**Title: Diagnostic value of blood-derived microRNAs for schizophrenia: results of a meta-analysis and validation**

**Authors:** Sha Liu, Fuquan Zhang, Xijin Wang, Yin Yao Shugart, Yingying Zhao, Xinrong Li, Zhifen Liu, Ning Sun, Chunxia Yang, Kerang Zhang, Weihua Yue, Xin Yu, Yong Xu

Supplementary table 1. RT primers of miRNAs.

| miRNA | RT primers (5'-3') |
|---|---|
| hsa-miR-181b-5p | GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACACCCAC |
| hsa-miR-21-5p | GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACTCAACA |
| hsa-miR-195-5p | GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACGCCAAT |
| hsa-miR-137 | GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACCTACGC |
| hsa-miR-346 | GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACAGAGGC |
| hsa-miR-34a-5p | GTCGTATCCAGTGCGTGTCGTGGAGTCGGCAATTGCACTGGATACGACACAACC |
| U6 | CGCTTCACGAATTTGCGTGTCAT |

U6 is the internal reference. RT = reverse transcription.

Supplementary table 2. Real-time PCR primers of miRNAs.

| miRNA | | Real-time PCR primers (5’-3’) |
|---|---|---|
| hsa-miR-181b-5p | F: | GGGAACATTCATTGCTGTCG |
| | R: | GTGCGTGTCGTGGAGTCG |
| hsa-miR-21-5p | F: | GGGTAGCTTATCAGACTGA |
| | R: | GTGCGTGTCGTGGAGTCG |
| hsa-miR-195-5p | F: | GGGTAGCAGCACAGAAAT |
| | R: | GTGCGTGTCGTGGAGTCG |
| hsa-miR-137 | F: | GGGTTATTGCTTAAGAATAC |
| | R: | GTGCGTGTCGTGGAGTCG |
| hsa-miR-346 | F: | GGGTGTCTGCCCGCATGCCT |
| | R: | GTGCGTGTCGTGGAGTCG |
| hsa-miR-34a-5p | F: | GGGTGGCAGTGTCTTAGCT |
| | R: | GTGCGTGTCGTGGAGTCG |
| U6 | F: | GCTTCGGCAGCACATATACTAAAAT |
| | R: | CGCTTCACGAATTTGCGTGTCAT |

F = forward primer, R = reverse primer.

Supplementary table 3. Summary of included studies in meta-analysis.

| Study ID | Authors | Sample size (SZ vs. NC) | Specimen | AUC (95% CI) | SEN | SPE | TP a | FP b | FN c | TN d | QUADAS | miRNAs profile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Xu et al. 2010[33] | 43 vs. 40 | PBMC | 0.74 (0.61-0.87) | 80.0% | 64.2% | 34 | 14 | 9 | 26 | 11 | miR-30e |
| 2 | Shi et al.2012[37] | 115 vs. 40 | Serum | 0.85 (0.78-0.91) | 85.0% | 80.7% | 98 | 8 | 17 | 32 | 11 | miR-181b-5p, miR-219-2-3p, miR-195-5p, miR-346, miR-1308, let-7g |
| 3 | Fan, et al. 2015[39] | 55 vs. 28 | PBMC | 0.97 (0.95-1.00) | 89.3% | 94.6% | 49 | 2 | 6 | 26 | 12 | miR-1273d, miR-1303, miR-21-5p, miR-3064-5p, miR-3131, miR-3687, miR-4428, miR-4725-3p, miR-5096 |
| 4 | Sun et al. 2015[40] | 25 vs. 13 | PBMC | 0.76 (0.58-0.93) | 81.8% | 68.0% | 20 | 4 | 5 | 9 | 10 | miR-30e |
| 5 | Lai et al. 2016[42] | 48 vs. 37 | PBMC | 0.80 (0.69-0.93) | 75.7% | 86.5% | 36 | 5 | 12 | 32 | 11 | miR-34a-5p, miR-449a,miR-564, miR-432, miR-548d, miR-572, miR-652 |
| 6 | Wu et al. 2016[43] | 44 vs. 44 | PBMC | 0.80 (0.70-0.89) | 70.5% | 84.1% | 31 | 7 | 13 | 37 | 13 | miR-137 |
| | Total | 330 vs. 202 | | | | | | | | | | |

AUC = the area under the curve, SEN = Sensitivity, SPE = Specificity, TP = true positives, FP = false positives, TN = true negatives, FN = false negatives, NA = not available, QUADAS = Quality Assessment of Diagnostic Accuracy Studies.

Supplementary table 4. The demographic characteristics of subjects.

| | SZ | HC | *P* value |
|---|---|---|---|
| Age (years) | 36.4 ± 9.7 | 36.0 ± 7.3 | 0.921 |
| Males, n (%) | 15 (38.9%) | 18 (36%) | 0.834 |
| Age of onset (years) | 28.2 ± 10.0 | | |

SZ = schizophrenia patients, HC = healthy controls. Age was expressed as mean ± standard deviation.

Supplementary table 5. Relative miRNA levels in PBMNCs from controls and SZ patients.

| MiRNAs | HC (n=50) | SZ (n=39) | *P* |
|---|---|---|---|
| miR-181b-5p | 0.811±0.108 | 1.854±0.187 | < 0.001 |
| miR-21-5p | 0.987±0.135 | 2.237±0.384 | 0.008 |
| miR-195-5p | 1.662±0.315 | 5.350±0.678 | < 0.001 |
| miR-137 | 0.469±0.052 | 2.079±0.231 | < 0.001 |
| miR-346 | 0.414±0.054 | 0.221±0.030 | 0.004 |
| miR-34a-5p | 2.465±0.307 | 8.174±1.064 | < 0.001 |

All data were expressed as mean ± standard error of the mean.

Supplementary table 6. The diagnostic value of 6 miRNAs in PBMNCs for SZ.

| MiRNAs | Sen | Spe | Youden index | AUC | P-value | 95% CI |
|---|---|---|---|---|---|---|
| miR-181b-5p | 0.813 | 0.792 | 0.605 | 0.831 | <0.001 | 0.740-0.923 |
| miR-21-5p | 0.719 | 0.708 | 0.427 | 0.746 | <0.001 | 0.639-0.854 |
| miR-195-5p | 0.875 | 0.771 | 0.646 | 0.848 | <0.001 | 0.759-0.937 |
| miR-137 | 0.844 | 0.875 | 0.719 | 0.928 | <0.001 | 0.877-0.980 |
| miR-34a-5p | 0.719 | 0.854 | 0.573 | 0.857 | <0.001 | 0.777-0.938 |
| miR-346 | 0.646 | 0.625 | 0.271 | 0.653 | 0.021 | 0.534-0.772 |

Sen = sensitivity, Spe = specificity.

Supplementary table 7. Altered miRNAs in PBMNCs among SZ, bipolar disorder and major depressive disorder.

| Schizophrenia | Bipolar disorder | Major depressive disorder |
|---|---|---|
| miR-30e | miR-140-3p | miR-589 |
| miR-181b-5p | miR-30d-5p | miR-579 |
| miR-219-2-3p | miR-330-5p | miR-941 |
| miR-195-5p | miR-378a-5p | miR-133a |
| miR-346 | miR-21-3p | miR-494 |
| miR-1308 | miR-330-3p | miR-107 |
| let-7g | miR-345-5p | miR-148a |
| miR-1273d | miR-134 | miR-652 |
| miR-1303 | | miR-425-3p |
| miR-21-5p | | miR-330-3p |
| miR-3064-5p | | miR-345-5p |
| miR-3131 | | miR-24-3p |
| miR-3687 | | miR-425-3p |
| miR-4428 | | let-7a-5p |
| miR-4725-3p | | let-7d-5p |
| miR-5096 | | let-7f-5p |
| miR-34a-5p | | miR-517b |
| miR-449a | | miR-636 |
| miR-564 | | miR-1243 |
| miR-432 | | miR-381 |
| miR-548d | | miR-200c |
| miR-572 | | |
| miR-652 | | |
| miR-137 | | |