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Comprehensive data for studying serum exosome microRNA transcriptome in Parkinson's disease patients

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Parkinson's disease (PD), the second most prevalent neurodegenerative disorder, was classically attributed to alpha-synuclein aggregation and consequent loss of dopaminergic neurons in the substantia nigra pars compacta. Recently, emerging evidence suggested a broader spectrum of contributing factors, including exosome-mediated intercellular communication, which can potentially serve as biomarkers and therapeutic targets. However, there is a remarkable lack of comprehensive studies that connect the serum exosome microRNA (miRNA) transcriptome with demographic, clinical, and neuroimaging data in PD patients. Here, we present serum exosome miRNA transcriptome data generated from four cohort studies. Two of these studies include 96 PD patients and 80 age- and gender-matched controls, with anonymised demographic, clinical, and neuroimaging data provided for PD patients. The other two studies involve 96 PD patients who were evaluated both before and after one year of treatment with rasagiline, a widely prescribed anti-parkinsonism drug. Together, the datasets provide a valuable source for understanding pathogenesis and discovering biomarkers and therapeutic targets in PD.

Background & Summary

Parkinson's disease (PD) is a neurodegenerative disorder characterised by bradykinesia, rest tremor and rigidity[1]. According to the 2016 Global Burden of Disease study, PD is estimated to affect approximately 6.1 million people, rendering it the second most prevalent neurodegenerative disorder worldwide[2,3]. With the ageing of the world population and the extension of life expectancy, the prevalence of PD is predicted to increase to 12–17 million people by 2040, posing an imminent public health challenge[4–6]. Traditionally, the aetiology of PD is attributed to aberrant accumulation of misfolded alpha-synuclein species and subsequent loss of dopaminergic neurons in the substantia nigra pars compacta (Snpc)[7]. Nonetheless, recent research highlighted the contribution of systemic factors to PD initiation and progression, such as exosome-mediated intercellular communication[8–11], dysbiosis of the gut microbiota[12,13] and inflammation[14,15].

Although neuropathological confirmation is considered to be the gold standard for PD diagnosis, due to the inaccessibility of the brain, neuroimaging measures are widely applied to assist in diagnosis and monitor disease progression[16]. In the peripheral nervous system, as Lewy body disease (LBD) pathology is accompanied by denervation in the cardiac sympathetic nerves, Radioiodinated Metaiodobenzylguanidine (MIBG) has been proposed to robustly differentiate LBD from other diseases, as well as brain-first and body-first subtypes of PD[8,17,18]. As for the central nervous system, dopamine transporter imaging (DaTscan) has demonstrated efficacy in detecting presynaptic dopaminergic deficits and thereby facilitating the differential diagnosis of neurodegenerative

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Parkinsonian Syndrome and non-dopamine deficiency aetiologies of Parkinsonism[19]. Notwithstanding, the association between neuroimaging measures and other biomarkers in PD remains largely unexplored.

Recently, serum exosome miRNAs have increasingly gained recognition as potential biomarkers[20–22]. Exosomes, extracellular vesicles in the size range of ~30 to ~200 nm, are instrumental in intercellular communication under both physiological and pathological conditions[23]. Exosomes contain diverse constituents ranging from nucleic acids, lipids, proteins, and metabolites, with miRNAs emerging as indispensable cargo molecules[24]. Discovered as a group of small non-coding RNA approximately 22 nucleotides in length, miRNAs regulate gene expression by binding to target mRNAs and promoting their degradation and/or inhibiting translation[25,26]. Abounding literature has highlighted the pivotal roles of circulating exosome miRNAs in orchestrating communication between cells, tissues, and organs[27–29]. Importantly, in neurodegenerative disease research, several serum exosome miRNAs have been identified as promising biomarkers[30,31] and therapeutic targets[11,32,33]. Therefore, we propose exploring the association between serum exosome miRNA levels and demographic, clinical and neuroimaging characteristics could expand the landscape of biomarkers and drug candidates for PD.

Currently, available anti-parkinsonism medications are primarily symptomatic therapies, temporarily improving motor function and quality of life in PD patients[34,35]. Nonetheless, early-start treatment with rasagiline, a monoamine oxidase B inhibitor, attenuated the decline of motor function and reduced the requirement for additional anti-parkinsonism medication in PD patients, suggesting potential neuroprotective effects[36–39]. Consequently, we hypothesised that investigating alteration in serum exosome miRNA transcriptome induced by rasagiline treatment could provide a unique opportunity to highlight the paramount pathogenetic factors in PD.

In this comprehensive study, we present our multi-year accumulation of serum exosome miRNA transcriptome data from four independent cohorts of Japanese participants[40–44]. Our dataset comprises two sections: two cohort studies of serum exosome miRNA profiles from 96 PD patients and 80 age- and gender-matched controls (PD/Control cohorts), and two cohort studies investigating changes in the serum exosome miRNA transcriptome from 96 PD patients before and after one year of rasagiline treatment (rasagiline cohorts). (Fig. 1) Anonymised demographic, clinical and neuro-imaging measures are also included for PD patients who participated in the PD/Control cohorts. To the best of the authors' knowledge, our collection represents the first comprehensive dataset providing multi-layer information for understanding the association between demographical, clinical and neuro-imaging parameters and serum exosome miRNA transcriptome in PD patients. We believe our dataset will contribute to open science and precision medicine by providing a valuable resource for identifying potential biomarkers and promising therapeutic targets for PD.

Methods

Ethics statement. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Juntendo University (approval number M08-0477). The research protocol adhered to the Ethical Guidelines for Medical and Health Research Involving Human Subjects and complied with the Declaration of Helsinki.

Participants. As in our previous clinical researches[8,45–47], participants with PD were recruited from patients seeking anti-parkinsonian medication at the Department of Neurology, Juntendo University Hospital. The control groups were recruited through poster advertisements and included spouses of patients, outpatients seeking hypertension or dyslipidaemia treatment, and voluntary hospital/laboratory staff.

Informed consent was obtained as outlined in our recent cohorts[48–50]. Potential participants received detailed information from attending physicians regarding study goals, enrolment and withdrawal, sample collection and management, data sharing, and personal information protection policies. Enrolled participants were fully aware that their anonymised genomic data might be stored in public databases and accessed by third parties. All individuals included in this dataset provided written informed consent for sharing anonymised genomic data. Each participant was assigned a unique identifier to maintain anonymity, preserving key demographic details (age, sex) for analysis while excluding directly identifiable information (name, date of birth, medical record number).

PD patients were diagnosed by board-certified neurologists, in accordance with the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease[1]. For practical and ethical reasons, Hoehn and Yahr's (H&Y) stages and Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) scores were measured during the "on" phase. The control group were free of any neurodegenerative disorders during the enrolment periods. The demographic characteristics of the enrolled PD patients are summarised in Table 1.

Serum exosome miRNA extraction. Serum sample collection[51] and exosome miRNA extraction[8] were conducted as previously described. Serum samples were collected from participants at the outpatient department of Juntendo University Hospital. Upon collection, the serum samples were immediately stored at −80 °C until use. For the extraction of serum exosome miRNA, the Total Exosome RNA and Protein Isolation Kit (Thermo Fisher Scientific, Waltham, MA) was applied, following the manufacturer's instructions.

Small RNA library preparation and sequencing. As described in our previous work[8], staff at Thermo Fisher Scientific constructed, aligned and mapped small RNA libraries. The small RNA libraries were prepared with the Ion Total RNA-Seq Kit version 2 on the Ion PGM System (Thermo Fisher Scientific, Waltham, MA). Quality control of the generated small RNA library was carried out using the Agilent High Sensitivity DNA kit on the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). Generated sequencing data was then aligned and mapped to miRBase[52] using the Bowtie2[53] package.

^{123}I-metaiodobenzylguanidine scintigraphy. We slightly modified ^{123}I-Metaiodobenzylguanidine Scintigraphy (MIBG) procedures from our previous studies[8,54,55]. Participants received an intravenous injection of iodine-123 metaiodobenzylguanidine (MyoMIBG-I 123 injection, 111 MBq; FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan). Scintigraphic images were acquired using E CAM 30 minutes (early) and 3 hours (delayed)

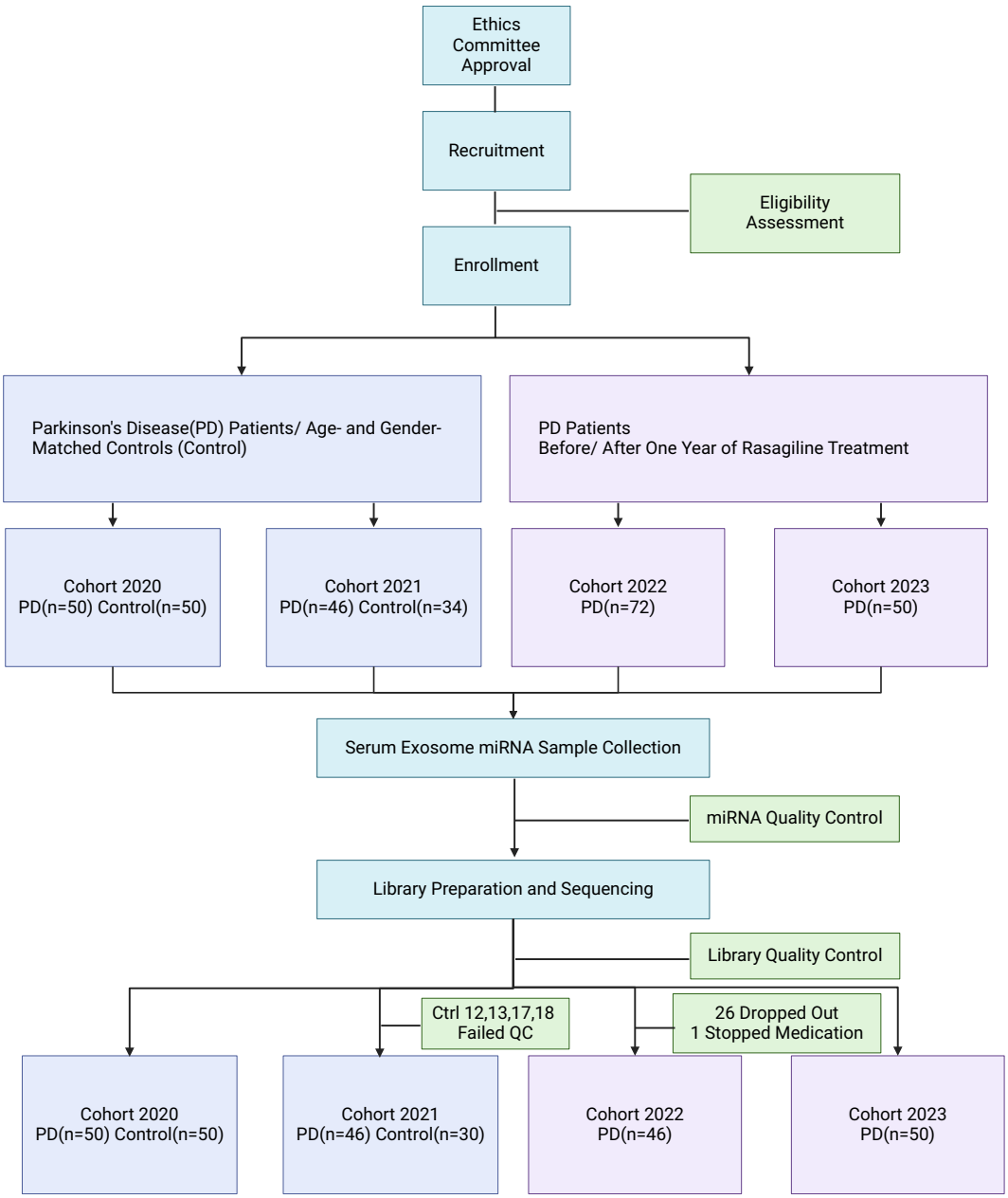

Fig. 1 Comprehensive diagram illustrating the key stages of the study. The numbers of participants enrolled, excluded, and ultimately included in the data analysis are indicated in the brackets.

	2020	2021	2022	2023
Male Gender (male/all)	24/46 (52%)	50/50 (100%)	27/46 (59%)	23/50 (46%)
Age (Mean(Sd))	66.39(7.94)	64.18(10.73)	65.40(8.68)	61.98(8.95)
H&Y stages (Mean(Sd))	1.51(0.60)	1.52(0.57)	1.59(0.61)	1.60(0.61)
UPDRS-III (Mean(Sd))	15.21(8.16)	18.23(11.37)	15.41(8.82)	15.84(8.46)

Table 1. Summary of demographic characteristics of PD patients whose samples were included for final analysis. UPDRS-III: Unified Parkinson's Disease Rating Scale Part III: Motor Examination; H&Y stages: Hoehn and Yahr stages.

after injection. Representative areas of the heart, thyroid, and mediastinum were semi-automatically positioned and measured using smartMIBG software (FUJIFILM Toyama Chemical Co., Ltd.). H/M and T/M ratios were calculated using the following formulas: H/M ratio = (mean count of the heart uptake)/(mean count of the mediastinum uptake), T/M ratio = (mean count of the thyroid uptake)/(mean count of the mediastinum uptake).

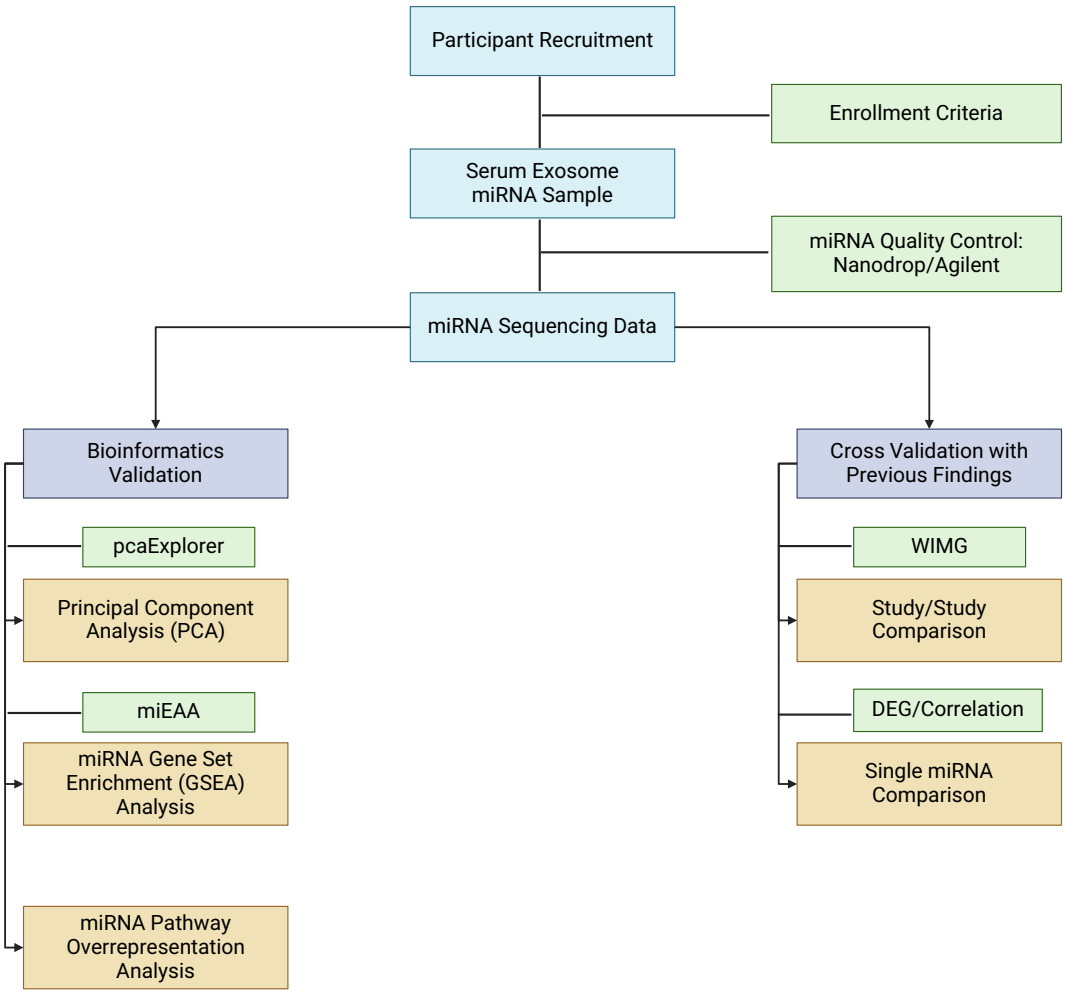

Fig. 2 General overview of the workflow for technical validation.

Dopamine transporter single-photon emission computed tomography. Dopamine Transporter Single-Photon Emission Computed Tomography (DAT-SPECT) imaging was conducted as in our previous reports[56,57]. Three hours after receiving 185 MBq of ^{123}I-FP-CIT injection, projection data were obtained in a 128 × 128 matrix on a Siemens Symbia T16 mounted with low- to medium-energy general-purpose collimators (Siemens, Munich, Germany) for 28 minutes. Data were reconstructed using the ordered subset expectation maximisation method (iteration 8 and subset 6) with Flash 3D software. Based on Bolt's method, specific Binding Ratio (SBR) values were semi-quantitatively calculated using DAT VIEW software (Nihon Medi-Physics, Tokyo, Japan). SBR was calculated as the mean value of right and left SBRs.

Data Records

The miRNA sequencing data are deposited as Superseries in the Gene Expression Omnibus (GEO) repository under the accession number GSE269781[40].

The raw sequencing fatsq and generated miRNA count matrix xlxs files are organised according to the year in which each cohort was conducted. miRNA transcriptomic data from PD patients and healthy individuals are stored in Subseries GSE269775[41] (2020 cohort) and GSE 269776[42] (2021 cohort), while data from PD patients before and after rasagiline treatment were saved in GSE269777[43] (2022 cohort) and GSE269779[44] (2023 cohort).

miRNA transcriptome data of participants deemed unsuitable for downstream analysis were retained for data integrity. Detailed nomenclature, usage and data structure for the data repository are provided in Supplementary Table 1.

Technical Validation

Quality control for biological samples was accomplished during participant enrolment and serum exosome miRNA purification. The quality of the generated miRNA transcriptomic data was further examined with bioinformatics analysis and cross-validation with findings from other groups (Fig. 2).

Participant enrolment and follow-up. The initial diagnosis of Parkinson's disease was made by a team of board-certified neurologists at Juntendo University Hospital, according to the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease[1]. PD Patients with concurrent cognitive impairment (Mini-Mental

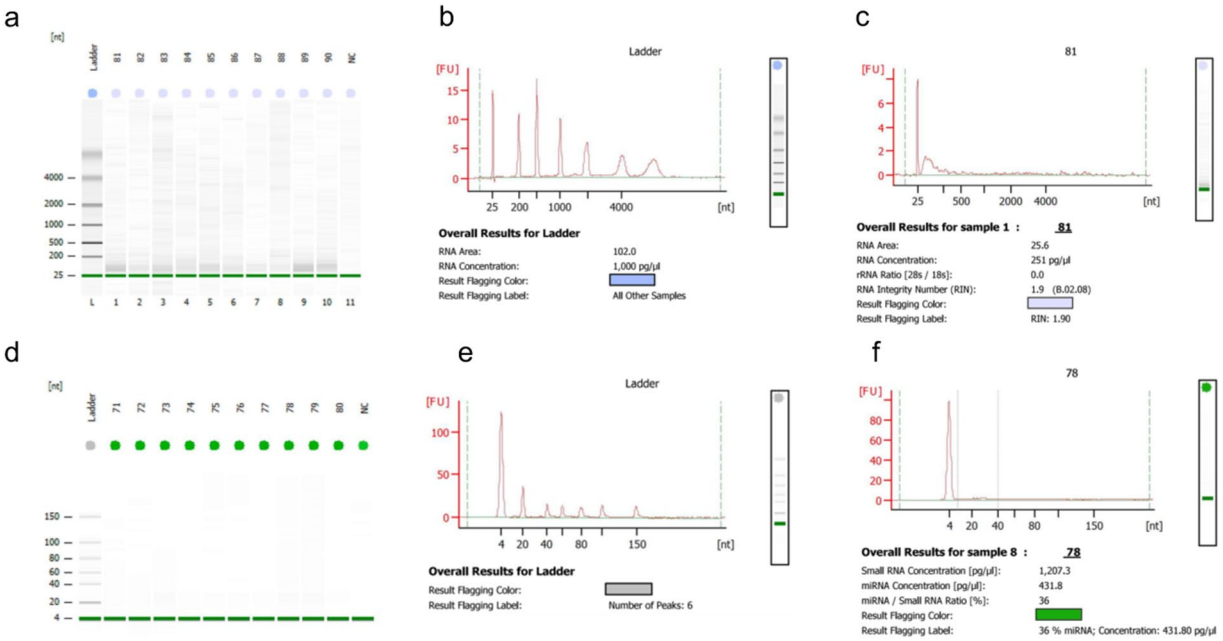

Fig. 3 Representative results of quality control results of serum exosome miRNA samples. (**a**) Gel-like image and electropherograms for (**b**) RNA ladders and (**c**) typical samples using the Agilent Total RNA 6000 Pico Kit. (**d**) Gel-like image and electropherograms for (**e**) miRNA ladders and (**f**) representative samples generated using the Agilent Small RNA Kit.

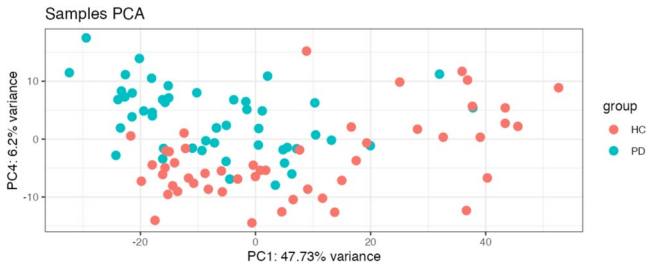

Fig. 4 A principal component analysis (PCA) plot of serum exosome miRNA profiles of the 2020 cohort, with red dots representing healthy controls and green dots representing PD patients.

State Examination (MMSE) score $< = 24$) were excluded to avoid possible overlap between PD and dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). All participants, including PD patients and control, had no self-reported history of cancer, aspiration pneumonia, gastrointestinal diseases, or collagen vascular diseases. During the period of sample collection, potential participants undergoing acute infectious disease or acute/chronic liver or renal dysfunction, as indicated by conventional blood chemistry test results, were also excluded.

Quality control of serum exosome miRNA samples. The successful extraction of serum exosome miRNAs was evaluated using the Nanodrop One Kit (Thermo Fisher Scientific, Waltham, MA). The amount of total RNA and miRNA were further validated by utilising Agilent Total RNA 6000 Pico Kit and Agilent Small RNA Kit on Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). Representative electropherogram results for the miRNA quality control are shown in Fig. 3. A summary of the quantitative results available from the miRNA quality control is provided in Supplementary Table 2.

The robustness and efficiency of our protocol and quality control were validated in our previous studies[58]. Using the 2020 cohort, we conducted concurrent research utilizing sebum RNA from the same patient and control groups as the miRNA study. Machine learning algorithms efficiently distinguished RNA in skin surface lipids (SSL-RNAs) profiles in PD patients from controls with an area under the curve of 0.806.

Bioinformatics validation. Principal component analysis (PCA) reduces high-dimensional data to its approximation on a two-dimensional plane constructed with major components, while preserving covariance[59]. The method provides an unbiased visualisation of the naturally occurring congregation of miRNA expression profiles[60]. Using the pcaExplorer[61] package, we showed the serum exosome miRNA profiles of PD patients and healthy individuals in the 2020 cohort clustered into two groups, highlighting the global effect of PD on serum exosome miRNA expression (Fig. 4).

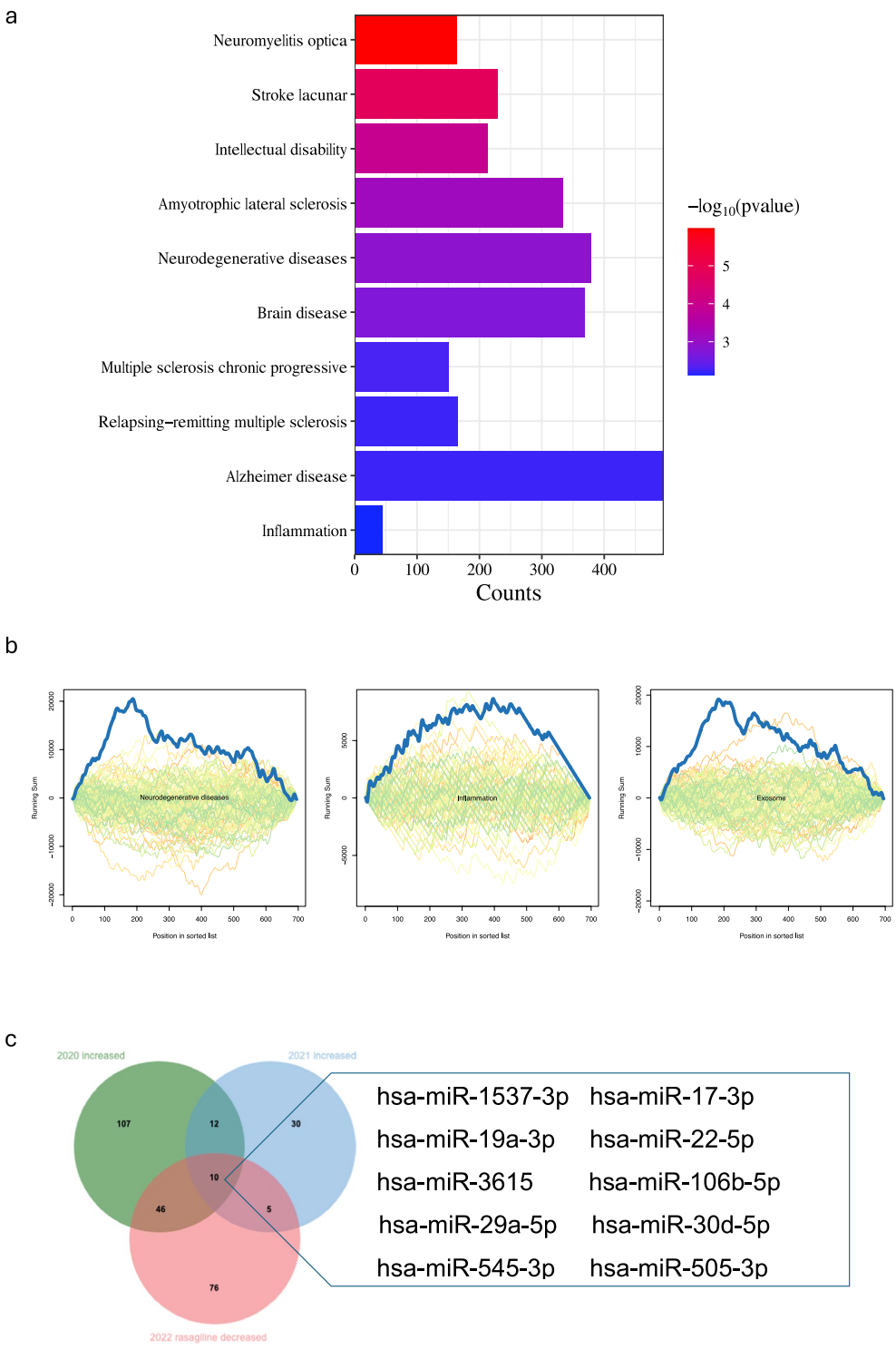

Fig. 5 (**a**). Visualisation of representative diseases in which miRNAs upregulated in PD patients were significantly enriched. The x-axis indicates the count of upregulated miRNAs, while the colour of columns reflects the -log10-transformed p-values., transitioning from blue to red as the p-values decrease. (**b**) Representative diagrams of significantly enriched categories as identified by GSEA on miRNAs ranked by FC * -log10(padj) between PD and controls. Blue lines indicate the actual enrichment, whereas background lines simulate random enrichments of permutation experiments. (**c**) A Venn diagram showing the overlap of significantly increased miRNAs in the 2020 cohort (green), the 2021 cohort (blue), and those decreased following rasagiline treatment in the 2022 cohort (red).

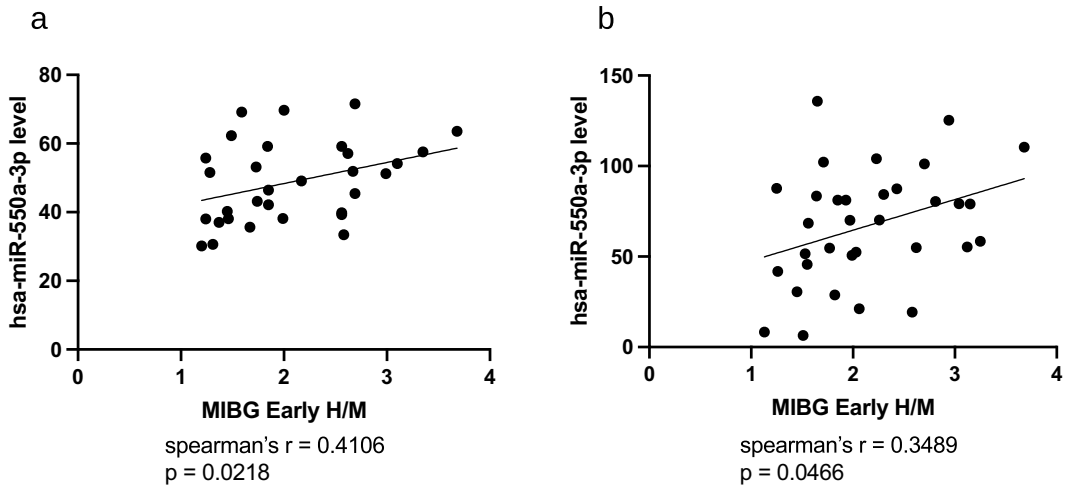

Fig. 6 (**a**,**b**) Dot plots showing the correlation between miR-550a-3p levels and MIBG heart/mediastinum ratio in the 2020 cohort (Fig. 5a, spearman's r = 0.4106, p = 0.0218) and the 2021 cohort (Fig. 5b, spearman's r = 0.3489, p = 0.0466).

miEAA[62] was widely used to investigate the systemic change in serum exosome miRNA profiles[63]. Leveraging miRNA gene set enrichment analysis[64] and gene overrepresentation analysis[65], significant enrichment was found in categories linked to brain disorders and inflammation (Fig. 5a, Supplementary Tables 3, 4). Of particular interest, these categories included "neurodegenerative diseases" (padj = 0.001) and "inflammation" (padj = 0.007), aligning with the neurodegenerative and neuroinflammatory nature of PD[66]. Also, the localisation of these upregulated miRNAs was significantly enriched in the term "exosome" (padj = 2.44×10^{-5}), further supporting the robustness of our experiment protocols (Fig. 5b).

Alignment with other groups' findings. Using a novel study/study comparison database[67] developed by Makjaroen J. *et al.*[68], serum exosome miRNAs increased in PD patients in our 2020 cohort significantly overlapped (padj = 0.0004) with miRNAs increased in CD4 + T-cells in PD patients[69], while downregulated miRNAs overlapped (padj = 3×10^{-11}) with miRNAs downregulated in the brain of Alzheimer's disease patients[70]. The consistency suggested our serum exosome miRNA dataset reliably reflected systemic changes in miRNA profiles in PD.

At the individual miRNA level, inspection of miRNAs significantly increased in PD patients within the 2020 and the 2021 cohorts, but decreased following rasagiline treatment in the 2022 cohort, identified ten candidate miRNAs (Fig. 5c). Among these, miR-22-5p[30] and miR-106b-5p[71] have been previously reported to be increased in PD. Additionally, miR-550a-3p levels were consistently positively associated with the heart/mediastinum ratio in PD patients (2020: spearman's r = 0.4106, p = 0.0218; 2021: spearman's r = 0. 3489, p = 0. 0466, Fig. 6a,b). This association aligned with its potential role in polyneuropathy in previous reports[72]. The congruency between our study and precedent research further consolidated the quality and credibility of the dataset.

Code availability

The code for differential miRNA expression is publicly available on GitHub (https://github.com/SSaikiLab/SciData). The analysis was performed on R (version: 4.2.2). The details for open-source R-based and web-based analysis were provided in Technical Validation.

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Author contributions

Shinji Saiki and Nobutaka Hattori were responsible for the concept and design of the study. Zhiyang Yu was responsible for data management, processing, and analysis and wrote the paper. Tetsushi Kataura aided in the analyses and revision of the manuscript. Kenta Shiina, Tatou Iseki, Kei-Ichi Ishikawa, Noriko Nishikawa, Wataru Sako, Genko Oyama and Taku Hatano facilitated the establishment of the study cohorts, managed participants and collected blood samples. Yukiko Sasazawa, Ayami Suzuki, and Sanae Soma designed and performed serum exosome miRNA extraction and purification procedures. All authors read and commented on drafts of the manuscript and approved the final submitted manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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