

**International Congress of
Parkinson's Disease and
Movement Disorders®**



International Parkinson and
Movement Disorder Society

Late-Breaking Abstracts



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International Congress of Parkinson's Disease and Movement Disorders®

2026 Late-Breaking Abstracts

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J-Y. Lee, H-J. Kim, T-B. Ahn, J-M. Kim, J-W. Cho, D. Yoo, JH. Shin, R. Kim, B. Jeon, Y. Nam, S. Kim (Seoul, Korea)

LBA 2: Baseline characteristics of a Phase 3 double-blind, randomized trial of amlenetug for the treatment of multiple system atrophy

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Y. Zhang, M. Niu, Z. Zhu, J. Liu (Shanghai, People's Republic of China)

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J. Ferreira, HF. Fernandez, WP. Poewe, DKS. Simon, OR. Rascol, MAN. Nance, KK. Kiebertz, RC. Costa, RBM. Bouca-Machado, FP. Pereira, MF. Fonseca, JR. Reis, DR. Ramos, GC. Cordeiro, TF. Fonseca, FR. Rocha, AG. Guimarães, DM. Magalhães, JH. Holenz (Lisbon, Portugal)

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R. Llorens Arenas, A. Siderowf, A. Lang, M. Yang, O. Mabrouk, C. Paisan-Ruiz, B. Hersch, D. Jennings, S. Huntwork-Rodriguez, J. Kluss, R. Maciucă, P. Roychowdhury, S. Dhuria, P. Wang, K. Harrison, J. Goldman, G. Curiale, M. Wald, D. Graham, M. King, R. Hauser (Cambridge, MA, USA)

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Z. Yu (Beijing, People's Republic of China)

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R. Hauser, H. Sarva, A. Karbowniczek, C. Carroll, O. Rascol, S. Tisch, N. Brice, K. Kiebertz, A. Ellenbogen (Tampa, FL, USA)

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E. Eitan, I. Laquian, J. Connell, M. Thomsen (Natick, MA, USA)

LBA 24: α-Synuclein Strain Identity Links Air Pollution to Cognitive Decline in Lewy Body Diseases: From Environmental Driver to Prognostic Biomarker

X. Zhang, Z. Mao (Baltimore, MD, USA)

LBA 1: 72-Week Safety and Efficacy of GV1001 in Progressive Supranuclear Palsy: Phase 2a Open-Label Extension Results

J.-Y. Lee, H.-J. Kim, T.-B. Ahn, J.-M. Kim, J.-W. Cho, D. Yoo, J.H. Shin, R. Kim, B. Jeon, Y. Nam, S. Kim (Seoul, Korea)

Objective: To evaluate the safety and efficacy of GV1001 48-week open-label extension (OLE) trial following the 24-week double-blind phase 2a trial in participants with progressive supranuclear palsy (PSP).

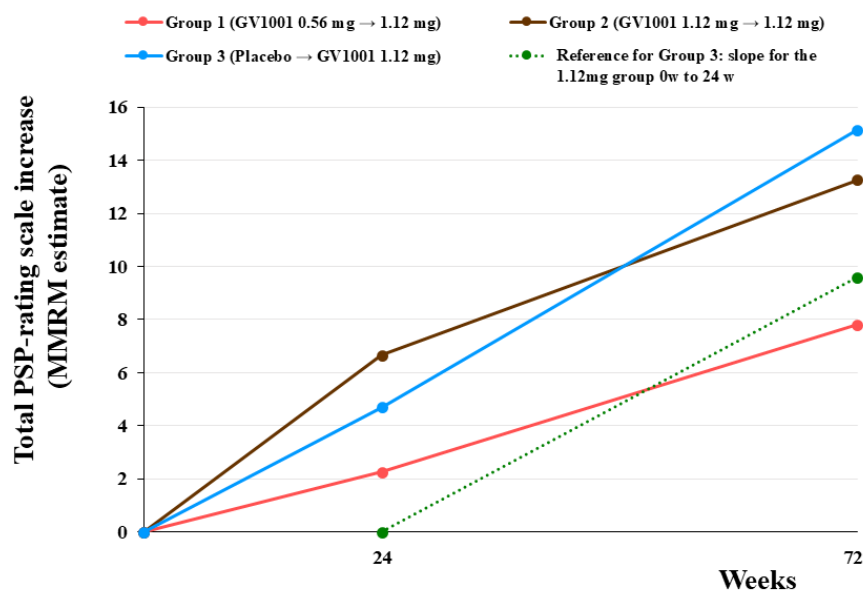
Background: GV1001, a synthetic hTERT-derived peptide with neuroinflammation-modulating activity, is being tested as a new drug for PSP.

Methods: 67 participants entered the OLE receiving GV1001 1.12 mg from Week 24 through Week 72; treatment-emergent adverse events (TEAEs) were monitored. Three groups defined by double-blind treatment assignment, Group 1 (GV1001 0.56 mg), Group 2 (GV1001 1.12 mg), and Group 3 (placebo), were subsequently received GV1001 1.12 mg in the OLE. The PSP-rating scale progression during the phase-2a (Weeks 0-24) and OLE period (Weeks 24-72) were estimated using a mixed-effects model for repeated measures (MMRM). Subgroup analysis was performed in participants dichotomized by baseline plasma NfL [1] into low-NfL and high-NfL subgroups. A matching-adjusted indirect comparison (MAIC) against placebo controls from three published PSP trials [2-4] was conducted to provide an external efficacy reference, weighted to match baseline PSPRS, age, and sex using established methodology [5,6].

Results: Among the 67 participants, 15 dropped out during the OLE phase. No new safety signals were identified through Week 72, with no drug-related serious adverse events. The three groups entered the OLE at Week 24 with different total PSPRS scores, reflecting treatment-group differences. Despite all groups subsequently receiving GV1001 1.12 mg throughout the OLE, PSP-rating scale trajectories continued to diverge, with Group 1 consistently demonstrating the most favorable course and Group 3 the least favorable, suggesting the potential disease modifying effect of early start of GV1001 0.56 mg. This trajectory divergence was particularly pronounced in the PSP-RS subgroup. The potential disease modifying effect was supported by the low-NfL group analysis. In the MAIC, Group 1 showed an adjusted mean PSP-rating scale change of 3.31 at Week 72 versus 10.66 in the external placebo controls at Week 52 ($p < 0.0001$), providing supportive evidence for sustained long-term treatment effects of GV1001 treatment.

Conclusion: GV1001 demonstrated a favorable 72-week safety profile. Consistent findings across period-specific trajectory, NfL-defined subgroup, and MAIC analyses support a potential disease-modifying effect of early GV1001 treatment. These results warrant large-scale phase 3 confirmatory trial of GV1001 0.56mg in PSP patients, particularly in PSP-RS subtype and early stage with low-NfL.

Figures:



- References:** [1] Boxer AL, et al. *Lancet Neurol.* 2014;13(7):676-685.
 [2] Dam T, et al. *Nat Med.* 2021;27(8):1451-1457.
 [3] Höglinger GU, et al. *Lancet Neurol.* 2021;20(3):182-192.
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 [5] Signorovitch JE. et al. *Value Health.* 2012;15(6):940-7.

LBA 2: Baseline characteristics of a Phase 3 double-blind, randomized trial of amlenetug for the treatment of multiple system atrophy

L. Kjærsgaard, M. Schiavon Krabbe, A-K. Berger, A. Rasmussen, M. Nørbæk Jørgensen, M. Folden Flensburg, B. Svanholm Fogh, K. Nighah, J. Wiedemann, J. Streffer, S. Zanigni, J. Luthman, G. Höglinger (Copenhagen, Denmark)

Objective: Describe baseline characteristics for the MASCOT Phase 3 trial of amlenetug for MSA.

Background: Amlenetug is a human IgG1 monoclonal antibody targeting aggregated α -synuclein to inhibit pathological seeding and propagation. Although the Phase 2 trial (Kjærsgaard et al., *Lancet Neurol* 2026) did not meet its primary endpoint, consistent clinical and biomarker findings alongside a favorable safety profile supported advancement to a similarly designed Phase 3 study.

Methods: MASCOT (NCT06706622) is a randomized, placebo-controlled Phase 3 trial evaluating amlenetug vs placebo, administered by intravenous infusion every four weeks, with a 72-week double-blind period and optional open-label extension. Eligible participants are aged 40-75 years with clinically probable or established MSA, within five years of motor symptom onset, and with

UMSARS Part I (omitting item 11) ≤ 16 at screening. The joint primary endpoint is the modified UMSARS Part I (items are scored 0-3 after collapsing categories 0 and 1; item 11 omitted) and time-to-death in North America and other regions, and UMSARS total score and time-to-death in the EU and Japan, analyzed using a Bayesian joint model of functional decline and survival.

Results: Between 03 Dec 2024 and 30 Jan 2026, 525 patients were screened, of whom 401 were randomized and 400 were treated; one withdrew pretreatment. The cohort was 54.8% male, with 61% MSA-C and 39% MSA-P, 38% clinically probable and 62% established MSA, and 88% showing supportive MRI findings. Mean $\pm$ SD age was 60.9 $\pm$ 7.2 years, with mean time since symptom onset of 3.2 $\pm$ 1.2 years and time since diagnosis of 1.2 $\pm$ 1.0 years. The population reflects a broad spectrum of MSA patients, with mean $\pm$ SD mUMSARS Part I score of 4.8 $\pm$ 2.7, total UMSARS score of 33.9 $\pm$ 8.3, UMSARS Part I score of 15.6 $\pm$ 4.4, UMSARS Part II score of 18.3 $\pm$ 5.4. Based on clinical global impression (n=396, n=4 missing), 41.3% were mildly, 54.3% moderately, and 3.5% severely impaired; 71% were receiving concomitant treatment for MSA, including 54.5% for parkinsonian symptoms and 42.8% for autonomic dysfunction.

Conclusion: Participant characteristics are consistent with the Phase 2 trial. MASCOT is the first prospective Phase 3 study of amlenetug vs placebo aimed at slowing clinical progression in MSA, with results expected in Q3 2027.

References: Kjærsgaard L, Wiedemann J, Singer W et al. Safety and efficacy of the anti- α -synuclein monoclonal antibody amlenetug for the treatment of patients with multiple system atrophy (AMULET): a phase 2, randomised, double-blind, multicentre trial. *Lancet Neurol*, 2026; 25, 560-570.

LBA 3: First South Asian Genome-Wide Association Study of Progressive Supranuclear Palsy Identifies Novel Neuroimmune, Endosomal, and Mito-Nuclear Risk Loci

R. Menon, VL. Ramprasad, RM. Kandadai, SD. Desai, S. Mehta, PM. Wadia, J. Ganguly, D. Joshi, D. Garg, V. Paramanandam, L. Sahoo, TAV. Reddy, A. Mukherjee, S. Krishnan, K. Shetty, C. Sankhla, P. Agarwal, HS. Shah, S. Bowmick, M. Chandarana, D. Elangovan, Al. Khan, S. Kola, T. Syed, M. Venkat, TS. Geetha, S. Charugulla, S. Murugan, R. Gupta, N. Kumar, A. Biswas, H. Kumar, R. Borgohain, C. Blauwendraat, A. Singleton, H. Morris, PL. Kukkle (Bangalore, India)

Objective: To define the common-variant genetic architecture of PSP in a deeply phenotyped South Asian cohort from the Indian PAIR-PSP consortium.

Background: Progressive supranuclear palsy (PSP) is a primary 4-repeat tauopathy in which genetic discovery has been driven almost entirely by European-ancestry cohorts, repeatedly implicating MAPT, MOBP, STX6, EIF2AK3, SLCO1A2, RUNX2, C4A/NFASC-related glial and immune pathways. South Asians, however, represent one of the world's largest genetically diverse populations and remain absent from hypothesis-free PSP GWAS.

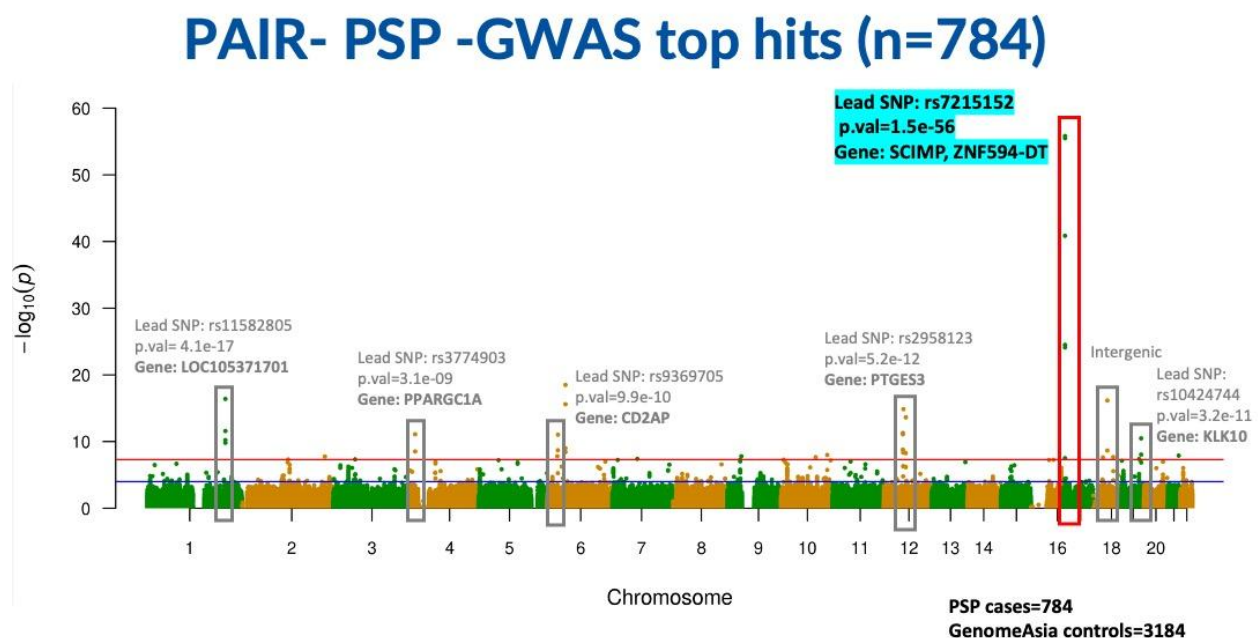
Methods: We performed a genome-wide association study in 784 Indian PSP cases fulfilling MDS-PSP criteria, and 3,184 genetically matched South Asian controls from GenomeAsia. Cases were genotyped on the Illumina Neurobooster Array v1.0 across 14 batches. Multi-stage quality control included call-rate filtering, inferred gender matching, heterozygosity rate filtering,

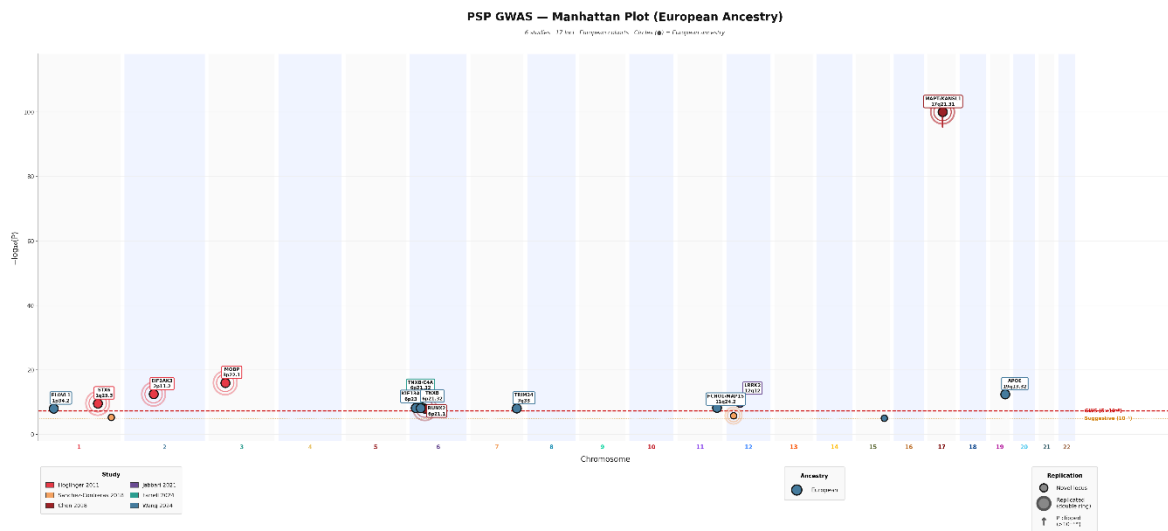
relatedness exclusion, batch-effect QC, PCA/UMAP based South Asian ancestry characterization. Additive model logistic regression was used for association testing with age, gender and top PCs as covariates using PLINK2 tool. Mitochondrial haplogroups were predicted in cases.

Results: Six independent genome-wide significant loci were identified: rs7215152 at SCIMP/ZNF594-DT ($p=1.5\times 10^{-56}$), rs11582805 at LOC105371701 ($p=4.1\times 10^{-17}$), rs2958123 at PTGES3 ($p=5.2\times 10^{-12}$), rs10424744 at KLK10 ($p=3.2\times 10^{-11}$), rs9369705 at CD2AP ($p=9.9\times 10^{-10}$), and rs3774903 at PPARGC1A ($p=3.1\times 10^{-9}$). (Fig-1) These loci did not recapitulate the European lead-risk architecture, suggesting population-specific discovery rather than simple trans-ethnic replication. (Fig-2) The dominant SCIMP/ZNF594-DT signal nominates an immune/lncRNA regulatory axis; PTGES3 supports prostaglandin-mediated inflammatory biology; CD2AP provides a potential PSP–Alzheimer’s cross-tauopathy link through synaptic/endosomal scaffolding; and PPARGC1A, together with high M-clade mitochondrial haplogroup frequency among cases, suggests mito-nuclear vulnerability. (Fig-3)

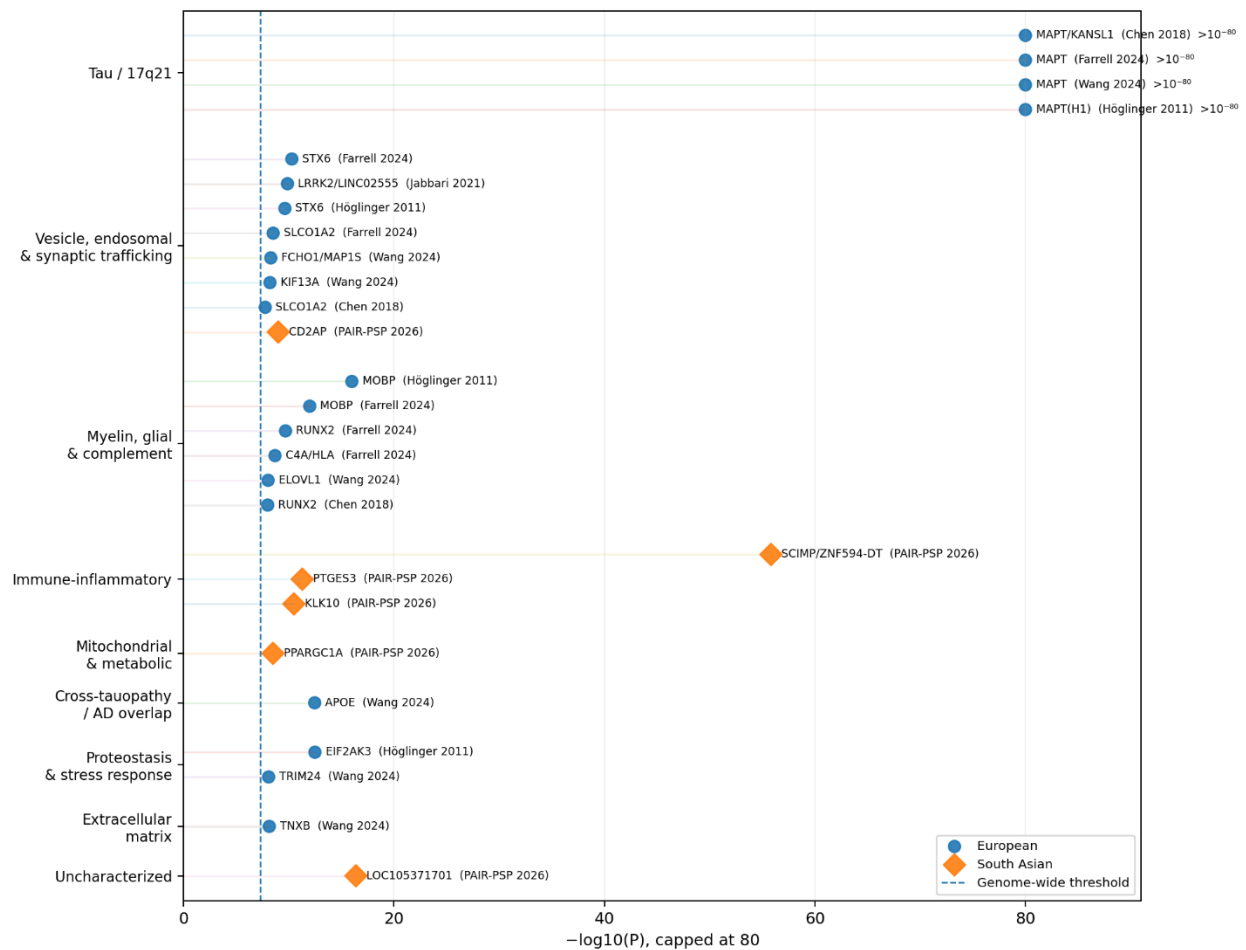
Conclusion: This first South Asian PSP-GWAS identifies six novel genome-wide significant signals and expands PSP genetics beyond the MAPT-centered European framework. The results needs further validation, replication studies. The present findings nominate neuroimmune, endosomal-synaptic, prostaglandin-inflammatory, and mitochondrial pathways for replication, fine-mapping, and functional validation.

Figures:





Biological axes emerging from PSP genetic association studies
South Asian loci add immune-inflammatory and mitochondrial signals to the MAPT-centered landscape



References: Kukkle PL, Garg D, Ganguly J, Desai S, Kandadai RM, Mehta S, Wadia PM, Joshi D, Sahoo L, Paramanandam V, Reddy TAV, Mukherjee A, Krishnan S, Shetty K, Sankhla C, Agarwal

P, Shah HS, Bhowmick S, Chandarana M, Venkata M, Geetha TS, Menon R, Charugulla S, Murugan S, Gupta R, Kumar N, Biswas A, Kumar H, Borgohain R, Morris H, Ramprasad VL; Parkinson's Research Alliance of India (PRAI) and the Global Parkinson's Genetic Program (GP2). Progressive Supranuclear Palsy in India: Insights from a Large Multicenter Clinical Cohort (Project PAIR-PSP). *Mov Disord Clin Pract*. 2026 May 24. doi: 10.1002/mdc3.70672. Epub ahead of print. PMID: 42178271.

LBA 4: Long-Term Safety and Efficacy of Once-Daily Valbenazine in Huntington's Disease Chorea: Results From the 5-Year KINECT®-HD2 Study

R. Mehanna, E. Furr Stimming, E. Kayson, Z. Demir, J. Goldstein, S. Hinton, M. Schmolesky, S. Karpuram, O. Klepitskaya, G. Liang, F. Shi, H. Zhang, D. Haubenberger (Houston, TX, USA)

Objective: To evaluate long-term safety/tolerability of valbenazine (VBZ) and its maintenance of effect on Huntington's disease (HD) chorea in KINECT®-HD2 (K-HD2 [NCT04400331]), a 5-year open-label study.

Background: In KINECT®-HD (K-HD), a 12-week phase 3 clinical trial, HD chorea significantly improved with VBZ versus placebo [1]. To date, K-HD2 is the longest prospective evaluation of a vesicular monoamine transporter 2 (VMAT2) inhibitor for any condition.

Methods: K-HD participants (after K-HD study drug washout) and other eligible adults with HD chorea received VBZ ≤ 80 mg once-daily, per response/tolerability. Treatment-emergent adverse events (TEAEs) were monitored throughout the study. Follow-up was conducted 2 weeks after end of treatment or early discontinuation. VBZ effects on chorea severity were assessed using UHDRS® Total Maximal Chorea (TMC) score.

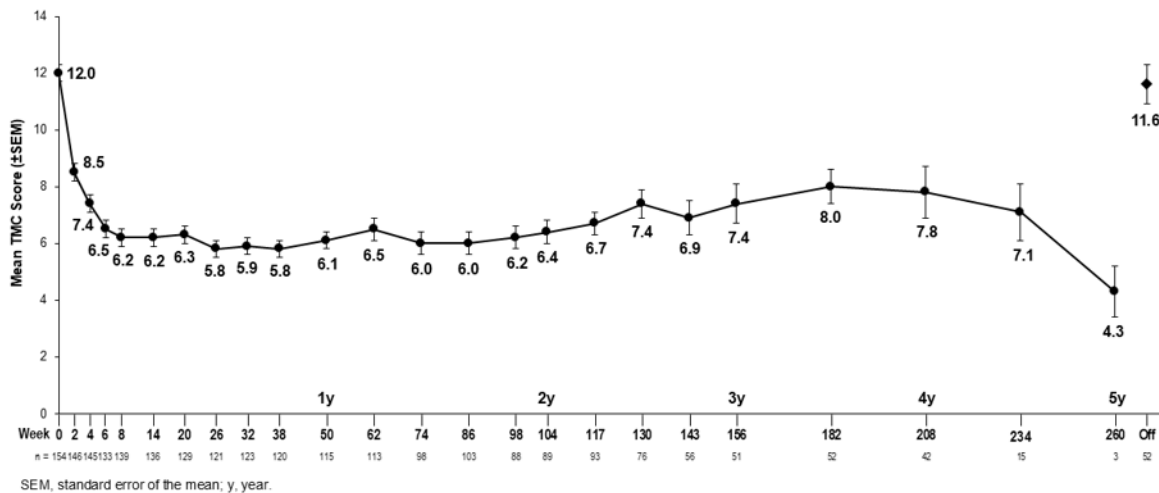
Results: Of 154 enrolled participants, 78 (50.6%) were female and 144 (93.5%) were White; mean age ($\pm$ SD) was 54.1 ± 11.5 years. The median duration of VBZ exposure was 980 days (range: 1 to 1803 days). TEAEs and serious TEAEs (SAEs) were reported in 151 (98.1%) and 38 (24.7%) participants, respectively. Three TEAEs were reported in $\geq 20\%$ of participants: fall (45.5%), somnolence (26.0%), and fatigue (21.4%). The only SAE reported in $\geq 2\%$ of participants was fall (3.2%). The majority of SAEs were judged as unrelated to treatment, and most were managed with medications and/or VBZ dose reduction. The figure presents mean TMC scores at baseline and by study visit. Mean TMC score changes from baseline ($\pm$ SEM) included: -5.7 ± 0.4 (Week 50); -5.1 ± 0.5 (Week 104); -3.5 ± 0.7 (Week 156); -3.4 ± 1.0 (Week 208); -7.3 ± 2.0 (Week 260); and -0.8 ± 0.6 (off-treatment).

Conclusion: Results from the K-HD2 study of VBZ reflect the longest prospective evaluation of treatment with a VMAT2 inhibitor for any condition. Observed TEAEs (including SAEs) were consistent with HD-related symptoms, e.g., fall, and/or TEAEs in previous clinical trials of VMAT2 inhibitors for HD chorea, e.g., somnolence, fatigue. Robust improvements in chorea were maintained long-term in participants with HD, including those who were treated for up to 5 years with once-daily VBZ. Chorea severity returned to baseline after VBZ discontinuation. These results complement the findings of the pivotal K-HD study, support the long-term safety/tolerability of VBZ, and demonstrate maintenance of effect on chorea in individuals with HD.

References: [1] Furr Stimming E, et al. Lancet Neurol. 2023;22:494-504.

Figures:

Figure: Mean Total Maximal Chorea (TMC) Score by Study Visit



LBA 5: Forecasting clinical progression in Huntington's disease from longitudinal deep speech representations

C. Le Moine Veillon, R. Massart, K. Youssov, P. Rémy (Créteil, France)

Objective: To test whether longitudinal deep representations learned from raw speech can forecast future clinical status and individual change in Huntington's disease (HD).

Background: HD progression is heterogeneous, making one-year worsening difficult to anticipate and complicating trial enrichment. Speech-prognosis studies in HD and related disorders have shown that predefined acoustic or language features can predict meaningful progression [1-3]. NDSNet, a previously developed raw-speech deep-learning model, moved beyond this paradigm and has shown strong value for monitoring motor, cognitive and functional status across HD stages [4]. Adapting NDSNet for prognosis is therefore a natural next step.

Methods: Longitudinal speech and clinical data from premanifest and manifest HD participants were analysed. Visit-wise NDSNet speech profiles were extracted from raw recordings and modelled over time as sequences with visit timing and core covariates to forecast future Unified Huntington's Disease Rating Scale (UHDRS) and cognitive outcomes. Evaluation used patient-level cross-validation.

Results: One-year forecasts were evaluated in 123 visits. The model accurately predicted future motor, functional and cognitive status across HD stages, with future-score intraclass correlation coefficients (ICCs) around 0.8 for Independence Scale and composite UHDRS, and 0.7-0.8 for cognitive measures. Prediction of individual one-year change, a stricter endpoint, was more challenging but informative for functional and cognitive outcomes: Total Functional Capacity

(ICC 0.31), Independence Scale (0.42), Stroop interference (0.33), Stroop colour (0.40) and verbal fluency (0.44).

Conclusion: Longitudinal deep modelling of raw speech captured prognostic information in HD, supporting scalable prognosis, patient stratification and trial enrichment.

References: [1] Puig-Davi A, Franch-Martí C, Caler-Gameiro L, et al. Spontaneous speech and language measures as predictive biomarkers of clinically meaningful disease progression and neurodegeneration in Huntington's disease. *Journal of Neural Transmission*. 2026. doi:10.1007/s00702-026-03143-x.

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[4] Le Moine Veillon C, et al. A deep learning model for speech-based prediction of clinical scores in people with Huntington's disease: a longitudinal study with cross-sectional replication. *The Lancet Digital Health*. In press.

LBA 6: Knowledge-grounded scoring of MDS-UPDRS finger tapping severity by large language models from video kinematics

S.C. Wang, T.E.M. Nordling (Tainan, Taiwan)

Objective: To test whether a pre-trained large language model (LLM), given kinematic features extracted directly from video together with the clinical scoring rubric, can use its clinical-literature knowledge to automatically score Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) finger tapping severity with agreement rivaling that of expert raters.

Background: Automated MDS-UPDRS motor scoring is dominated by task-specific vision and pose models; LLMs in Parkinson's disease are applied almost only to diagnosis, speech-based detection, or treatment. Only isolated studies use LLMs for motor severity, and these address gait; to our knowledge none scores finger tapping. Yet a pre-trained LLM already encodes clinical-literature knowledge; pairing it with compact, video-derived measurements offers a route to automated finger-tapping scoring.

Methods: From 53 finger-tapping videos (16 Parkinson's disease patients), kinematic features were constructed from trajectories extracted directly from video by CoTracker. A small subset of these features, together with the MDS-UPDRS item 3.4 scoring rubric, was given to a 32-billion-parameter open-source reasoning model, prompted zero- and few-shot to reason about the case and return a 0 to 4 severity score. The model thus combines the video-derived measurements with the clinical knowledge it acquired during pre-training. Scores were compared against the two-neurologist consensus and against each neurologist's agreement with that consensus.

Results: Prompted few-shot using four fixed reference cases (one each for grades 0 to 3), the model reached quadratic-weighted kappa (QWK) 0.65, mean absolute error (MAE) 0.52, and within-one-point accuracy 94 percent against the two-neurologist consensus. This falls within the range of the two neurologists' own agreement with the consensus (QWK 0.50 and 0.73), the practical human ceiling.

Conclusion: Combining measurements extracted directly from video with a knowledge-grounded, pre-trained language model offers a potential path to low-cost, deployable automated MDS-UPDRS finger tapping assessment. This holds even with an open-source LLM, without proprietary systems or raw-trajectory input. Grounding the model in the clinical literature appears central to this result.

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LBA 7: GCH1 genetic variation as a prognostic factor in Parkinson's disease across populations

JH. Shin, MT. Perinán, JW. Jang, L. Screven, LM. Lange, C. Klein, J. Shulman, Z. Gan-Or, M. Ghamgosar Shahkali, K. Senkevich, P. Dusek, I. Miliukhina, R. Alcalay, C-H. Lin, R-M. Wu, H. Morris, E-K. Tan, B-R. Zhang, G. Cogan, A. Brice, N. Mencacci, IJK. Sarmiento, T. Simuni, SB. Sassi, MJ. Martí, P. Pastor, YW. Tay, AH. Tan, S-Y. Lim, M. Stamelou, F. Chafota, M. Rentería, W. Mohamed, I. Mata, MC. Olivas, M. Cesarini, A. Rivera, M. Avenali, EM. Valente, TM. Foroud, K. Nudelman, M. Brumm. T. Gasser, R. Weil. C. Shepherd, KR. Kumar, R. Kruger, K. Marek, R. Kaiyrzhanov, S. Gentleman, J-S. Lee, H-J. Kim, B. Jeon (Seoul, Korea)

Objective: To characterize the genetic and clinical spectrum of GCH1-associated Parkinson's disease (PD), focusing on age at onset, disease progression, motor, and non-motor outcomes.

Background: Variants in GCH1 have been implicated in Parkinson's disease (PD); however, the pathogenic contribution and associated clinical trajectory remain incompletely defined.

Methods: Whole-genome sequencing (WGS) and clinical exome sequencing (CES) data from the Global Parkinson's Genetics Program (GP2) were analyzed together with unpublished and published GCH1-positive PD cases. Variant pathogenicity was classified according to ACMG criteria. Demographic, clinical, and longitudinal features were compared between GCH1 variant carriers and non-carrier PD cases; individuals with known pathogenic variants in PD-associated genes were excluded from both groups.

Results: In the GP2 cohort (PD, n = 22,825; controls, n = 4,453), 16 pathogenic or likely pathogenic (P/LP) GCH1 variants were identified in 58 individuals, including 54 PD cases, one control, and three individuals with other neurodegenerative phenotypes (two with progressive supranuclear palsy and one with dementia with Lewy bodies). In the pooled-ancestry WGS analysis, GCH1 P/LP variants were enriched in PD cases versus controls (0.267% vs 0.023%; OR=11.854; p=0.0006). Variant frequencies ranged from 0.121% to 0.714% across ancestries. In the CES cohort, P/LP variants were identified in 0.201% of PD cases. After integrating GP2 with additional unpublished and published datasets, 119 GCH1-positive PD cases were analyzed. Compared with non-carriers, GCH1 variant carriers had earlier disease onset (53.7 ± 14.8 vs 59.2 ± 11.7 years; p=8.99x10⁻⁵), lower levodopa equivalent daily dose requirements (467.5 ± 331.7 vs 680.3 ± 466.39 mg/day; p=4.21x10⁻⁸), and more frequent family history of PD (47.6% vs 19.9%; p=1.09x10⁻⁸). Adjusted Cox models showed significant delayed progression to motor fluctuations (HR=0.32, 95% CI=0.16-0.62) and levodopa-induced dyskinesias (HR=0.51, 95% CI=0.30-0.87).

Conclusion: GCH1 pathogenic variants are enriched in PD and define a clinically distinct subgroup with earlier disease onset and slower progression of motor complications. These findings suggests that GCH1 genetic variant may serve as a genetic biomarker for disease stratification and prognosis in PD.

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LBA 8: Genome-Wide Association Study of Idiopathic Parkinson's Disease Identifies Novel Loci in the Korean Population

WY. Lim, T. Kim, S-W. Yoo, J-S. Kim, YS. Hwang, SJ. Chung, S-M. Choi, J-H. Lee, MJ. Lee, SH. Moon, HK. Na, SJ. Chung, PH. Lee, YS. Cho, YJ. Kim (Chuncheon-si, Korea)

Objective: To identify genetic loci for idiopathic Parkinson's disease (IPD) in Koreans, test whether aggregate genetic burden is associated with age at onset, and replicate previous novel risk loci reported in East Asian.

Background: Although more than 90 IPD risk loci have been reported by genome-wide association studies (GWASs), most were identified in European-ancestry populations, limiting their generalizability to East Asians. Several East Asian-specific loci have been reported but await further replication.

Methods: We performed a two-stage GWAS using the Korean Biobank Array, optimized for Korean/East Asian ancestry with 1.66 million population-specific tagging SNPs. The discovery stage included 2,642 IPD cases from four Korean Parkinson's disease (PD) cohorts (30 sites) and 23,332 Korea Genome and Epidemiology Study (KoGES) controls. The replication stage included 1,246 IPD cases from one cohort (2 sites) and 23,333 KoGES controls. Stages were combined by meta-analysis and joint analysis of merged data. A weighted genetic risk score (GRS) was built from meta-GWAS lead SNPs and tested against age at onset.

Results: Meta-analysis identified 17 genome-wide significant signals: 11 at previously reported loci (8 genes: SNCA, SLC45A3/NUCKS1, MCCC1, TMEM175, LINC02471, SLC2A13, MMRN1, LRRK2 [G2385R, A419V]) and 6 novel (NEK4, SLC16A7, ACAD10, NAA25/TRAFF1, MFSD12, BCR). We confirmed two independent SNPs at the 5' (rs6532191) and 3' (rs74347922) ends of SNCA. Joint analysis yielded 10 SNPs at known loci (all overlapping meta-GWAS) and 12 at novel loci, 3 of which (NEK4, ACAD10, MFSD12) overlapped meta-GWAS. These genes have possible PD relevance: mitochondrial dynamics/respiration (NEK4), mitochondrial fatty-acid oxidation (ACAD10), and lysosomal homeostasis/glycosphingolipid metabolism (MFSD12), pending functional confirmation. None of the previously reported East Asian specific novel loci (WBSR17, SV2C, HEATR6, and ZNF322) reached genome-wide significance in Koreans. The GRS was associated with earlier age at onset in PD ($\beta = -0.426$; 95% CI -0.631 to -0.211; $P = 4.77 \times 10^{-5}$).

Conclusion: This Korean IPD GWAS identified 17 genome-wide significant signals, including six novel, and showed higher genetic burden was associated with earlier age at onset. These findings expand the genetic architecture of East Asian PD and support ancestry-specific polygenic risk score development for Koreans.

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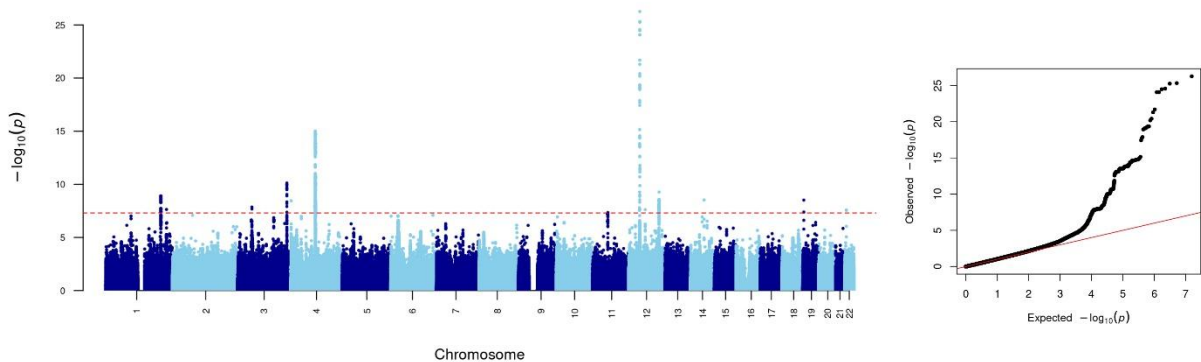
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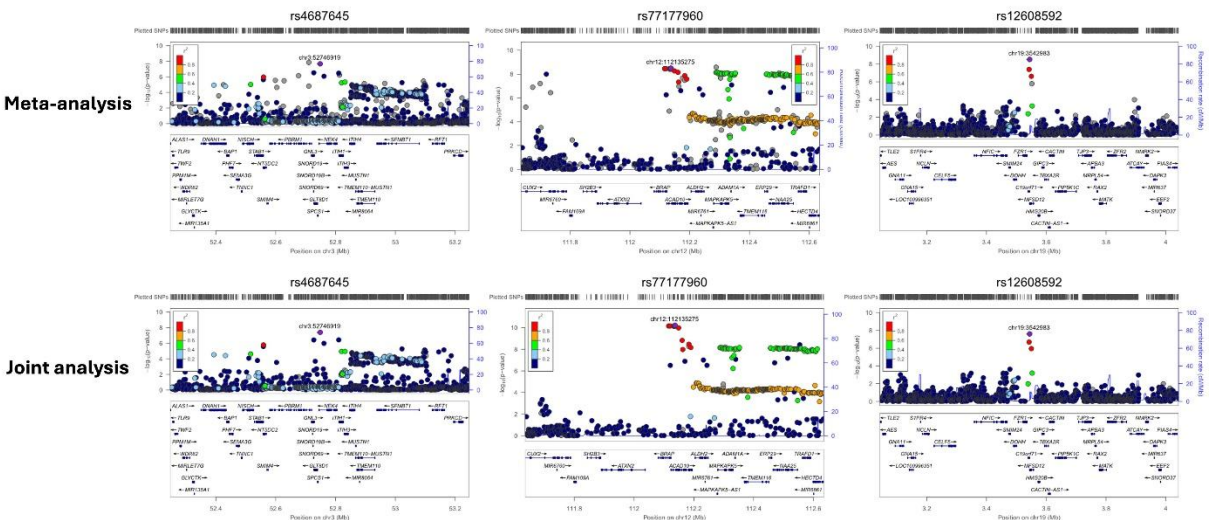
Figures:

Manhattan Plot and Q-Q Plot of Genome-Wide Meta-Analysis Results for Korean Parkinson's Disease



Manhattan plot displaying the association results across 22 autosomes. The x-axis represents the chromosomal position, and the y-axis indicates the negative logarithm of the P-value ($-\log_{10}(P)$). Each dot corresponds to a single-nucleotide polymorphism (SNP). The horizontal red line marks the conventional genome-wide significance threshold ($P < 5 \times 10^{-8}$). Quantile-Quantile (Q-Q) plot comparing the observed distribution of $-\log_{10}(P)$ -values (y-axis) against the expected distribution under the null hypothesis (x-axis). The diagonal red line represents the expected distribution. The upward deviation of the plotted SNPs at the tail end indicates the presence of significant association signals beyond what is expected by chance.

Regional plots of 3 novel SNPs overlapped between meta-GWAS and joint analysis



Regional association plots of three novel IPD-associated loci. Meta-analysis results are shown in the upper row and joint-analysis results in the lower row. From left to right, the plots show the NEK4, ACAD10, and MFSD12 loci, with lead SNPs rs4687645, rs77177960, and rs12608592, respectively. In each panel, the purple diamond (or circle) indicates the lead SNP with the lowest P-value. Surrounding SNPs are colored according to their linkage disequilibrium (r^2) with the lead SNP, based on the 1000 Genomes East Asian reference panel (red: $r^2 > 0.8$, orange: $0.6 < r^2 < 0.8$, green: $0.4 < r^2 < 0.6$, blue: $r^2 < 0.4$). The x-axis represents the chromosomal position (Mb), and the y-axis shows the association strength ($-\log_{10}(P)$). Gene annotations are provided in the bottom track.

LBA 9: Long-Term Safety and Effect of Ecopipam, a Selective Dopamine D1 Receptor Antagonist, in Children, Adolescents, and Adults with Tourette Syndrome

DL. Gilbert, KJ. Black, K. Kompoliti, PM. Rice, JA. Flatt, GB. Karkanas, SP. Wanasaki, TM. Cunniff, KK. Tomczak (Cincinnati, OH, USA)

Objective: To evaluate the long-term safety and effect of ecopipam, a selective dopamine D1 receptor antagonist in development for Tourette syndrome (TS).

Background: TS is a childhood-onset neurodevelopmental disorder, and pharmacologic intervention is recommended when behavioral therapy is unavailable, ineffective, or not preferred. In previous phase 2 and 3 trials in TS, ecopipam was well tolerated and induced a clinically meaningful reduction in tic severity for up to 12 months.

Methods: Individuals ≥ 6 years with TS who completed a previous ecopipam trial (phase 3 or phase 2b open-label extension [OLE]) and had tapered off ecopipam were enrolled in a 36-month OLE trial. Ecopipam was titrated to a target dose of 1.8 mg/kg/day. Study visits are being conducted monthly for 12 months and every 3 months thereafter. An interim analysis was conducted 27 months after study initiation.

Results: Of 120 enrolled participants, 118 received ≥ 1 ecopipam dose (69.5% male; 23.7% aged 6-11 years, 59.3% aged 12-17 years, and 16.9% aged ≥ 18 years). Median duration of ecopipam exposure was 14.9 months (range, 1.2-27.0 months), with 97 (82.2%) continuing treatment. At baseline (n=118), mean (SD) Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) was 28.1 (9.7). At Month 12 (n=88), mean (SD) change from OLE baseline in YGTSS-TTS was -12.0 (8.7; $P < 0.0001$), a 40.1% improvement, and Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) was -1.2 (1.1; $P < 0.0001$). At Month 18 (n=33), mean (SD) change from OLE baseline in YGTSS-TTS was -13.9 (9.3; $P < 0.0001$), a 45.6% improvement, and CGI-TS-S was -1.6 (1.2; $P < 0.0001$). The most commonly reported adverse events (AEs) were nasopharyngitis (16.1%), upper respiratory tract infection (12.7%), and anxiety (9.3%). Weight gain as an AE occurred in 4 (3.4%) participants, hyperprolactinemia in 1 (0.8%), and no drug-induced movement disorders were reported. Serious AEs (suicidal ideation, asthmatic crisis; both unrelated to ecopipam) were reported in 2 (1.7%) participants. Four (3.4%) participants discontinued due to an AE.

Conclusion: Ecopipam was well tolerated and maintained meaningful tic suppression during long-term treatment in children, adolescents, and adults with TS. The study is planned to continue for up to 36 months of participant exposure.

LBA 10: Association of Accelerometer-Derived Nocturnal Motor Signatures with α -Synuclein Status in Isolated REM Sleep Behavior Disorder and Early Parkinson's Disease

AJ. Campbell, M.H. Nilsson, M. Lindh-Rengifo, K.O. Hauer, TE. Anijärvi, S. Caldera, A. Ticca, P. Parchi, M. Sommerauer, R. Smith, S. Hall, S. Palmqvist, E. Stomrud, A. Nahimi, O. Hansson, N. Mattsson-Carlsson (Lund, Sweden)

Objective: To evaluate whether wrist-worn accelerometry during sleep correlates with rapid eye movement sleep behavior disorder (RBD) symptom burden and classifies cerebrospinal fluid

(CSF) α -synuclein (α -Syn) status in people with probable isolated RBD (iRBD), early Parkinson's disease (PD), and healthy controls (HCs).

Background: iRBD is a prodromal synucleinopathy currently diagnosed using video-polysomnography (v-PSG) [1]. Recent evidence suggests that accelerometers can capture nocturnal motor activity characteristic of RBD.

Methods: We included 64 participants from the Swedish BioFINDER Sleep Study (9 HCs, 24 early PD, 31 probable iRBD; 34 α -Syn+; age 67.2 ± 7.9 years; 67% men) with accelerometry, CSF α -Syn seed amplification assay (SAA) [2], and RBD Screening Questionnaire (RBDSQ) data. Participants wore wrist-worn accelerometers for approximately one week. After extracting global (whole night profile) and local (movement bout) nocturnal motor features [3], we assessed group differences (Mann-Whitney U, Rank-Biserial Correlation [RBC]) and clinical correlations (Spearman's ρ). Features associated with α -Syn status were selected via Least Absolute Shrinkage and Selection Operator (LASSO) and multivariable logistic regression, validated using Leave-One-Out Cross-Validation (LOOCV).

Results: Participants contributed an average of 7.2 ± 1.3 nights of sleep data. RBDSQ scores were higher in iRBD than PD ($p < .001$, $RBC = .703$) and HCs ($p < .001$, $RBC = .918$). In iRBD/PD combined, higher RBDSQ scores correlated with shorter median bout duration ($\rho = -.38$, $p = .004$) and increased peak frequency variability ($\rho = .37$, $p = .005$). Univariately, four of five motor features differentiated α -Syn SAA status (all $p \leq .001$). Specifically, α -Syn+ individuals exhibited higher global movement intensity distribution and bout spectral complexity variance ($RBC: -.669$ to $-.629$), alongside lower median duration and rhythmic consistency of bouts ($RBC: .561$ to $.602$). Logistic regression identified global movement intensity distribution ($p = .027$) and median bout duration ($p = .031$) as significant independent classifiers of α -Syn+, achieving an AUC of .899 (LOOCV AUC = .840).

Conclusion: Our findings suggest that accelerometer-derived nocturnal motor features scale with RBD symptom burden and assist in the classification of α -Syn status. Wrist-worn accelerometry shows potential as a scalable, non-invasive screening tool for identifying nocturnal motor disturbances associated with synucleinopathy.

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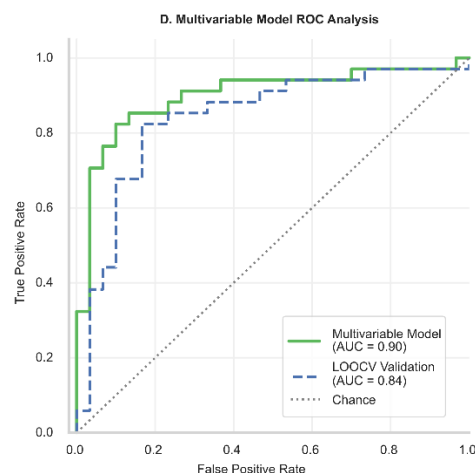
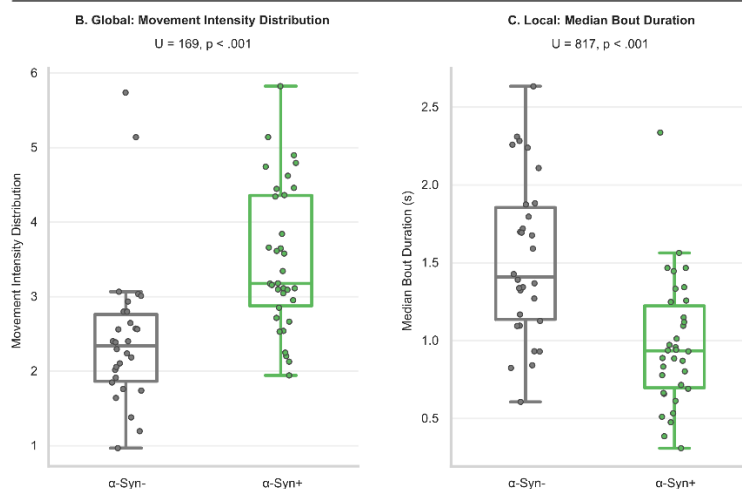
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Figures:

A. Differences in Motor Features (Probable IRBD/Early PD vs. HCs)

Feature	Feature Level & Description	P	RBC
Spectral complexity variance	Local: Variance of movement frequencies across bouts	.001	.673
Rhythmic consistency of movement	Local: Rhythmicity and temporal regularity of bouts	.008	-.556
Median bout duration	Local: Median time duration of movement bouts	.009	-.552
Movement intensity distribution	Global: Skewness of activity intensity across the night	.011	.531
Peak frequency variability	Local: Dispersion of peak frequencies within bouts	.051	.410



E. Multivariable Classifiers of α -Synuclein

Feature	OR	95% CI	p
Movement intensity distribution	2.61	1.11 – 6.14	.027
Median bout duration	0.39	0.16 – 0.92	.031
Spectral complexity variance	2.03	0.93 – 4.43	.075
Age	1.66	0.89 – 3.13	.114

Figure 1. Nocturnal motor features differentiate clinical cohorts and classify CSF α -synuclein status. (A) Cross-sectional comparison of motor features between probable IRBD/early PD and HCs (Mann-Whitney U). (B, C) Box-and-swarm plots of the top global and local features, stratified by α -synuclein positivity (Mann-Whitney U). (D) ROC curve of the multivariable logistic regression model classifying α -synuclein status. (E) Independent predictors of α -synuclein status from the multivariable logistic regression model. (α -Syn, α -synuclein; AUC, Area Under the Curve; CI, Confidence Interval; HCs, Healthy Controls; IRBD, Isolated Rapid Eye Movement Sleep Behavior Disorder; LOOCV, Leave-One-Out Cross-Validation; Odds Ratio; PD, Parkinson's Disease; RBC = Rank-Biserial Correlation; ROC = Receiver Operating Characteristic).

LBA 11: Reduced cancer risk after Parkinson's disease: disentangling bias from biology using FinnGen

RJ. Chu, M. Kaakinen, F. , M. Reeve, V. Kaasinen (Turku, Finland)

Objective: To clarify the direction and site-specificity of Parkinson's disease (PD)–cancer associations using complementary epidemiological and genetic approaches.

Background: Previous studies have reported reduced cancer incidence after PD [1,2], but whether this reflects methodological bias or shared biology remains unresolved.

Methods: FinnGen (DF13) is a nationwide biobank-based cohort integrating genomic and linked health registry data from 520,210 participants [3]. PD cases were identified using diagnostic codes or medication reimbursement records. Individuals diagnosed with cancer <5 years before follow-up were excluded. Cox proportional hazards models were used to analyze an age- and sex-matched (1:10) cohort. Sensitivity analyses included Fine-Gray competing-risk models accounting for mortality, exclusion of individuals diagnosed with cancer <2 years after follow-up, and smoking-adjusted models. Genetic analyses included linkage disequilibrium score regression (LDSC) [4], two-sample Mendelian randomization (MR) [5-9] and polygenic score (PGS) analyses [10].

Results: Individuals with PD (n=4,277; median age [IQR] 70 [14] years; 60% male) had a lower risk of subsequent overall cancer, with inverse associations observed for most cancer types except melanoma, brain and skin cancers (Table 1,2). Results remained broadly consistent across sensitivity analyses. MR provided evidence consistent with inverse causal effects of PD genetic liability on respiratory, gastrointestinal and skin cancers. Higher PD PGS was associated with

lower odds of respiratory, gastrointestinal, genitourinary and skin cancers, as well as higher odds of breast cancer. LDSC identified a significant positive genetic correlation between PD and melanoma and breast cancer.

Conclusion: PD was associated with a markedly reduced risk of subsequent cancer. Consistent findings across sensitivity analyses suggest that smoking, detection bias, and competing mortality are unlikely to fully explain this association. Genetic findings were largely concordant for respiratory and gastrointestinal cancers, whereas melanoma and breast cancer showed divergent epidemiological and genetic patterns, indicating biological heterogeneity rather than a single inverse-risk model. These findings provide new evidence for cancer site-specific shared genetic mechanisms contributing to the reduced cancer incidence observed after PD.

Figures:

Table 1: Cancer incidence; age at PD and subsequent cancer diagnosis, and their interval; number of cases and controls for genetic analyses.

Cancer		ICD-10	Epidemiology					Genetics	
			No. (%) individual with PD	No. (%) comparison person	Age at PD (years) ^c	Age at cancer (years) ^c	PD – cancer interval (years) ^c	Case	Control
Any cancer		C00–C96	565 (13.2)	8899 (20.8)	69.1 (12.5)	74.5 (10.4)	4.3 (6.5)	–	
Cancer categories	Respiratory	C32–C34	29 (0.7)	1142 (2.7)	71.2 (10.6)	75.3 (9.1)	3.9 (4.3)	11,353	387,990
	Gastrointestinal	C15–C25	107 (2.5)	1868 (4.4)	70.0 (11.5)	74.9 (9.3)	5.4 (7.4)	21,438	387,990
	Genitourinary	C61, C63–C68	167 (3.9)	2802 (6.6)	67.8 (11.6)	74.5 (9.6)	4.7 (6.8)	30,299	387,990
	Hematological	C81–C96	42 (1.0)	690 (1.6)	69.1 (13.0)	75.2 (10.6)	3.8 (6.2)	10,439	509,533
	Brain	C71	10 (0.2)	116 (0.3)	58.2 (24.6)	62.5 (16.1)	3.9 (9.7)	2,072	387,990
	Gynecological ^a	C51–C57	19 (1.1)	380 (2.2)	69.9 (11.4)	76.1 (6.9)	4.9 (7.3)	7,795	228,091
	Breast ^a	C50	60 (3.5)	934 (5.5)	65.2 (16.0)	71.2 (11.4)	5.5 (7.3)	26,009	228,091
	Skin	C43, C44	258 (6.0)	2972 (6.9)	70.6 (11.1)	75.9 (9.1)	4.2 (6.1)	37,785	387,990
Individual cancers	Melanoma	C43	32 (0.7)	410 (1.0)	68.6 (15.2)	74.3 (11.6)	4.0 (4.5)	6,381	387,990
	Lung	C34	27 (0.6)	1095 (2.6)	71.2 (11.0)	75.6 (9.3)	3.9 (4.4)	10,648	387,990
	Prostate ^b	C61	126 (4.9)	2081 (8.1)	66.8(10.7)	74.2(10.1)	4.7(7.1)	22,097	159,899

^a Women only

^b Men only

^c Median (IQR)

Table 2. Hazard ratios (HR) ^a for incident cancers after Parkinson's disease; genetic association ^a between PD and cancer.

Cancer	Epidemiological analyses				Genetic analyses		
	Cox analysis HR	2-years lag analysis	Fine-gray analysis	Adjusted for sex, age, smoking	LDSC: correlation (rg)	MR: causal effect (IVW OR)	PGS: association (OR)
Any cancer	0.66 [0.61,0.72]	0.62 [0.56,0.69]	0.59 [0.55,0.65]	0.69 [0.62,0.76]	-		
Respiratory	0.28 [0.19,0.40]	0.29 [0.19,0.44]	0.25 [0.17,0.36]	0.33 [0.22,0.50]	-0.034 (<i>P</i> = 0.682)	0.943 [0.900,0.985]	0.959 [0.940,0.979]
Gastrointestinal	0.62 [0.51,0.75]	0.60 [0.47,0.75]	0.56 [0.46,0.68]	0.59 [0.45,0.76]	-0.054 (<i>P</i> = 0.539)	0.966 [0.932,0.999]	0.974 [0.960,0.989]
Genitourinary	0.64 [0.55,0.74]	0.60 [0.50,0.72]	0.58 [0.50,0.68]	0.60 [0.50,0.74]	-0.021 (<i>P</i> = 0.789)	0.978 [0.942,1.013]	0.984 [0.970,0.998]
Hematological	0.66 [0.49,0.91]	0.63 [0.43,0.92]	0.60 [0.44,0.82]	0.71 [0.48,1.04]	-0.054 (<i>P</i> = 0.615)	0.978 [0.932,1.025]	0.992 [0.972,1.013]
Brain	0.95 [0.49,1.81]	0.90 [0.50,1.62]	0.85 [0.44,1.63]	0.84 [0.38,1.85]	-0.003 (<i>P</i> = 0.984)	1.021 [0.938,1.109]	1.019 [0.973,1.068]
Gynecological ^b	0.55 [0.35,0.87]	0.54 [0.31,0.93]	0.49 [0.31,0.78]	0.68 [0.37,1.25]	0.082 (<i>P</i> = 0.478)	0.991 [0.947,1.036]	1.005 [0.980,1.030]
Breast ^b	0.69 [0.53,0.90]	0.68 [0.50,0.92]	0.63 [0.49,0.82]	0.68 [0.49,0.93]	0.161 (<i>P</i> = 0.006)	1.027 [0.982,1.075]	1.016 [1.001,1.030]
Skin	0.94 [0.83,1.07]	0.95 [0.82,1.09]	0.86 [0.75,0.97]	1.01 [0.86,1.18]	0.064 (<i>P</i> = 0.254)	0.967 [0.943,0.991]	0.985 [0.973,0.997]
Melanoma	0.85 [0.60,1.22]	0.89 [0.59,1.33]	0.77 [0.54,1.10]	0.99 [0.63,1.55]	0.194 (<i>P</i> = 0.016)	1.009 [0.977,1.042]	0.978 [0.952,1.004]
Lung	0.27 [0.18,0.39]	0.29 [0.19,0.45]	0.24 [0.16,0.35]	0.32 [0.21,0.49]	-0.056 (<i>P</i> = 0.497)	0.953 [0.910,0.998]	0.960 [0.940,0.981]
Prostate ^c	0.65 [0.54,0.78]	0.63 [0.51,0.78]	0.58 [0.49,0.70]	0.61 [0.48,0.76]	0.029 (<i>P</i> = 0.684)	1.000 [0.968,1.033]	0.988 [0.972,1.004]

^a HRs, ORs and rg in bold are statistically significant (*P* < 0.05)

^b Women only

^c Men only

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LBA 12: Shared LRRK2 pathway activation in sporadic and LRRK2-associated Parkinson's disease defined by cerebrospinal fluid biomarkers

E. Jabbari, C. Paisan-Ruiz, K. Ferber, J. Frost, D. Vaughan, R. Real, R. Fumi, M. Theilmann, E. Stafford, L. Wu, GP2, O. Ansorge, A. Quaegebeur, K. Allinson, T. Warner, Z. Jaunmuktane, A. Misbahuddin, B. Ghosh, K. Bhatia, A. Church, C. Kobylecki, M. Hu, J. Rowe, A. Shomo, D. Graham, T. Foltynie, H. Morris, O. Mabrouk (London, United Kingdom)

Objective: To assess the role of LRRK2 pathway activation, defined by novel cerebrospinal fluid (CSF) biomarkers, in sporadic Parkinson's disease (PD) and LRRK2-associated PD.

Background: Common variants in the LRRK2 gene have been associated with sporadic PD, and approximately 5% of familial PD is due to rare pathogenic LRRK2 variants (LRRK2-PD) (1). Furthermore, there are active clinical trials of LRRK2-targeting therapies in sporadic PD and LRRK2-PD patients (2). Pathogenic LRRK2 variants are known to increase LRRK2 kinase activity, and phospho-Rab10 (pRab10) has been used as a marker of LRRK2 kinase activity (3). However, increased levels of pRab10 have not been detectable in established translational blood-based assays in sporadic PD or the commonest LRRK2 mutation associated with PD, G2019S, compared with age-matched controls (4).

Methods: We have applied a novel SISCAPA-based assay for measuring total LRRK2 and pRab10 levels in CSF samples from two independent cohorts of PD participants: Parkinson's Progression Markers Initiative (PPMI) cohort, n=379 (baseline and V06 (2 years post-baseline) samples) – Sporadic PD n=112, LRRK2-PD n=67, Prodromal-LRRK2 n=80, Healthy Controls n=120; UCL Parkinsonism cohort, n=117 (baseline samples) – Sporadic PD n=57, Progressive Supranuclear Palsy n=51, Healthy Controls n=9. Furthermore, in the PPMI cohort we have assessed the relationship between our CSF biomarkers of the LRRK2 pathway and: a) common LRRK2 genetic variants; b) CSF alpha-synuclein seed amplification assay (SAA) status; c) clinical disease progression.

Results: In the PPMI cohort, we found significantly higher levels of CSF pRab10 in sporadic PD, LRRK2-PD and prodromal-LRRK2 carriers compared with age-matched controls (Figure 1). This result was replicated in the UCL Parkinsonism cohort with higher levels of pRab10 in sporadic PD compared with progressive supranuclear palsy and age-matched controls. In the PPMI cohort healthy control and sporadic PD groups, we found that the common PD case-control risk variant (rs76904798) was a protein quantitative trait locus with significantly higher levels of CSF LRRK2 in rs76904798 risk allele carriers compared with rs76904798 non-carriers (Figure 2). In the PPMI cohort LRRK2-PD group, pRab10 levels were associated with CSF alpha-synuclein SAA status with higher levels in SAA negative compared with SAA positive participants (Figure 3). Clinically, in LRRK2-PD, higher levels of pRab10 at baseline were associated with increased worsening of Montreal Cognitive Assessment and Schwab and England Activities of Daily Living scale scores over two years (Figure 4).

Conclusion: Our findings suggest that there is shared LRRK2 pathway activation in sporadic PD and LRRK2-PD, defined by novel CSF biomarkers. Furthermore, stratification of biomarker

results by genetic and alpha-synuclein SAA status may identify subgroups of sporadic PD and LRRK2-PD patients who would benefit most from LRRK2-targeting therapies.

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Figures:

Figure 1

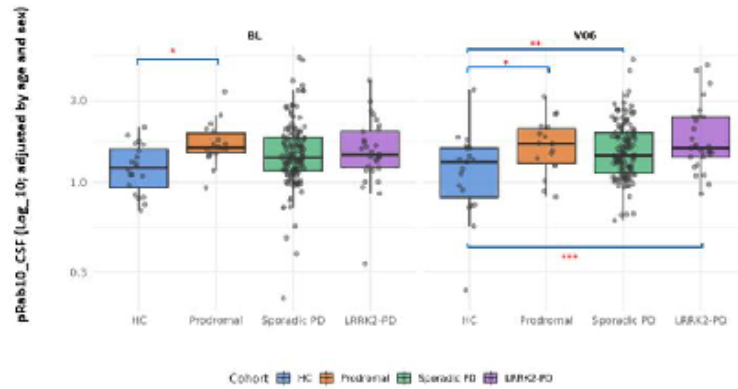


Figure 1: CSF pRab10 levels in the PPMI cohort baseline (BL) and V06 (2 years post-baseline) samples. Group-level comparisons were performed using linear mixed effects models via log transformed biomarker values that were sex and age adjusted.

Figure 2

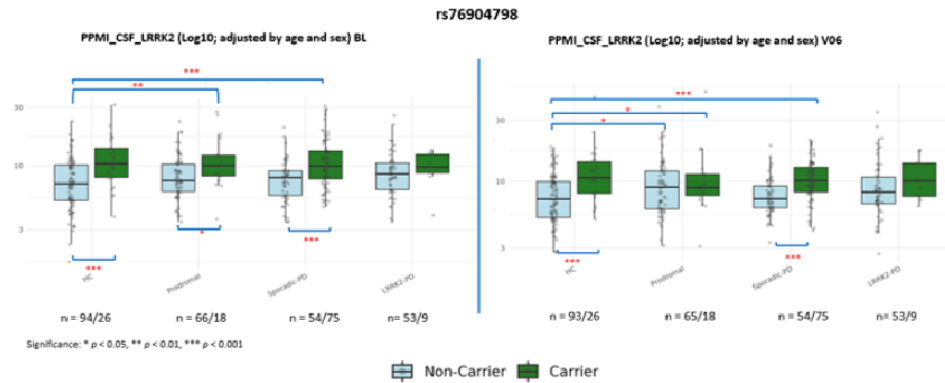


Figure 2: CSF LRRK2 levels in the PPMI cohort baseline (BL) and V06 (2 years post-baseline) samples, stratified by rs76904798 genotype status (carrier = CT or TT genotype; non-carrier = CC genotype). Group-level comparisons were performed using linear mixed effects models via log transformed biomarker values that were sex and age adjusted.

Figure 3

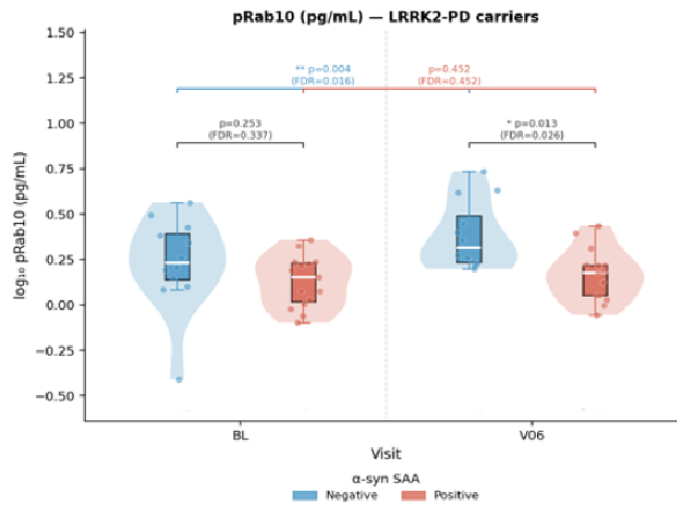


Figure 3: CSF pRab10 levels in the PPMI cohort baseline (BL) and V06 (2 years post-baseline) samples from LRRK2-PD participants, stratified by alpha-synuclein seed amplification assay (a-syn SAA) status (positive or negative). Group-level comparisons were performed using linear mixed effects models via log transformed biomarker values that were sex and age adjusted.

Figure 4

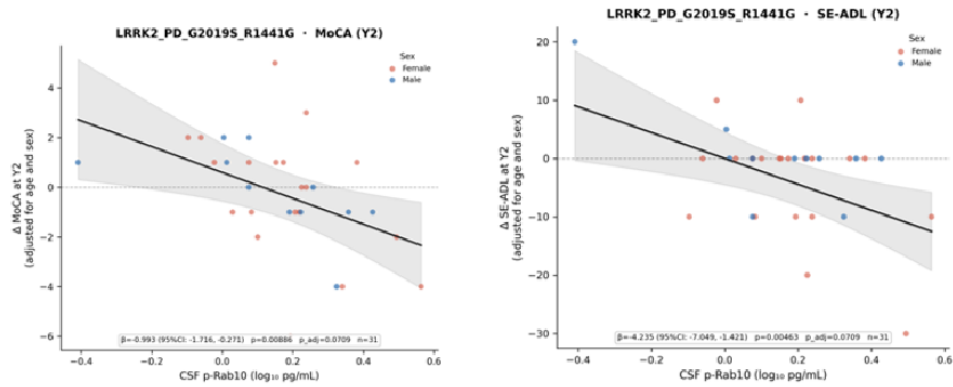


Figure 4: Baseline CSF pRab10 levels predicting clinical decline in LRRK2-PD participants in the PPMI cohort over 2 years. MoCA = Montreal Cognitive Assessment; SEADL = Schwab and England Activities of Daily Living. Analyses were performed using linear regression models via log transformed biomarker values that were sex and age adjusted.

LBA 13: Activity dependent retrograde axonal transport is required for ascending gut to brain synucleinopathy and hemispheric vulnerability in the body-first subtype of Parkinson's disease
T. Subramanian, D. Pokharel, K. Le, V. Peshattiwari, C. Swain, K. Venkiteswaran (Washington, DC, USA)

Objective: To determine the cause of hemispheric vulnerability in Parkinson's disease, we tested whether activity-dependent signaling through the left nigro-vagal pathway contributes to selective hemispheric vulnerability to ascending α -synuclein pathology in a paraquat plus lectin (P+L) rat model of Parkinson's disease (PD).

Background: Parkinson's disease is characterized by onset of symptoms in one side of the body causing stage I (hemiparkinsonism) disease. Why one hemisphere is more vulnerable is not well understood. Using rats that show remarkable hemispheric dominance patterns similar to humans, we demonstrate preferential left hemispheric vulnerability to P+L-induced parkinsonism. We hypothesized that retrograde transport through the left nigro-vagal pathway mediates gut-to-brain propagation of pathology and that selective chemogenetic inhibition would protect the ipsilateral substantia nigra pars compacta (SNpc).

Methods: Sprague-Dawley rats received Cre-dependent inhibitory HA-hM4Di-mCitrine viral vectors into the left SNpc and retrograde WGA-Cre vector into the left dorsal motor nucleus of the vagus, followed by chronic activation with JHU37160 and subsequent P+L administration. Chemogenetic targeting was verified by HA, mCitrine and tyrosine hydroxylase (TH) co-localization. Longitudinal motor function was assessed using the Vibrissae-Elicited Forelimb Placement Test, while TH immunohistochemistry and phosphorylated α -synuclein (S129) staining evaluated dopaminergic neuron survival and pathological propagation.

Results: Successful targeting was achieved in 4 animals. All demonstrated robust hM4Di-mCitrine expression within left TH-positive SNpc neurons, preservation of ipsilateral dopaminergic neurons, and complete absence of S129 α -synuclein pathology in the protected hemisphere. In contrast, the untreated right SNpc exhibited marked TH-positive neuronal loss and abundant pathological α -synuclein accumulation. Behaviorally, all 4 animals developed persistent left hemiparkinsonism without progression to bilateral disease. Whereas 4 control animals consistently developed bilateral dopaminergic degeneration, bilateral α -synuclein pathology, and bilateral parkinsonism.

Conclusion: Selective chemogenetic inhibition of the left nigro-vagal pathway prevented ipsilateral α -synuclein propagation and dopaminergic neurodegeneration following P+L exposure. These findings confirm that activity dependent retrograde transport is required via the vagus nerve and the nigrovagal pathway to cause ascending left hemispheric vulnerability and provide direct evidence that activity-dependent gut-brain transmission contributes to parkinsonian neurodegeneration. Targeting this circuit may represent a novel disease-modifying strategy for PD and the mechanistic basis for why one hemisphere is more vulnerable to parkinsonism than the other.

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LBA 14: Effects of a Long-Term Gluten-Free Diet on Motor Function, Cognition, Quality of Life, Biochemical Markers, and Metabolic Profile in Patients with Parkinson's Disease

H. Brozova, K. Polakova, T. Gentileova, M. Fialova, J. Rusz, H. Pelantova, J. Bartosova, B. Drabonova, M. Kuzma, D. Funda (Prague, Czech Republic)

Objective: To evaluate the effect of a 12-month gluten-free diet (GFD) on motor and cognitive functions, quality of life, biochemical markers, and serum metabolome in patients with Parkinson's disease (PD).

Background: A GFD influences inflammatory parameters and may be associated with changes in metabolomic parameters and clinical manifestations of the disease.

Methods: In this prospective, randomized, rater-blinded study, 57 patients with PD were enrolled: 30 assigned to a GFD (11 women; age 65.2 ± 7.5 years; disease duration 8 ± 5 years; BMI 26.9 ± 5 kg/m²) and 27 to a control group without dietary intervention (14 women; age 63.8 ± 6.7 years; disease duration 6 ± 4 years; BMI 28.6 ± 5 kg/m²). Assessments were performed at baseline, 1.5 months, and 12 months. Motor function was evaluated using the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Timed Up and Go test, cognition using the Montreal Cognitive Assessment (MoCA), and quality of life using the Parkinson's Disease Questionnaire-39 (PDQ-39). Laboratory parameters and serum metabolomic profiles were also analyzed.

Results: The gluten-free diet (GFD) was safe, well tolerated, and showed good adherence. No significant effect on motor function was observed; however, the GFD was associated with improved cognitive performance ($p = 0.046$), significant longitudinal changes in the lipid profile ($p < 0.05$), and improved quality of life (PDQ-39) over time and compared with the control group ($p = 0.005$ and $p = 0.035$, respectively). Serum metabolomic analysis revealed significant differences in the longitudinal changes of 5 of the 32 monitored metabolites between the GFD and control groups ($p < 0.05$). In patients with PD duration ≤ 5 years, changes predominantly involved energy metabolism, as reflected by methyloxovalerate and citrate, whereas patients with PD duration > 5 years exhibited changes in formate, mannose, and glucose.

Conclusion: A long-term gluten-free diet was associated with improved cognitive performance and quality of life in patients with PD. Serum metabolomic analysis indicated distinct metabolic adaptations, with responses differing according to disease duration. These findings support further investigation of the therapeutic potential of a gluten-free diet in larger cohorts, particularly in patients with early-stage PD.

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LBA 15: Phase 1 Study of ARV-102, a PROTAC LRRK2 Degradar, in Parkinson's Disease: Oculomotor and Biomarker Data

K. Fraser, L. van de Bult, L. Smits, S. Kosten, C. Ngaara-Woodward, J. Corradi, S. Aksenov, X. Luo, M. Alon, A. Costa Zaninotto, C. Lubeski, M. MacDougall, M. Leiononen, C. Fitzner-Attas, I. Conti, M. Forrest Gordon, P. Kremer (New Haven, CT, USA)

Objective: To evaluate the effects of ARV-102, a PROteolysis TArgeting Chimera (PROTAC) leucine-rich repeat kinase 2 (LRRK2) degrader, on oculomotor function and CSF biomarkers in participants with Parkinson's disease (PD).

Background: LRRK2 variants are linked to both autosomal-dominant and idiopathic PD. ARV-102 harnesses the ubiquitin-proteasome system to induce degradation of LRRK2. In phase 1 studies in healthy and PD populations, single and multiple doses of ARV-102 were well tolerated and demonstrated dose-dependent increases in exposure, LRRK2 degradation, and downstream pathway engagement in plasma and CSF. Saccadic hypometria, the tendency for eye movements to fall short of visual targets due to reduced saccade amplitude, is a marker of basal ganglia dysfunction and worsens as PD progresses.

Methods: In the multidose part of a single-center, double-blind, phase 1 study (EUCT 2024-516888-84-00), participants with PD without major motor fluctuation or dyskinesia, Hoehn and Yahr score ≤ 3 were randomized (1:1:1:1) to ARV-102 20, 40, or 80 mg, or placebo once daily for 28 days. Oculomotor function was tracked using a sensitive software-based platform (Neuralight). PD symptoms (MDS-UPDRS) and CSF proteomics (SomaScan) were also evaluated.

Results: 24 participants (median age: 62 y [range: 51–77]; 83% male) completed 28 days of treatment. Amplitude of saccadic hypometria (ASH) improved from baseline to day 28 with ARV-102 vs placebo without an observed effect on vigilance. Least square mean (95% CI) change from baseline (CFB) to day 28 in MDS-UPDRS Part III score was 4.8 (0.6, 8.9), 2.2 (-2.3, 6.7), 1.6 (-2.5, 5.7), and 0.8 (-3.6, 5.2) in the placebo, 20, 40, and 80 mg groups, respectively. ARV-102 decreased CSF measures of endolysosomal function and neuroinflammation (eg, CD68, GPNMB) and increased measures of synaptic integrity and axonal guidance (NPTX2, CBLN4). Baseline CSF LRRK2 levels did not correlate with % CFB in CSF LRRK2. However, % CFB in CSF LRRK2 correlated with changes in CSF pathway measures (CD68, $R=0.72$, $P<0.0001$) and ASH ($R=-0.58$, $P<0.01$).

Conclusion: ARV-102-induced LRRK2 degradation in CSF was accompanied by increases in oculomotor function and CSF synaptic biomarkers and decreases in endolysosomal and neuroinflammatory proteins in CSF of participants with PD, supporting LRRK2 degradation as a potential therapeutic approach.

LBA 16: Distinct roles of periventricular and deep white matter hyperintensities in the dopaminergic and cholinergic cognitive axes of Parkinson's disease

SH. Yoon, J. Lee (Goyang, Korea)

Objective: To determine whether periventricular (PVWMH) and deep white matter hyperintensities (DWMH) exert distinct effects on the dopaminergic-executive and cholinergic-visuospatial cognitive axes of Parkinson's disease (PD), and by what mechanism.

Background: Cognitive impairment in PD follows two dissociable syndromes: a dopaminergic frontostriatal syndrome affecting executive function and a cholinergic posterior-cortical syndrome affecting visuospatial function. Whether PVWMH and DWMH contribute differentially to these axes is unknown.

Methods: We retrospectively analyzed 215 patients with PD who underwent dual-phase ^{18}F -FP-CIT PET (early-phase perfusion and delayed-phase dopamine transporter [DAT] binding), MRI-based nucleus basalis of Meynert (NBM) volumetry and WMH subtyping, and neuropsychological assessment; 112 patients had longitudinal follow-up. We used serial and moderated mediation analysis, with bootstrapped confidence intervals and false discovery rate correction.

Results: Caudate DAT was most strongly associated with executive function and NBM with visuospatial function. PVWMH influenced executive function through a serial dopaminergic cascade via caudate perfusion and caudate DAT (indirect effect -0.030 , 95% CI -0.086 to -0.006). DWMH moderated the cholinergic pathway from NBM through precuneus perfusion to visuospatial function (index of moderated mediation -0.047 , -0.092 to -0.014) and abolished the indirect effect at high DWMH burden. The effects were doubly dissociable: DWMH did not moderate the dopaminergic axis, and PVWMH did not act serially on the cholinergic axis. Among five parieto-occipital regions, only precuneus and inferior parietal lobule survived correction.

Conclusion: PVWMH and DWMH contribute differentially to the two cognitive axes of PD through distinct mechanisms: PVWMH as an upstream serial factor in the dopaminergic-executive axis, and DWMH as a moderator of the cholinergic-visuospatial axis.

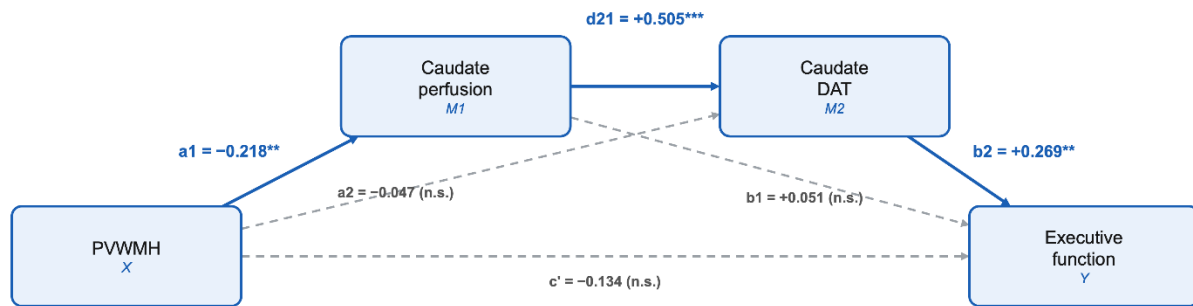
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Figures:

(A) Dopaminergic axis



Serial indirect effect ($X \rightarrow M1 \rightarrow M2 \rightarrow Y$) = -0.030 (95% CI $-0.086, -0.006$)

Standardized β . $^{**}p < 0.01$, $^{***}p < 0.001$; n.s., not significant. Dashed paths were not significant.

LBA 17: Nuclear CHCHD2 represses SNCA transcription: A novel endogenous regulatory axis disrupted in Parkinson's disease

Y. Zhang, M. Niu, Z. Zhu, J. Liu (Shanghai, People's Republic of China)

Objective: To determine whether CHCHD2 directly represses SNCA transcription and whether CHCHD2 deficiency or Parkinson's disease (PD)-linked CHCHD2 mutations promote α -synuclein (α -syn) pathology and dopaminergic neurodegeneration.

Background: Increased SNCA expression and α -syn accumulation are central to Parkinson's disease (PD) pathogenesis, yet endogenous nuclear mechanisms restraining SNCA transcription remain elusive. CHCHD2, a genetically validated PD-associated protein, is conventionally studied for mitochondrial function but has also been implicated in transcriptional regulation. Whether CHCHD2 directly restrains SNCA transcription via a nuclear mechanism in PD remains unknown.

Methods: CHCHD2 expression was quantified in substantia nigra (PD and controls) and peripheral blood (PD, MSA-P, and controls). Mechanistic studies used CHCHD2 knockout cells, Chchd2 knockdown mice, and PD model mice. SNCA promoter occupancy, direct DNA binding, and transcriptional repression were assessed by ChIP-qPCR, EMSA, promoter mapping, dual-luciferase assays, and molecular docking. In vivo AAV-mediated rescue tested wild-type CHCHD2 and PD-linked T61I/R145Q mutants against vector controls.

Results: CHCHD2 was downregulated in PD substantia nigra and blood, whereas blood CHCHD2 levels were preserved in MSA-P, supporting biomarker relevance for PD detection and PD/MSA-P differentiation. Mechanistically, CHCHD2 directly bound the proximal SNCA promoter (-65 to -45 bp) and repressed SNCA transcription. CHCHD2 deficiency and PD-linked

T61I/R145Q mutations converged on impaired SNCA repression, increasing SNCA mRNA, α -syn protein, phosphorylated α -syn (p- α syn) accumulation, and dopaminergic neurodegeneration, with the mutations weakening promoter binding. In PD mice, AAV-mediated expression of wild-type CHCHD2, but not T61I/R145Q mutants, reduced α -syn accumulation, attenuated p- α syn pathology, and rescued dopaminergic neurodegeneration.

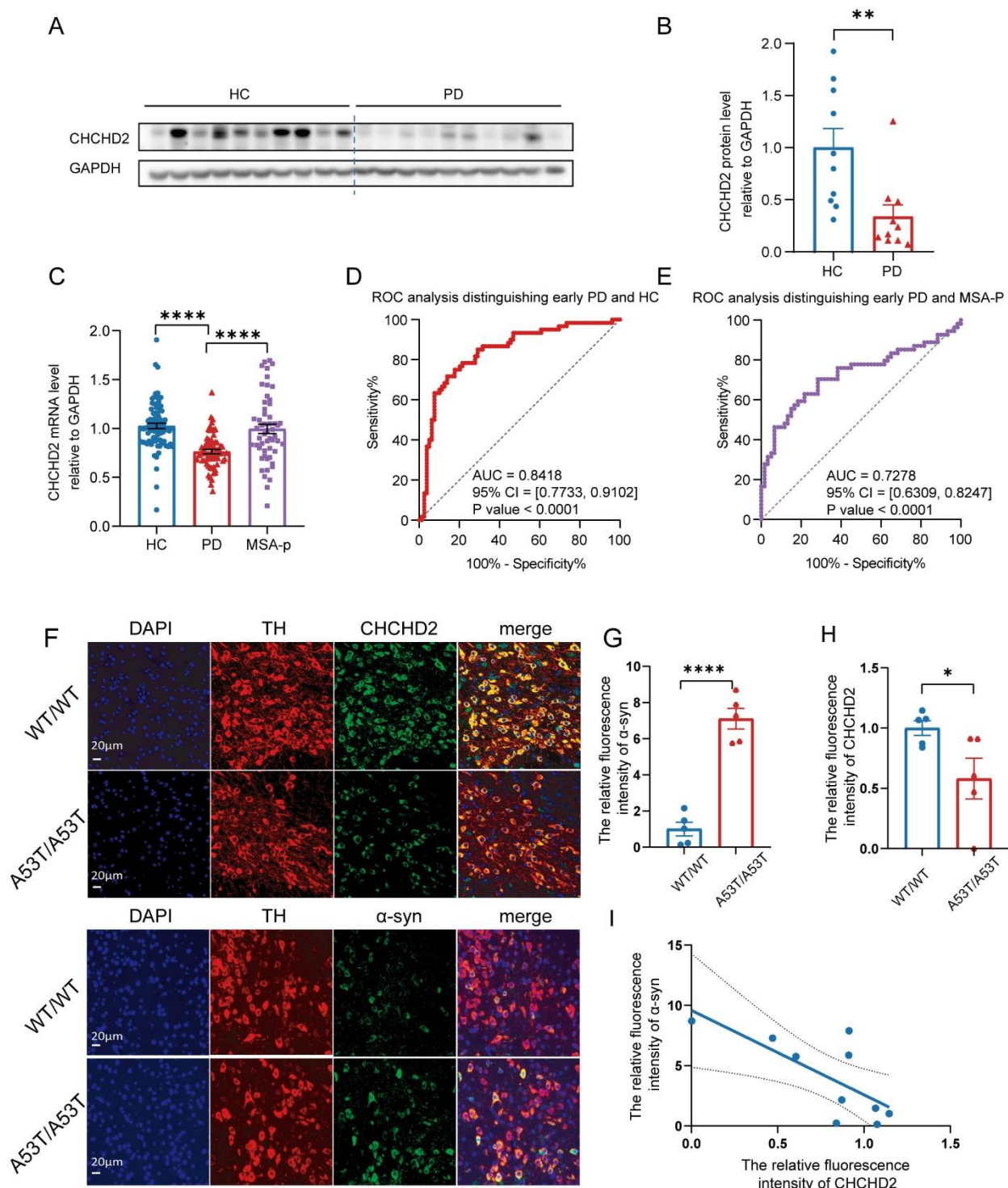
Conclusion: CHCHD2 is a direct nuclear repressor of SNCA, defining a previously unrecognized CHCHD2-SNCA transcriptional regulatory axis in PD. Disruption of this CHCHD2-SNCA axis—via reduced CHCHD2 expression in sporadic PD or T61I/R145Q mutations in familial PD—promotes SNCA derepression and α -syn-mediated neurodegeneration. These findings link CHCHD2 dysfunction to α -syn pathology and highlight endogenous SNCA transcriptional control as a disease-relevant mechanism with implications for PD detection, PD/MSA-P differentiation, and α -syn-lowering strategies.

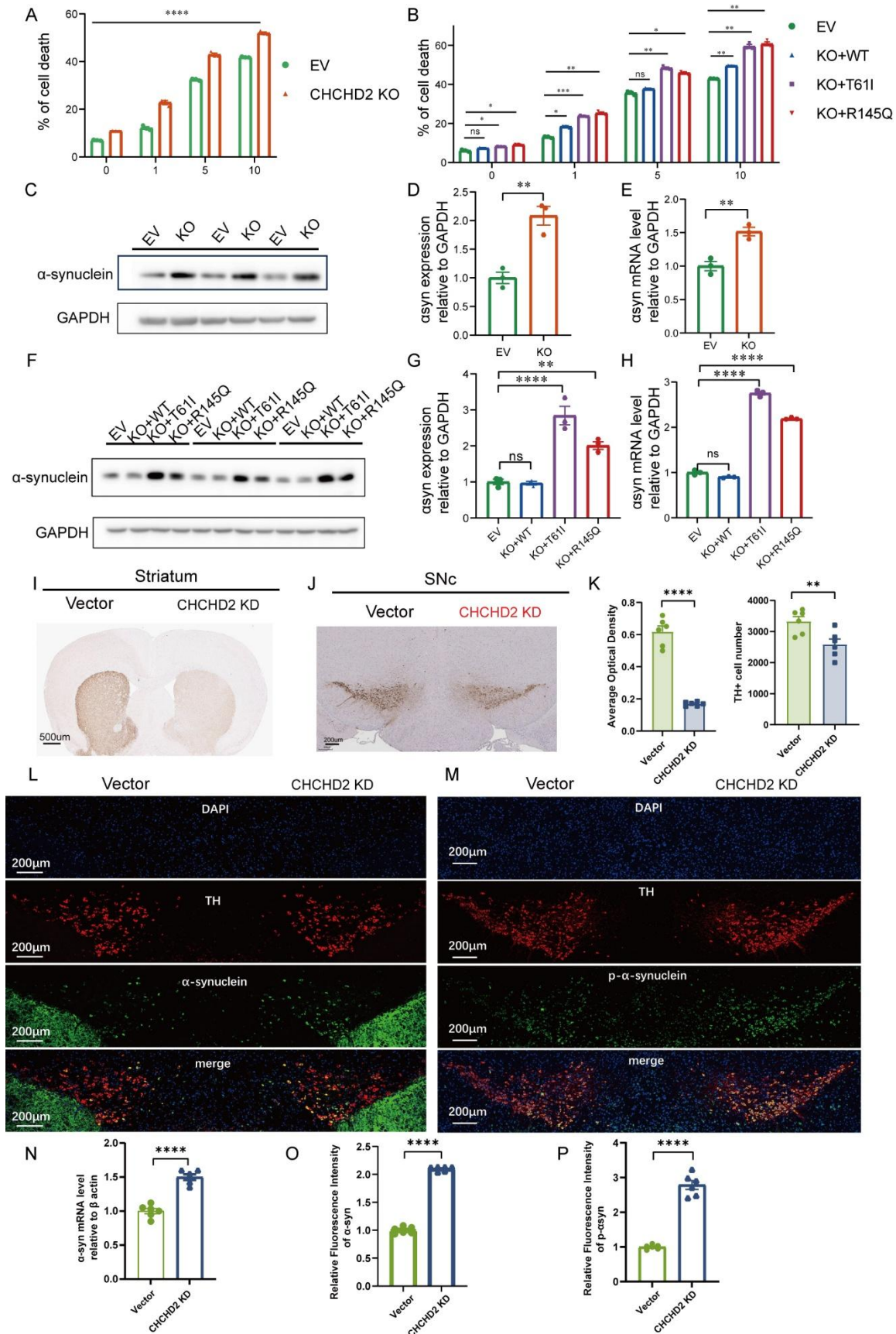
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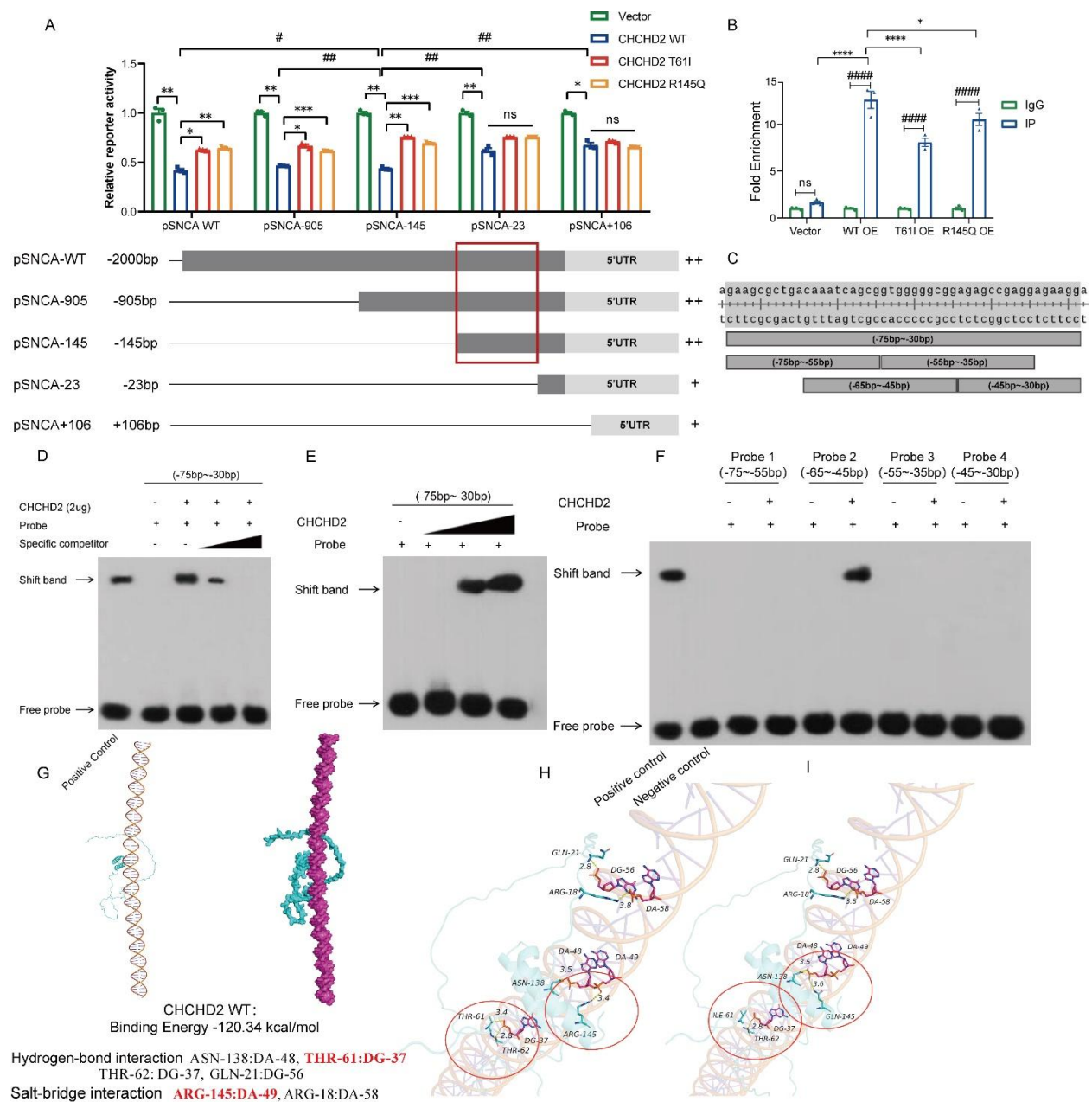
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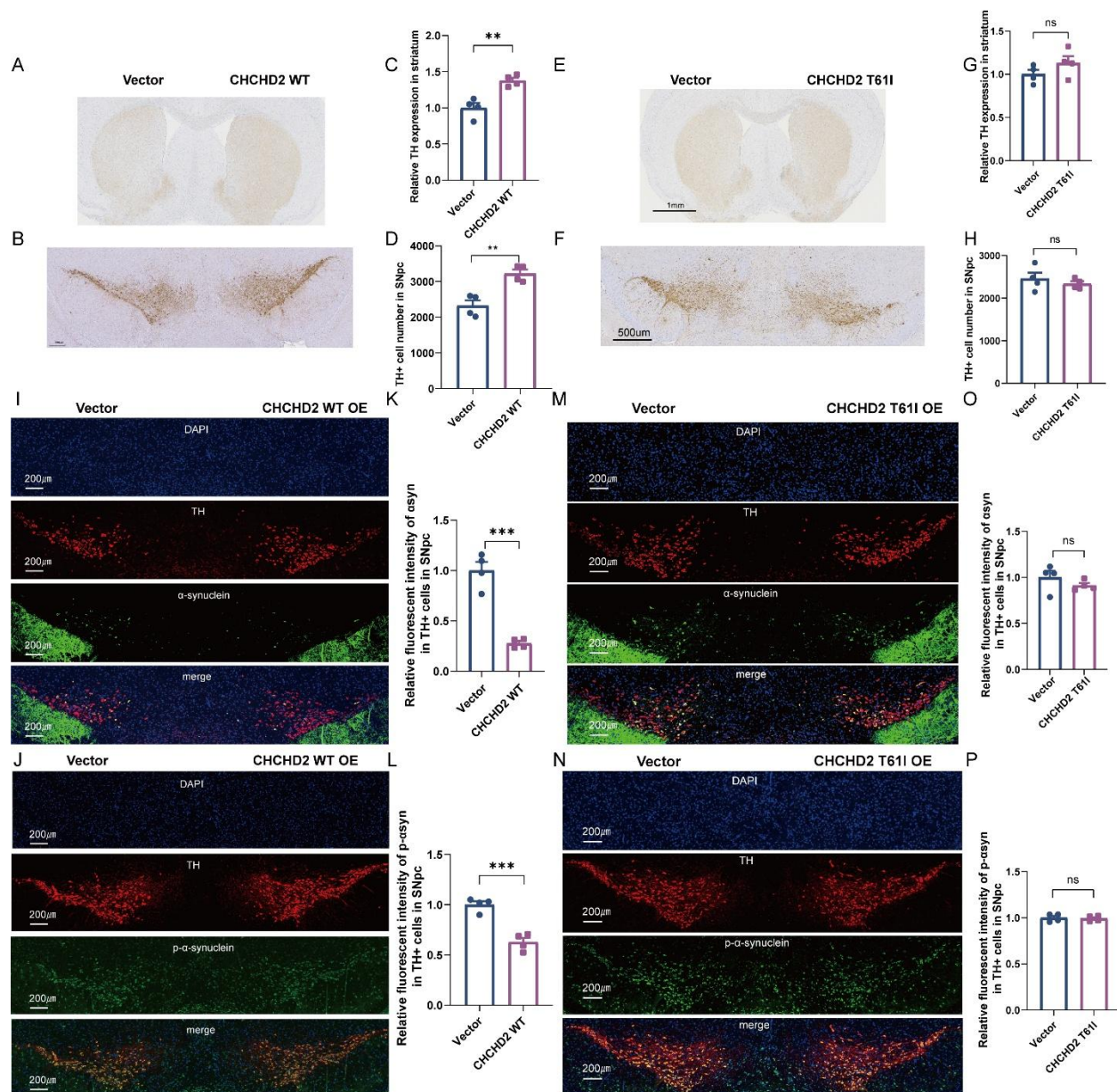
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Figures:









LBA 18: Efficacy and Safety of the GCase Activator BIA 28-6156 in GBA-Associated Parkinson's Disease: Results from the Phase 2b ACTIVATE Trial

J. Ferreira, HF. Fernandez, WP. Poewe, DKS. Simon, OR. Rascol, MAN. Nance, KK. Kiebertz, RC. Costa, RBM. Bouca-Machado, FP. Pereira, MF. Fonseca, JR. Reis, DR. Ramos, GC. Cordeiro, TF. Fonseca, FR. Rocha, AG. Guimarães, DM. Magalhães, JH. Holenz (Lisbon, Portugal)

Objective: To evaluate the efficacy and safety of BIA 28-6156, a novel beta-glucocerebrosidase (GCase) activator, in delaying clinical progression in patients with GBA-associated Parkinson's disease (GBA-PD).

Background: Pathogenic variants in the GBA1 gene reduce GCase activity and represent the most common genetic risk factor for Parkinson's disease. BIA 28-6156 is an orally administered, small-molecule positive allosteric activator of GCase, developed to target this underlying pathophysiology and potentially modify the disease trajectory in GBA-PD.

Methods: ACTIVATE was a 78-week, double-blind, placebo-controlled Phase 2b trial. Patients (disease duration 1–7 years; confirmed GBA1 variant; no significant motor fluctuations) were randomized (1:1:1) to BIA 28-6156 10 mg/day, 60 mg/day, or placebo. The primary endpoint was time to clinically meaningful progression, defined as a ≥ 2 -point increase in MDS-UPDRS Part II with no improvement in Part III. The key secondary endpoint was time to a ≥ 5 -point worsening in MDS-UPDRS Part III. Time-to-event outcomes were evaluated using adjusted Cox proportional-hazards models.

Results: The trial enrolled 272 patients (mean age 58.6 ± 10.0 years; 61.6% male; mean disease duration 3.7 ± 1.9 years). No significant treatment effect was observed for the primary endpoint: Hazard Ratio (HR) vs. placebo was 1.0 (95% CI: 0.72–1.51; $p=0.82$) for 60 mg and 1.0 (95% CI: 0.67–1.42; $p=0.90$) for 10 mg. BIA 28-6156 also failed to delay progression on the key secondary endpoint: HR 1.0 ($p=0.80$) for 60 mg and HR 0.9 ($p=0.41$) for 10 mg. Event rates for clinical progression were balanced across all cohorts. Exploratory analyses confirmed an absence of dose dependency or efficacy signals. BIA 28-6156 was well-tolerated; TEAE frequencies and trial discontinuation rates were comparable between the active and placebo arms.

Conclusion: Despite a strong biological rationale and a favorable safety profile, treatment with the allosteric GCase activator BIA 28-6156 (10 mg or 60 mg/day) over 78 weeks did not slow clinical disease progression in patients with early-to-moderate GBA-PD, as measured by the primary and key secondary endpoints. The data generated provide important insights for the field, especially around challenges and clinical endpoints associated with targeting GCase as a disease-modifying strategy.

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LBA 19: Results from a Phase 2b, Placebo-Controlled Study to Determine the Efficacy and Safety of BIIB122/DNL151 in Participants with Early-Stage Parkinson's Disease

R. Llorens Arenas, A. Siderowf, A. Lang, M. Yang, O. Mabrouk, C. Paisan-Ruiz, B. Hersh, D. Jennings, S. Huntwork-Rodriguez, J. Kluss, R. Maciucă, P. Roychowdhury, S. Dhuria, P. Wang, K. Harrison, J. Goldman, G. Curiale, M. Wald, D. Graham, M. King, R. Hauser (Cambridge, MA, USA)

Objective: To evaluate the efficacy and safety of BIIB122/DNL151 compared with placebo in delaying confirmed worsening of the clinical features of Parkinson's disease (PD) in participants with early-stage PD.

Background: BIIB122/DNL151 is an investigational, oral, selective, CNS-penetrant small molecule leucine-rich repeat kinase 2 (LRRK2) inhibitor.

Method: LUMA (NCT05348785) [1], a Phase 2b, multicenter, randomized, double-blind, placebo-controlled study enrolled adults aged 30–80 years with early-stage PD (diagnosis ≤ 2 years at screening; Hoehn & Yahr Stages I–II (in OFF state), approximately 80% treatment-naïve and 20% on stable symptomatic therapy with monoamine oxidase B inhibitors or levodopa for less than one year prior to screening). Participants were randomized to receive BIIB122/DNL151 225 mg orally once daily or matching placebo for a minimum of 48 to a maximum of 144 weeks. The primary efficacy endpoint was time to confirmed worsening in the modified MDS-UPDRS combined Parts II and III score over the treatment period, with worsening defined as an increase of ≥ 6 -points from baseline. Safety endpoints included incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

Results: 648 participants were randomized and dosed. Baseline demographics and disease characteristics were generally balanced between treatment groups. BIIB122/DNL151 did not demonstrate a statistically significant benefit on the primary endpoint compared to placebo, with hazard ratio=1.04 (95% CI, 0.85, 1.28), $p=0.4538$, and did not show benefit on secondary endpoints compared to placebo. BIIB122/DNL151 led to the following changes until week 48 in exploratory biomarkers relative to baseline: $>90\%$ reduction in whole blood pS935 LRRK2, $\sim 50\%$ reduction in urine BMP, and in a CSF substudy ($n=86$), a $\sim 30\%$ peak reduction in pRAB10 at week 24. TEAE and SAE incidences were similar between BIIB122/DNL151 (92.8%, 11.5%) and placebo (89.3%, 11.9%). Headache (17.1% BIIB122/DNL151; 9.2% placebo) and fall (13.1% BIIB122/DNL151; 12.5% placebo) were the most common TEAEs. TEAEs led to study drug withdrawal in 11.2% of BIIB122/DNL151 vs 4.6% of placebo.

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LBA 20: Neuron-derived ferritin-containing extracellular vesicles link alpha-synuclein pathology to nigral iron burden in Parkinson's disease

Z. Yu (Beijing, People's Republic of China)

Objective: To determine whether plasma neuron-derived ferritin-containing extracellular vesicles reflect nigral iron burden in Parkinson's disease and to define the underlying mechanism linking alpha-synuclein pathology to ferritin dysregulation.

Background: To determine whether plasma neuron-derived ferritin-containing extracellular vesicles reflect nigral iron burden in Parkinson's disease and to define the underlying mechanism linking alpha-synuclein pathology to ferritin dysregulation.

Methods: Plasma neuron-derived ferritin-containing extracellular vesicles were quantified by nanoscale flow cytometry in 100 patients with Parkinson's disease, 49 with multiple system atrophy, 20 with isolated rapid eye movement sleep behavior disorder, and 60 healthy controls. Nigral iron burden was assessed using quantitative susceptibility mapping magnetic resonance

imaging in a subgroup of patients with Parkinson's disease and healthy controls. Cellular models, co-immunoprecipitation, immunofluorescence, protein stability assays, and proteasome inhibition experiments were used to investigate the interaction among alpha-synuclein, ferritin, Itch, and the ubiquitin-proteasome pathway.

Results: Plasma neuron-derived ferritin-containing extracellular vesicle levels were significantly reduced in Parkinson's disease and isolated rapid eye movement sleep behavior disorder compared with healthy controls, and were lower in Parkinson's disease than in multiple system atrophy. These vesicles distinguished Parkinson's disease from healthy controls with an area under the curve of 0.83 and from multiple system atrophy with an area under the curve of 0.80. In Parkinson's disease, lower vesicle levels were associated with greater substantia nigra pars compacta susceptibility on quantitative susceptibility mapping and with higher motor severity. Mechanistically, pathological alpha-synuclein directly interacted with ferritin and enhanced the recruitment of the E3 ubiquitin ligase Itch. This promoted ferritin ubiquitination and proteasome-dependent degradation, leading to increased intracellular ferrous iron. Proteasome inhibition rescued alpha-synuclein-induced ferritin reduction.

Conclusion: Plasma neuron-derived ferritin-containing extracellular vesicles may serve as a peripheral indicator of neuronal ferritin dysregulation and nigral iron burden in Parkinson's disease. These findings identify an alpha-synuclein-Itch-ferritin pathway that links synuclein pathology to iron dyshomeostasis and suggest a more targeted strategy for restoring iron homeostasis beyond non-specific iron chelation.

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Figures:

Fig 1

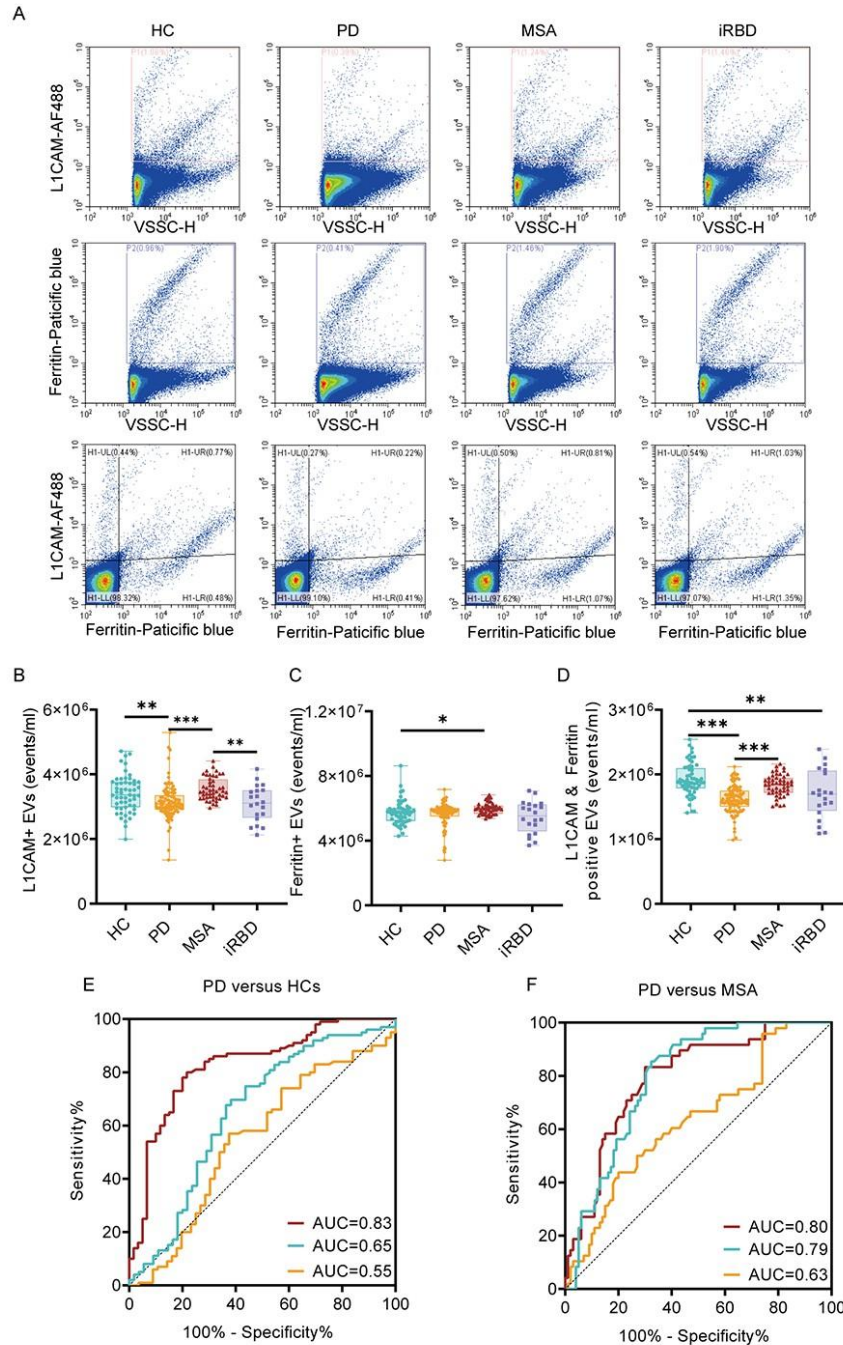


Fig 2

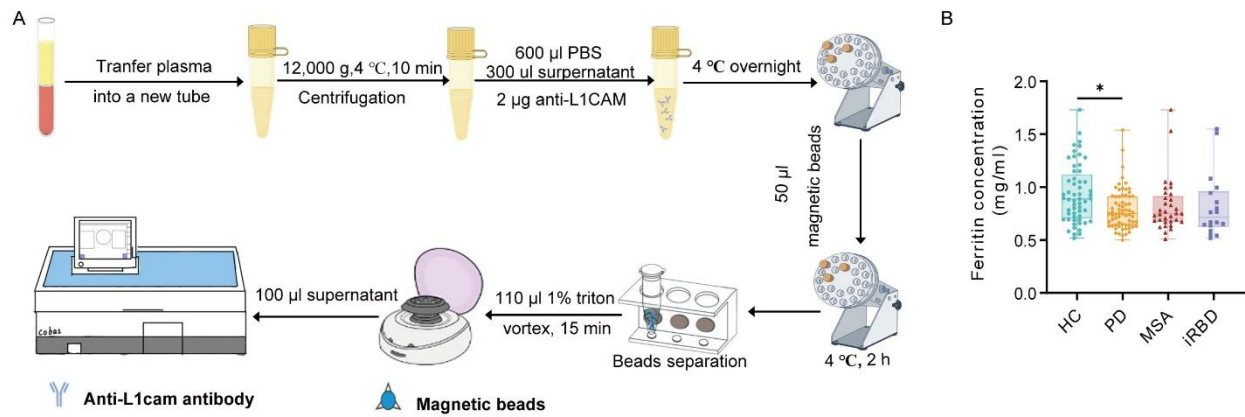


Fig 3

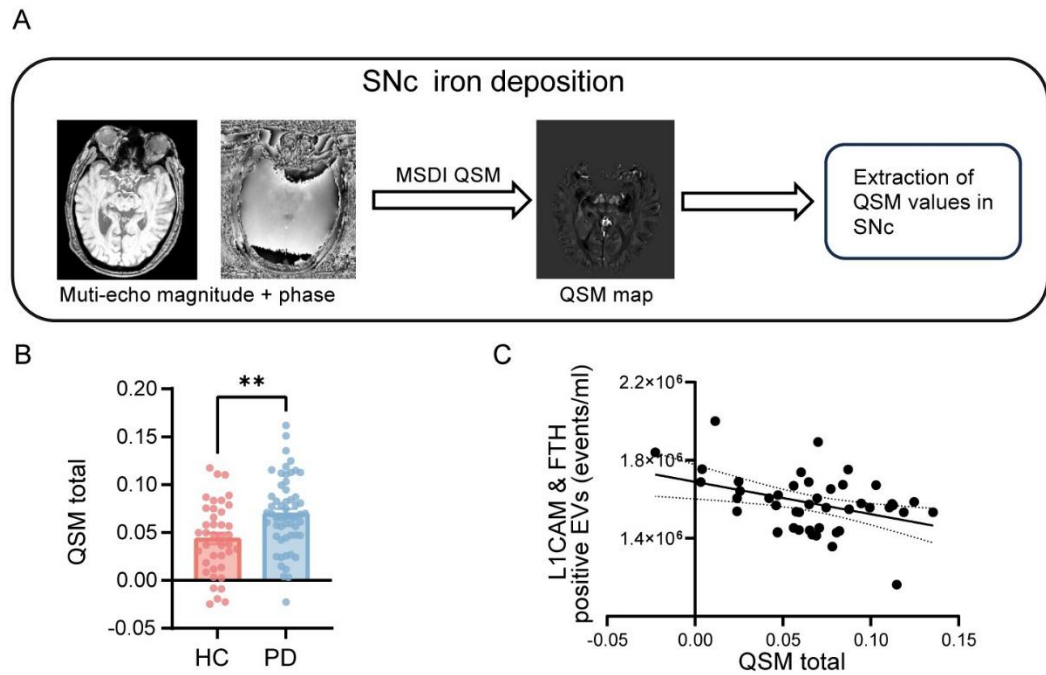


Fig 4

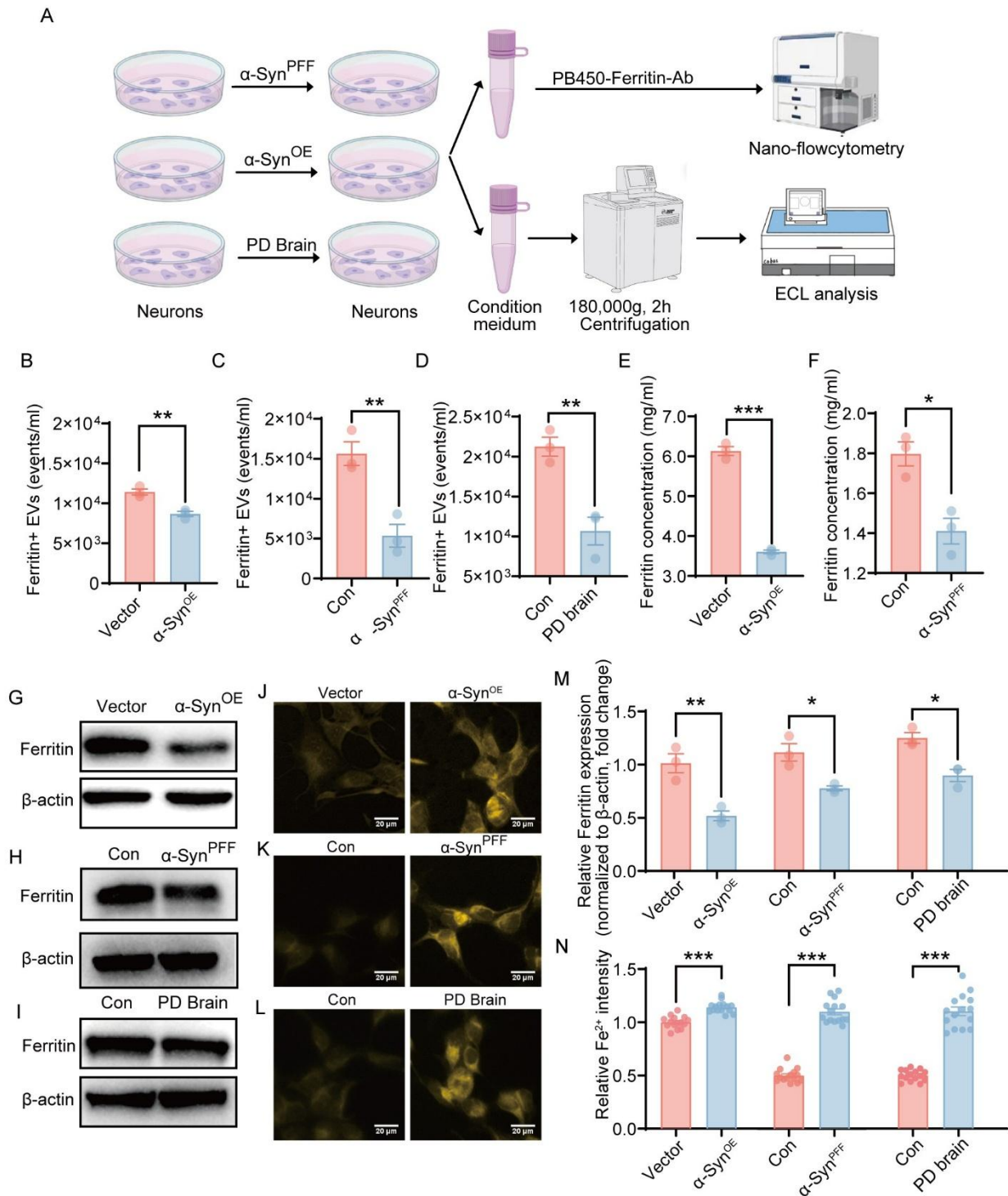


Fig 5

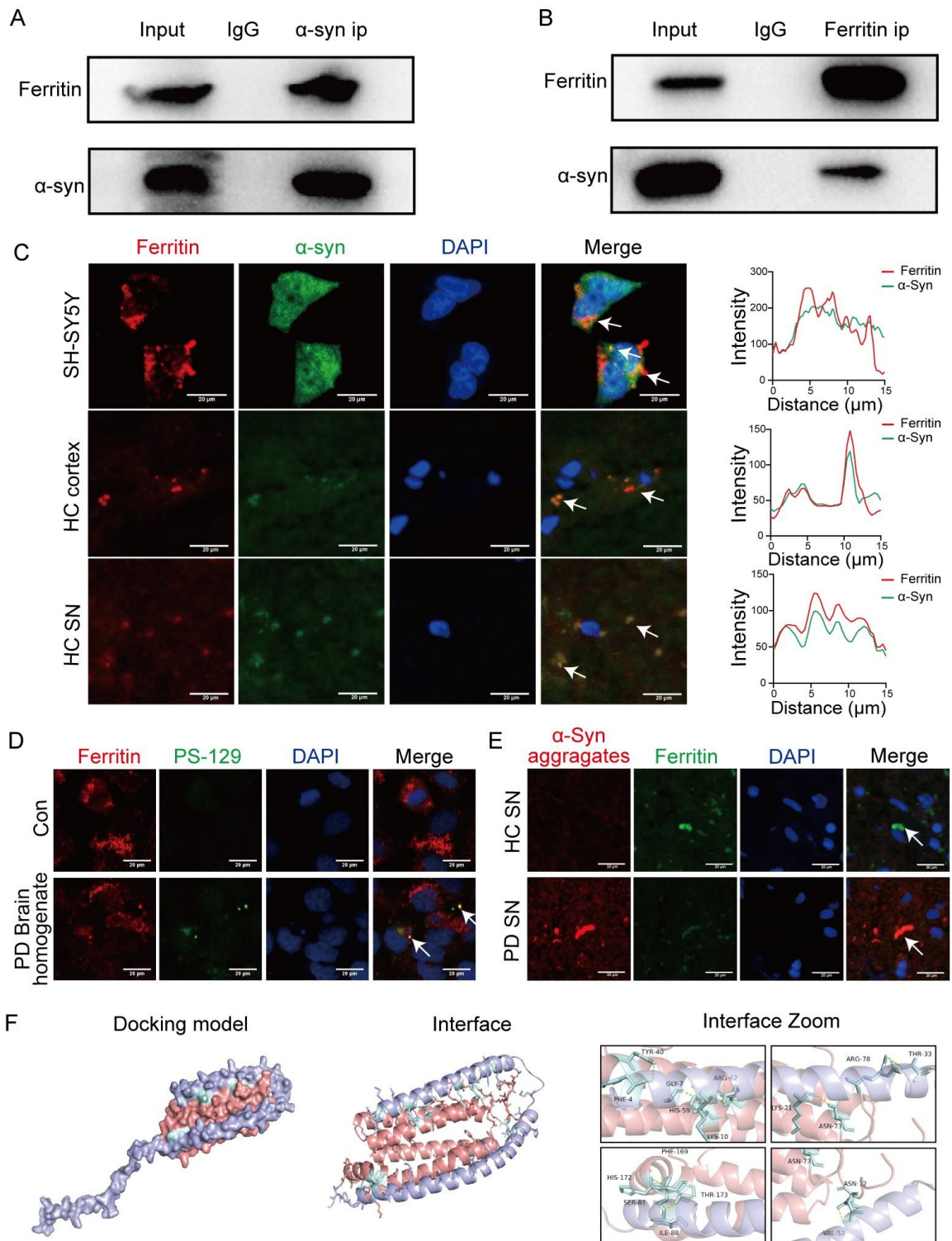
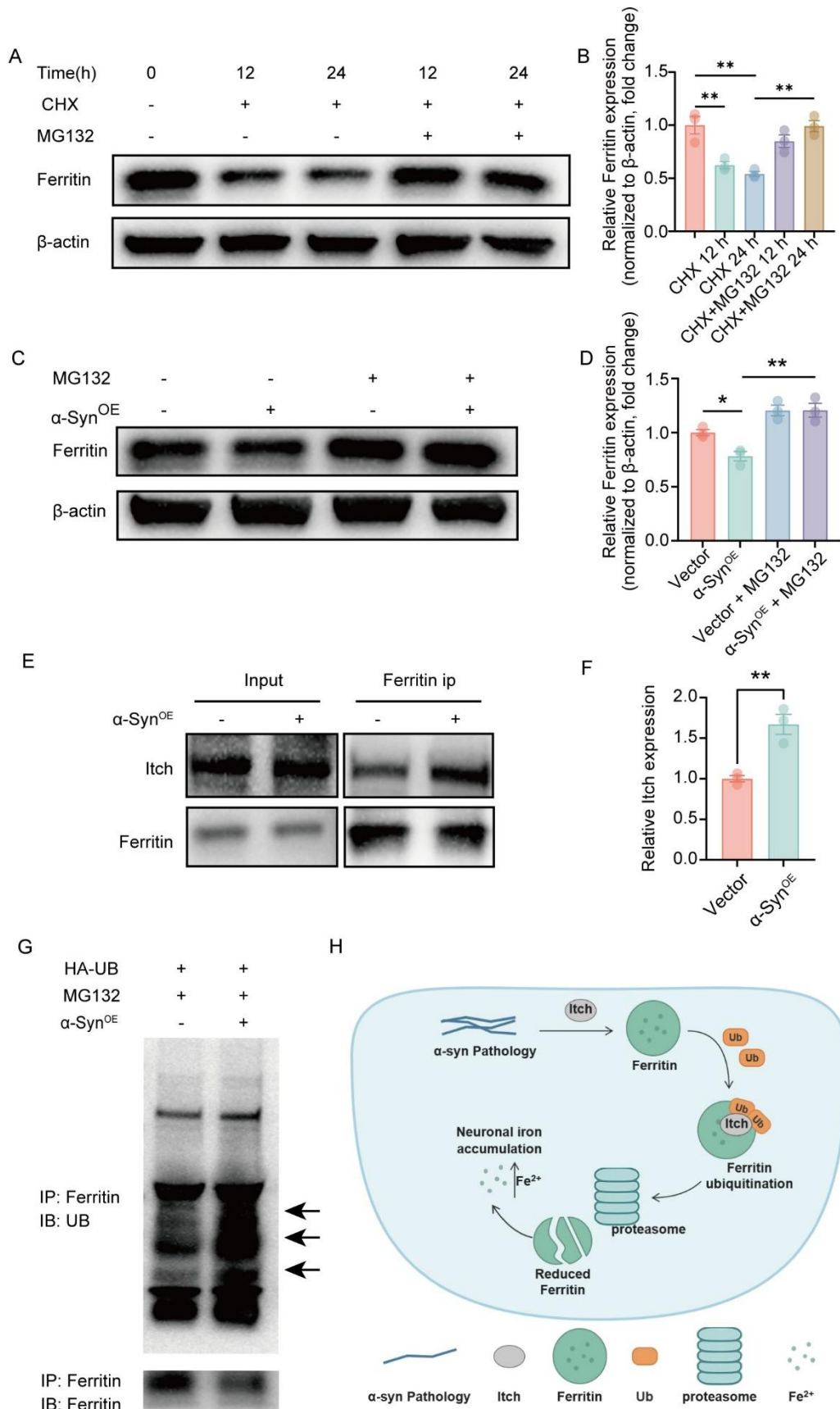


Fig 6



LBA 21: Results from ARISE: A pivotal phase 3 trial of solengepras in Parkinson's disease with motor fluctuations

R. Hauser, H. Sarva, A. Karbowniczek, C. Carroll, O. Rascol, S. Tisch, N. Brice, K. Kieburtz, A. Ellenbogen (Tampa, FL, USA)

Objective: To evaluate the effect of solengepras on OFF time in Parkinson's disease (PD) with motor fluctuations.

Background: Motor fluctuations remain a significant source of disability in patients with Parkinson disease despite available therapies. Solengepras is a clinical-stage, oral, brain-penetrant, specific inhibitor of GPR6, a receptor found primarily in medium spiny neurons of the indirect pathway involved in regulating movement. In a previous 4-week Phase 2 trial evaluating solengepras in PD patients with motor fluctuations, solengepras demonstrated a clinically meaningful reduction in OFF-time and was generally well-tolerated with minimal dopaminergic-related side effects.

Methods: ARISE is a randomized, double-blind, placebo-controlled, multi-center international study in PD patients with motor fluctuations. The study aimed to recruit 330 participants on stable dosages of PD medications with an average of ≥ 3 h total OFF time/day (minimum 2.5 hours each day) as measured by home diaries. Participants who met eligibility criteria were randomized (1:1:1) to receive solengepras 150mg or 75mg, or matching placebo (QD) for 12 weeks. The primary endpoint was change from baseline to week 12 in average daily OFF time. Secondary endpoints were change from placebo in ON time without troublesome dyskinesias, MDS-UPDRS II and III, ESS, and safety and tolerability.

Results: The study screened 710 participants of and randomized 341 patients from sites in the USA, EU, United Kingdom, and Australia. Enrollment commenced in September 2024 with last patient last visit anticipated August 2026 (NCT 06553027). As of June 2026, the study had a low dropout rate, with 27 participants discontinuing treatment, representing 7% of those recruited. Database lock and efficacy and safety analyses are anticipated prior to presentation.

Conclusion: ARISE is a pivotal Phase 3 trial evaluating solengepras in PD patients with motor fluctuations. Efficacy and safety results will be presented.

LBA 22: A multicenter, double-blind, randomized, placebo-controlled, phase 2a clinical trial of Vutiglabin in Early-Stage Parkinson's Disease

Y. Oh, JW. Cho, JS. Baik, HI. Ma, SB. Koh, PH. Lee, TB. Ahn, SJ. Kim, JS. Kim (Uijeongbu, Korea)

Objective: We investigated whether vutiglabin can provide disease-modifying effects by slowing motor symptom progression in patients with Parkinson's disease.

Background: Vutiglabin, a novel paraoxonase (PON) activator, has shown neuroprotective potential in preclinical mouse models of Parkinson's disease.

Methods: In this multicenter, double-blind, randomized, placebo-controlled, phase 2a trial, we randomly assigned, in a 1:1:1 ratio, participants with newly-diagnosed Parkinson's disease to receive daily doses of 400 mg, 800 mg vutiglabin or placebo for 24 weeks, followed by a 4-

week washout period. The primary endpoint was the change from baseline to 24 weeks in the Movement Disorder Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS) Part III (range, 0 to 132). Secondary endpoints included changes in MDS-UPDRS part III at 4, 12, and 28 weeks versus baseline or changes in MDS-UPDRS part II+III scores at week 4, 12, 24, and 28 versus baseline, Non Motor Symptom Scale (NMSS) at 12 weeks and 24 weeks versus baseline, and Clinical Global Impression of Change (CGI-C) at 4, 12, and 24 weeks versus baseline. Striatal dopamine uptake was assessed using 18F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane positron emission tomography at baseline and 24 weeks. Exploratory analysis also performed from baseline to 24 weeks in serum Neurofilament Light chain (NfL) levels and PON1 expressions and activities.

Results: A total of 118 were screened for eligibility, of whom 99 patients were randomly assigned to placebo, 400 mg and 800 mg of vutiglabridin groups. 77 patients were included in per-protocol set analysis for efficacy. At 24 weeks, scores on the MDS-UPDRS part III had changed -1.37 for 400 mg and -2.83 for 800 mg of vutiglabridin (indicating improvement) and +0.73 for placebo (indicating worsening). The mean difference of the MDS-UPDRS part III between placebo and 800 mg vutiglabridin groups was 3.56 (P=0.03). The vutiglabridin 800 mg group exhibited a tendency for an increase in serum PON1-specific activity. Vutiglabridin was well-tolerated with no drug-related serious adverse events.

Conclusion: Treatment with 800 mg vutiglabridin significantly improved MDS-UPDRS part III score in early Parkinson's disease (PD) patients as compared with placebo, with a favorable safety profile.

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LBA 23: Evaluating KP405, a CNS-penetrating GLP1/GIP analogue, in a randomized, placebo-controlled Phase I study in healthy elderly participants and Parkinson's disease patients with exploratory analysis of biomarkers in brain-derived extracellular vesicles

E. Eitan, I. Laquian, J. Connell, M. Thomsen (Natick, MA, USA)

Objective: To evaluate neuron-derived extracellular vesicles and measurement for biomarkers of inflammation: CD9, CD63, CD81, GRIN2a, NFkB, Alpha Synuclein, and of insulin signaling: Akt, IRS-1, mTOR, MAP Kinase after drug treatment in healthy elderly participants and Parkinson's disease patients.

Background: GLP-1 type drugs have shown improvements in Parkinson's disease (PD) patients [1,2]. KP405 is a novel, first-in-class brain-penetrating dual glucagon-like peptide 1 (GLP-1)/glucose dependent insulinotropic polypeptide (GIP) receptor agonist for the treatment of Parkinson's disease. Efficacy of KP405 has been extensively characterised in multiple models of Parkinson's disease.

Methods: In a randomised, placebo-controlled, Phase I multiple dose study (7 days of treatment) in healthy elderly participants and Parkinson's disease patients (8 subjects per cohort, 6 KP405-treated and 2 matching placebo-treated by subcut. injection, respectively), blood samples were collected for brain-derived exosome analysis (Day -1, Day 1, Day 8 and Day 14).

Results: Exploratory brain-derived extracellular vesicle analysis obtained from blood plasma in healthy elderly participants and participants with Parkinson's disease demonstrated treatment-related changes in insulin signalling, neuroprotection and neuroinflammation scores following treatment initiation. Across all three scores, placebo values generally remained close to baseline over time, whereas statistically significant changes from baseline and greater variability were observed in the drug treatment groups. Increases in insulin signaling and neuroprotection scores and decreases in neuroinflammation scores remained evident in some participants after 7 days of treatment and generally returned towards baseline by the follow-up visit. Alpha-synuclein levels were reduced in the healthy elderly cohort on day 1.

Conclusion: In this clinical study in healthy elderly participants and Parkinson's disease patients, extracellular vesicle analysis demonstrated improvements in insulin signaling and neuroprotection scores and decreases in inflammation markers in the brain following subcut. treatment with KP405.

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LBA 24: α -Synuclein Strain Identity Links Air Pollution to Cognitive Decline in Lewy Body Diseases: From Environmental Driver to Prognostic Biomarker

X. Zhang, Z. Mao (Baltimore, MD, USA)

Objective: To determine whether α -synuclein (α Syn) strain identity provides a unifying axis linking environmental exposure to cognitive decline in Lewy body diseases (LBD), and whether strain-resolved cerebrospinal fluid (CSF) biomarkers can quantify and predict cognitive transitions in Parkinson's disease (PD).

Background: LBD (PD and dementia with Lewy bodies, DLB) progress along heterogeneous cognitive trajectories with few validated environmental drivers or prognostic markers. α Syn propagates as distinct conformational strains that dictate pathology. We hypothesized that exogenous stressors and disease processes converge on α Syn conformation, such that the strain ensemble encodes both the cause and the future course of disease.

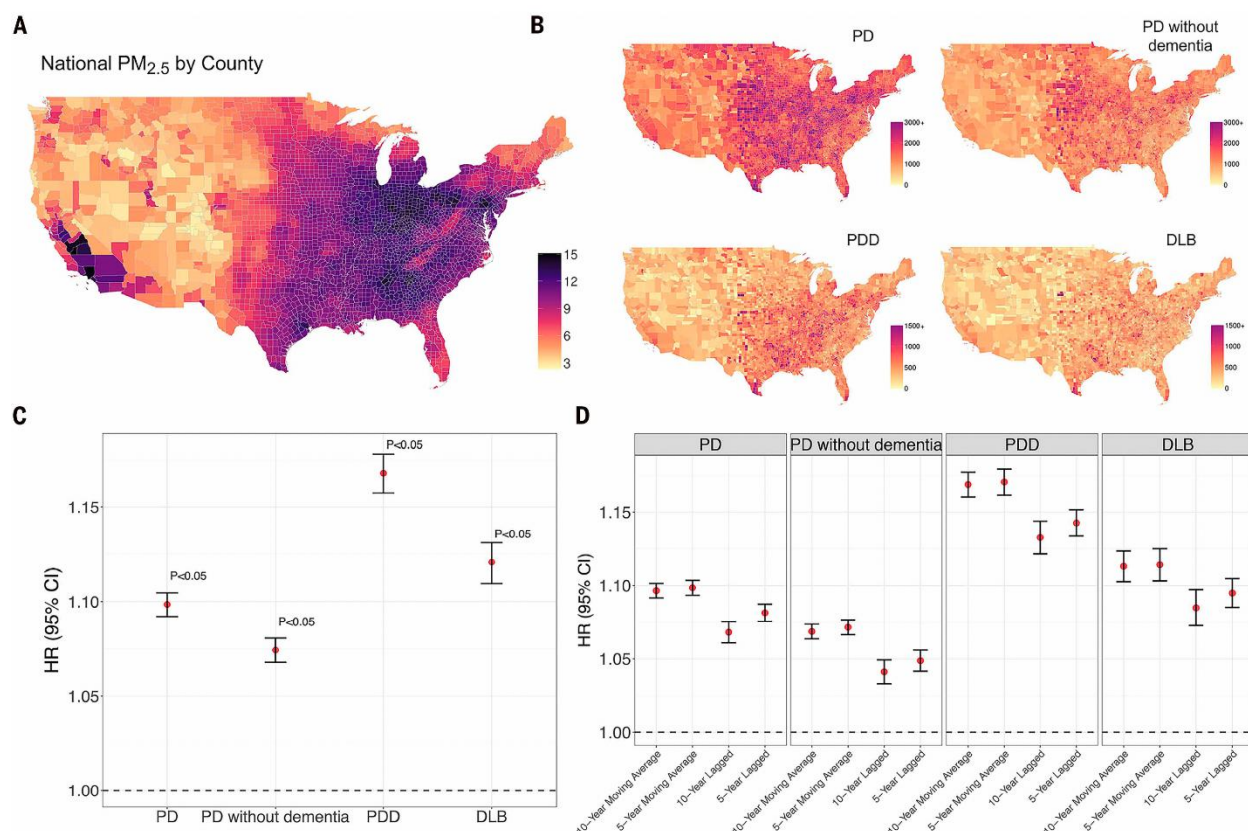
Methods: We combined (1) a longitudinal Medicare cohort (56.5 million individuals) linking fine particulate matter (PM_{2.5}) to first hospitalization for PD, PD without dementia, PD dementia (PDD), and DLB, with controlled nasal PM_{2.5} exposure in wild-type, α Syn-knockout, hA53T, and humanized- α Syn mice; and (2) seed amplification assays (SAA) of CSF from healthy controls (HC) and PD with normal cognition (PD-NC), mild cognitive impairment (PD-MCI), and dementia (PD-

D). Strains were profiled by thioflavin-T kinetics, dynamic light scattering (DLS), proteinase-K (PK) resistance, seeded neurotoxicity, and RNA-seq; machine-learning (ML) classifiers and longitudinal sampling tested prognostic value.

Results: PM_{2.5} exposure raised LBD risk (PDD hazard ratio 1.17; DLB 1.12), exceeding PD without dementia, and generated a PK-resistant, hypertoxic α Syn strain (PM-PFF) reproducing the biophysical, neuropathological, and immune-transcriptomic signatures of patient LBD strains; α Syn depletion was protective. In patients, CSF strain features differed stepwise across HC, PD-NC, PD-MCI, and PD-D; ML classifiers separated cognitive groups; and longitudinally, DLS peak number shifted ~1 year before conversion from PD-NC to PD-MCI.

Conclusion: Environmental exposure and clinical progression converge on α Syn conformation. Strain-resolved CSF biomarkers can advance from binary diagnostics into exposure-sensitive, prognostic tools, enabling risk stratification and measurable endpoints for prevention in synucleinopathies.

Figures:



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