

## Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

### Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement
- A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- The statistical test(s) used AND whether they are one- or two-sided  
*Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
- A description of all covariates tested
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g.  $F$ ,  $t$ ,  $r$ ) with confidence intervals, effect sizes, degrees of freedom and  $P$  value noted  
*Give  $P$  values as exact values whenever suitable.*
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen's  $d$ , Pearson's  $r$ ), indicating how they were calculated

*Our web collection on [statistics for biologists](#) contains articles on many of the points above.*

### Software and code

Policy information about [availability of computer code](#)

Data collection

Data analysis

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

### Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences  Behavioural & social sciences  Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

|                 |  |
|-----------------|--|
| Sample size     | <p>Post-hoc power calculation was performed after sample collection.<br/>t test power calculation on training cohort</p> <p>dn2PD = 72<br/>CTR = 59<br/>Effect size = 0.4956538<br/>sig.level = 0.05<br/>power = 0.8<br/>alternative = two.sided</p> |
| Data exclusions | No data have been excluded   |
| Replication     | A validation cohort with the same characteristics of training cohort have been collected to verify and validate results. However non all the observation made in the training cohort can be reproduced with the validation cohort                    |
| Randomization   | not relevant to our study  |
| Blinding        | not relevant to our study because it is not a clinical trial   |

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

- |                                     |   |
|-------------------------------------|---|
| n/a                                 | Involvement in the study  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                             |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines                  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms            |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Human research participants |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern           |

### Methods

- |                                     |   |
|-------------------------------------|---|
| n/a                                 | Involvement in the study                        |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Human research participants

Policy information about [studies involving human research participants](#)

|                            |  |
|----------------------------|--|
| Population characteristics | <p>The study population consists of a total of 329 German subjects, including dn2PD patients, advPD patients, and healthy CTR. In detail, patient cohorts were: 1) a training cohort, consisting of 72 dn2PD (age =65.1, male =40) and 59 CTR (age =64, male =64.5), for a total of 131 subjects from the baseline visit of the Kassel cohort; 2) an independent validation cohort consisting of samples from 156 dn2PD (age= 65, male =83), 20 CTR (age=71.7, male =8) and 22 advPD (age = 68.9, male=15) patients, for a total of 198 subjects, as part of the cross-sectional Kassel cohort.</p>  |
| Recruitment                | <p>Patients enrolled in this study were clinically phenotyped before sample collection. Phenotyping included 1.5 Tesla magnetic resonance imaging (MRI) to determine structural abnormalities, quantitative levodopa testing, smell identification test (Sniffin' sticks, Burghardt Messtechnik GmbH, Wedel, Germany), Mini Mental Status Examination (MMSE) followed by further cognitive testing and video-supported polysomnography to determine REM sleep behaviour disorder in a subset of patients. The phenotyping was done based on these results and in accordance to established criteria for PD (UK Brain Bank Criteria), Multiple System Atrophy (MSA), Dementia with Lewy bodies (DLB), Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Alzheimer's disease and Frontotemporal Dementia (FTD). Subjects with marked vascular lesions in MRI indicative of a vascular comorbidity and subjects with normal pressure hydrocephalus by MRI were excluded.</p> |

## Ethics oversight

The study was conducted according to the Declaration of Helsinki and with informed written consent provided by all subjects. The study was approved by the ethics committee of the Physician's Board Hesse, Germany (Approval No. FF89/2008 for DeNoPa) and the University Medical Center Goettingen, Germany (Approval No. 9/7/04 and 36/7/02 for Kassel cohort).

Note that full information on the approval of the study protocol must also be provided in the manuscript.