Results

A series of 2632 miRNAs were identified via miRNAs profiling with the miRbase database with mature miRNA records. To further explore the roles of the detected miRNAs, we compared the expression of them between high and low resilience individuals and found that 932 miRNAs were differentially expressed. As far as the preliminary results of sEV miRNAs expressions between high and low resilience, we identified 6 miRNAs which associated with psychological resilience with large fold changes respectively (i.e. let-7b, miR-151a, miR-335, miR-193a, miR-3605 and miR-6894).

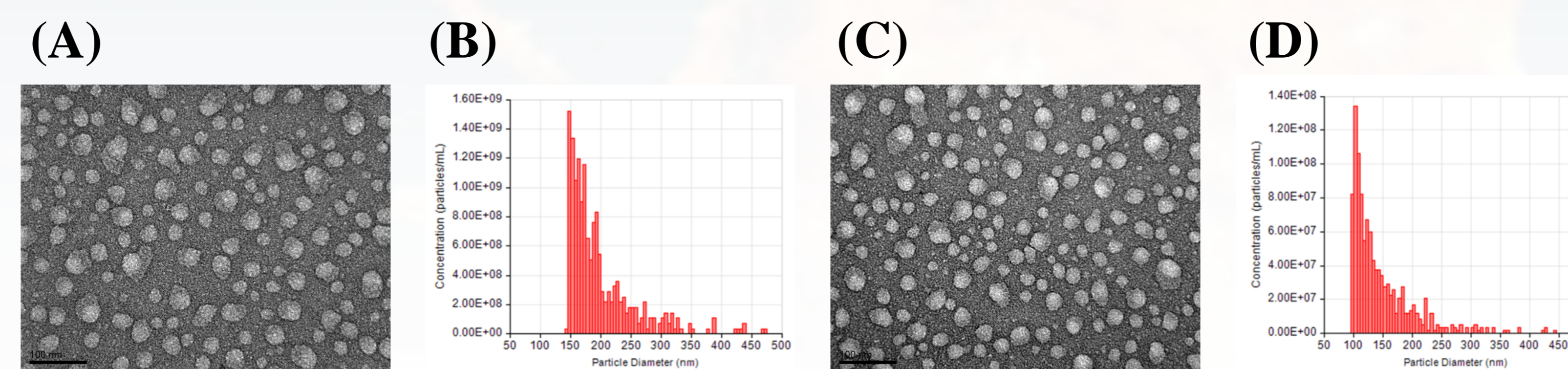


Fig. 1 Transmission electron micrograph of EVs, and determination of EV quality, composition and size distribution. (A) and (B) High resilience. (C) and (D) Low resilience.

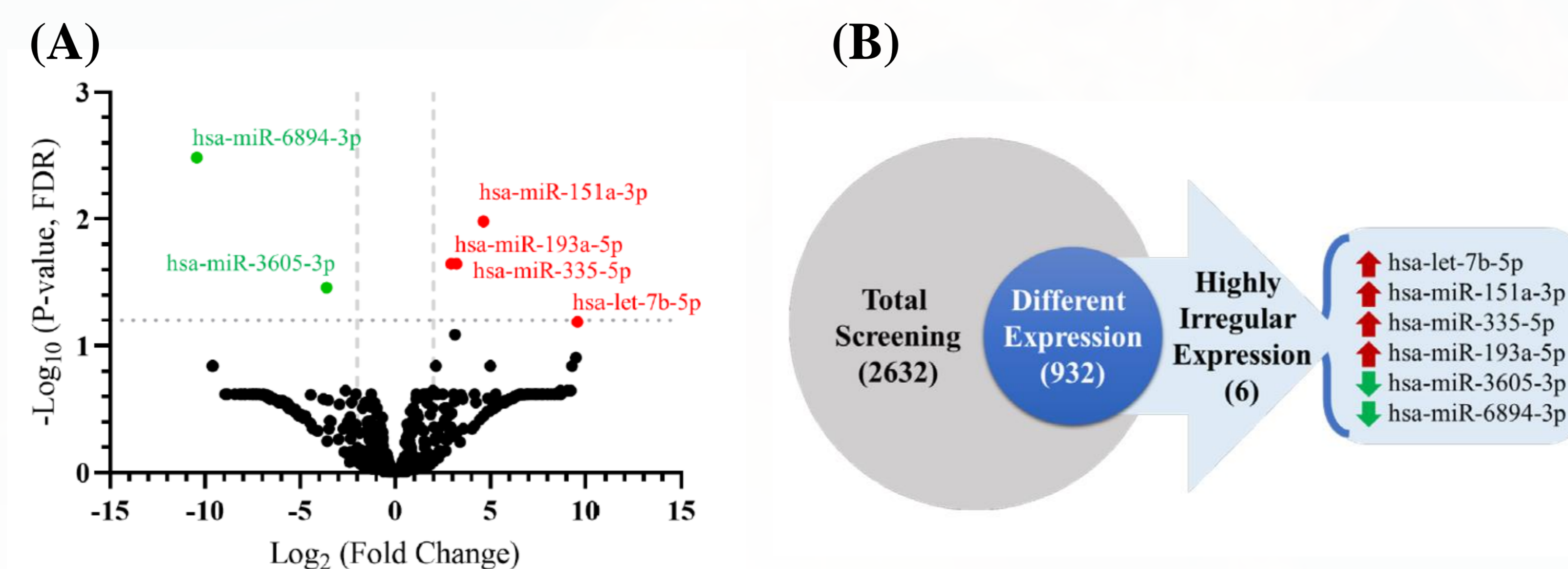


Fig. 2 Differentially expressed miRNAs in plasma sEV from low resilience compare to high resilience individuals.

Table 1 Differentially expressed miRNAs in plasma sEV from low resilience compare to high resilience individuals in profiling set.

miRbase ID	Log ₂ [FC]	P-value	False Discovery Rate
has-let-7b	2.499	3.522E-06	0.003
has-miR-151a	4.648	2.241E-05	0.010
has-miR-335	3.220	8.402E-05	0.023
has-miR-193a	2.942	9.685E-05	0.023
has-miR-3065	-3.608	0.000186	0.035
has-miR-6894	-10.435	0.000232	0.036

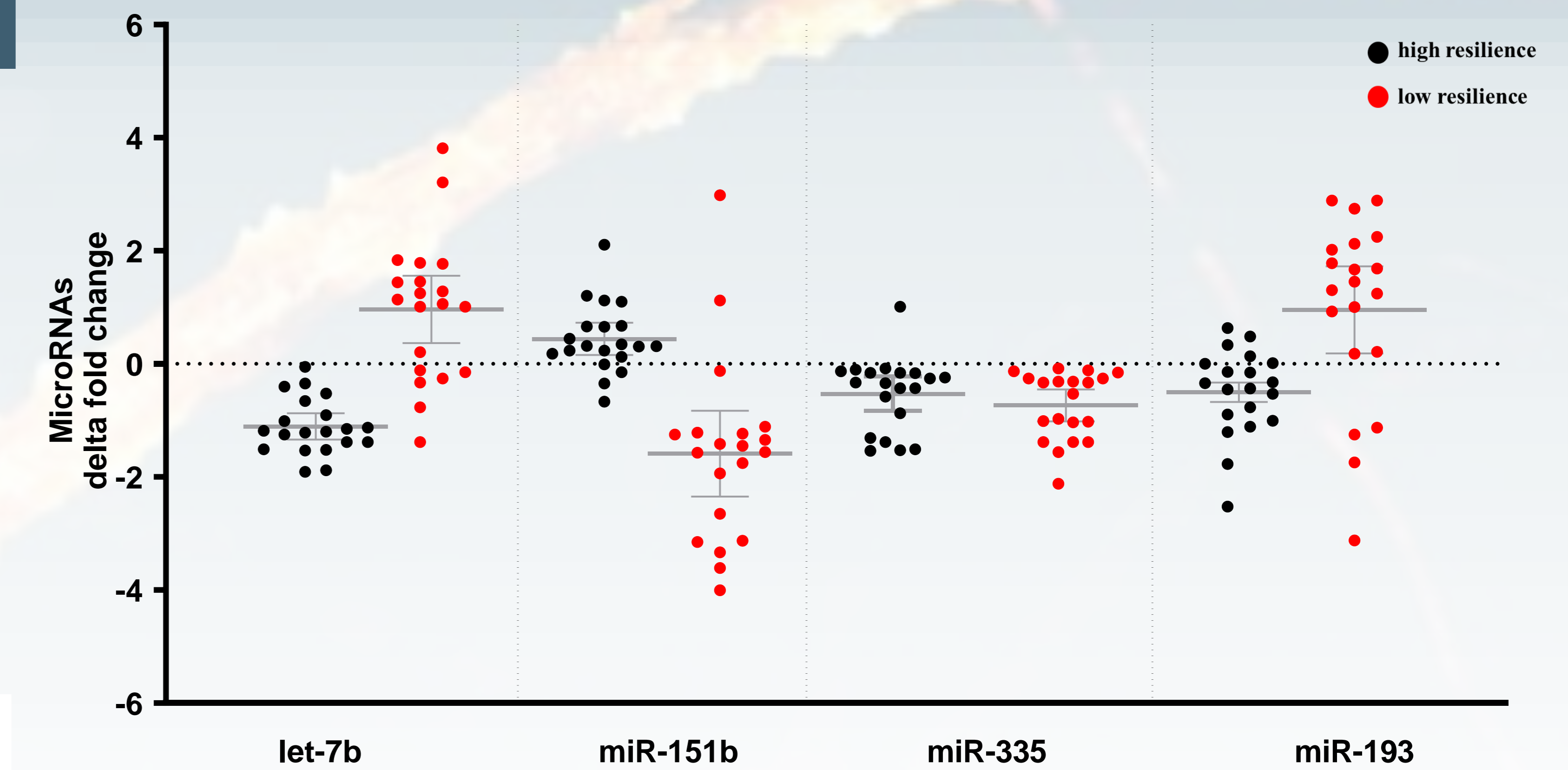


Fig. 3 Differentially expressed miRNAs in plasma sEV from low resilience compare to high resilience individuals in validation set.

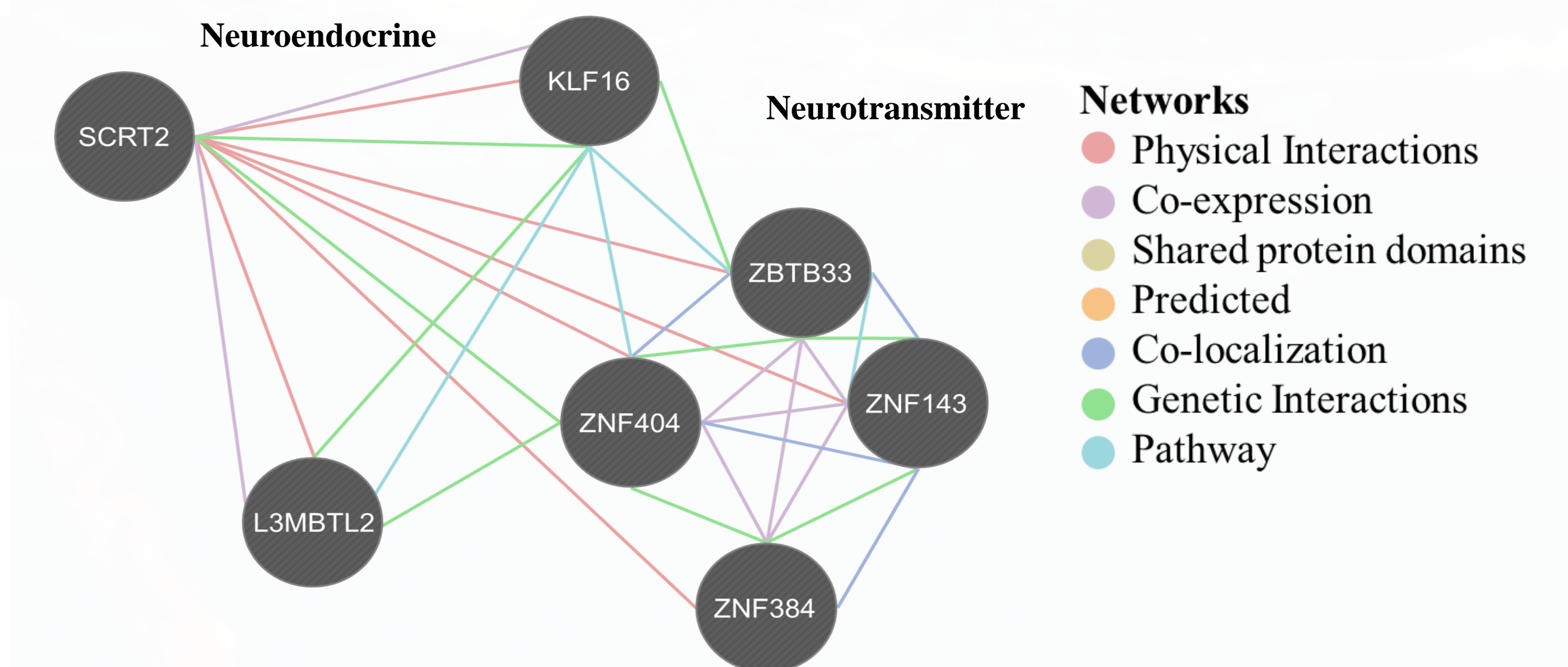


Fig. 4 The top 7 (linking scores > 0.80) of candidate miRNAs' target genes interaction networks.

Conclusion

The sEV miRNAs might play some crucial roles of psychological strength and resilience linked to numerous biochemical pathways. Thus, the sEV miRNAs expression patterns might provide the clues of epigenetics regulation across behavioral phenotypes.