

Title: Exosomal miR-146a-5p as a potential biomarker for sporadic Amyotrophic Lateral Sclerosis: Insights from meta-analysis and experimental validation

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Risk of bias assessment:

	Risk of Bias					
Study (First author, year)	Raw Data	Actual data processing	Sample Annotation and experiment variables	Experiment design	Annotation of array design	Experimental data processing protocol
De Felice et al. 2012 (23)	I	S	S	S	S	S
Freischmidt et al. 2014 (29)	S	S	S	S	S	S
Takahashi et al. 2015 (26)	I	S	S	S	S	S
Chen et al. 2016 (24)	I	S	S	S	S	S
de Andrade et al. 2016 (32)	I	S	S	I	I	S
Waller et al. 2017 (30)	I	S	S	S	I	S
Waller et al. 2018 (40)	I	S	S	S	S	S
De Felice et al. 2018 (22)	S	S	S	S	S	S

Liguori et al. 2018 (25)	I	S	S	S	S	S
Saucier et al. 2019 (34)	I	S	S	S	S	S
Katsu et al. 2019 (35)	I	S	S	S	S	S
Banack et al. 2020 (36)	I	S	I	S	S	S
Kmetzsch et al. 2021 (27)	I	S	S	S	N/A	S
Pregnotato et al. 2021 (38)	I	S	S	S	I	I
Dobrowolny et al. 2021 (31)	I	S	S	S	S	S
Lo et al. 2021 (39)	S	S	S	S	S	S
Aksu-Menges et al. 2022 (33)	I	S	S	S	S	I
Banack et al. 2022 (37)	I	S	I	S	I	S
Liu et al. 2023 (14)	I	S	S	S	I	S
Gomes et al. 2023 (28)	I	S	S	I	I	S

S – sufficient, I –insufficient, N/A –not available

MIAME and MIQE tools - definitions of domains

The six most critical elements contributing to MIAME are:

1. Raw data

Sufficient: A raw data provided by CEL or FASTQ file format for CKD and healthy control groups.

Insufficient: An incomplete data provided by CEL or FASTQ file format for CKD and healthy control groups.

Not reported: Not reported.

2. Actual data processing.

Sufficient: A final processed (normalized) data provided for each study group

Insufficient: Data normalization not conducted or insufficient information of data processing.

Not reported: Not reported.

3. Sample annotation and experiment variables

Sufficient: A clear definition of sample annotation including tissue, sex and age and the experimental factors and their values (e.g., compound and dose in a dose response study).

Insufficient: An incomplete definition of sample annotation including tissue, sex and age and the experimental factors and their values (e.g., compound and dose in a dose response study).

Not reported: Not reported.

4. Experiment design

Sufficient: A clear definition of experiment design including which raw data file relates to CKD and healthy control groups, and technical and biological replicates reported.

Insufficient: An incomplete definition of experiment design including which raw data file relates to CKD and healthy control groups, and technical and biological replicates reported.

Not reported: Not reported.

5. Annotation of array design

Sufficient: A clear definition of annotation of the array or sequence features examines including gene identifiers and genomic coordinates.

Insufficient: An incomplete definition of annotation of the array or sequence features examines including gene identifiers and genomic coordinates.

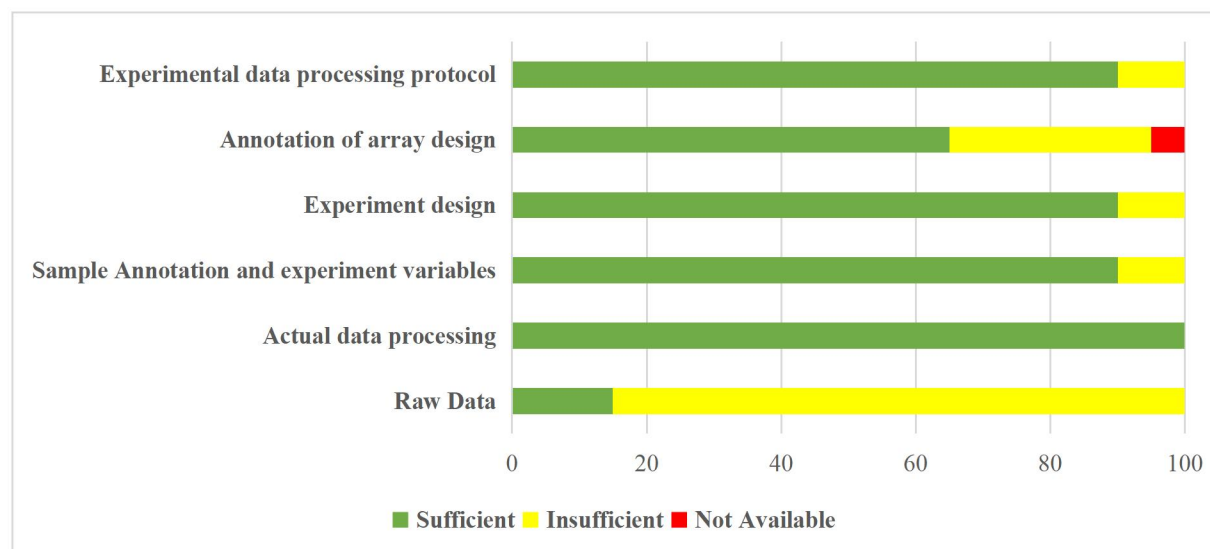
Not reported: Not reported.

6. Experimental data processing protocol

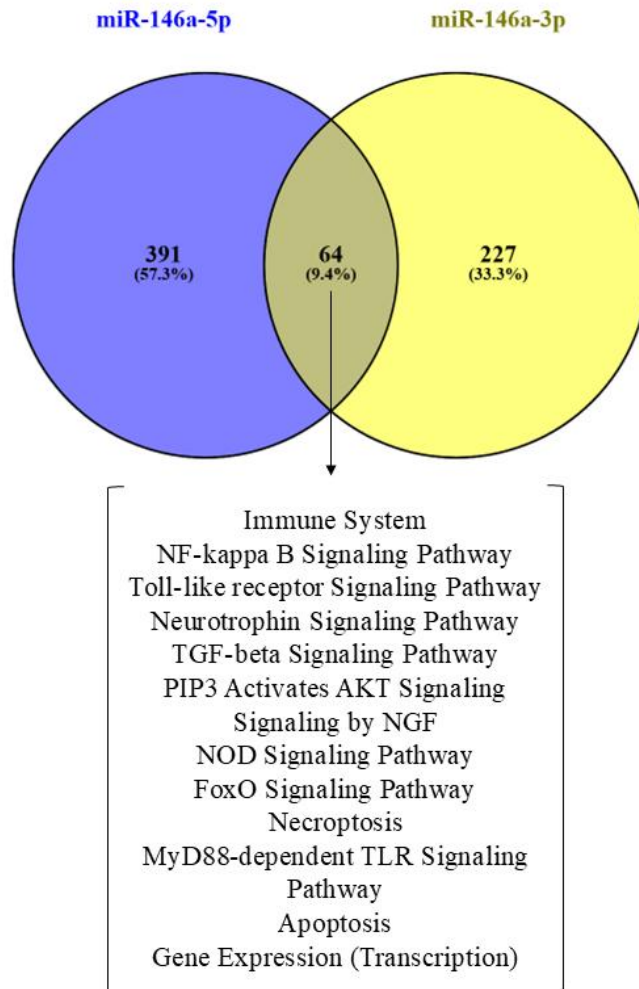
Sufficient: A clear definition of what normalization method has been used to obtain the final processed data.

Insufficient: An incomplete definition of what normalization method has been used to obtain the final processed data.

Not reported: Not reported.



Supplementary Figure 1. Risk of Bias assessment – MIAME and MIQE tools results for all included studies. Green bars, yellow bars, and red bars, respectively, indicate the items that were sufficient in annotation, insufficient in annotation, and not available.



Supplementary Figure 2. Common predicted pathways between miR-146a-5p and miR-146a-3p. Validated target genes of both the miRNAs were predicted using MultiMiR package as described in the Materials and Methods. Pathway enrichment analysis of the validated target genes of miR-146a-5p and -3p was performed using EnrichR software.