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Late-Breaking Abstracts

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5th Pan American Parkinson's Disease and Movement Disorders Congress®

2024 Late-Breaking Abstracts

LBA-1 A Strategic Training Blueprint to Bolster Research Capacity within the Global Parkinson's Genetics Program (GP2)

S. Dey, H. Leonard, M. Makarious, A. Martinez-Carrasco, A. Zirra, P. Reyes-Perez, P. Saffie Awad, A. Sanyaolu, P-J. Kung, Y-W. Tay, C. Shambetova, A J. Noyce, S. Bandres-Ciga, The global Parkinson´s Genetics Program (GP2) (*Sevilla, Spain*)

LBA-2 Clinical-Pathologic Findings in the US-Based Dementia with Lewy Bodies Consortium

P. Patel, LM. Bekris, S. Formica, DW. Tsuang, C. Zabetian, I. Litvan, J. Fleisher, S. Berman, D. Irwin, A. Bozoki, C. Lippa, O. Lopez, D. Galasko (*Cleveland, OH, USA*)

LBA-3 Peripheral Nervous System Involvement in CSF1R-Related Disorder – A Transmission Electron Microscopy Study

P. Jiang, W. Lin, DW. Dickson, ZK. Wszolek (*Jacksonville, FL, USA*)

LBA-4 Heterogeneous Contribution of Polygenic Scores to Comorbidities Presentation in Parkinson's Disease Patients

C. Villaman, C. Tejos, G. Repetto, I. Mata, AD. Klein, E. Pérez-Palma (*Santiago, Chile*)

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Objective: To promote and facilitate learning internationally by providing resources and expertise to address the training needs of the Global Parkinson's Genetics Program (GP2; www.gp2.org) and its collaborators.

Background: GP2 is an international collaborative effort committed to advancing the understanding of the genetic bases of Parkinson's disease (PD). Alongside building strong connections with global partners, training the next generation of PD researchers worldwide is a key priority for GP2.

Method: The Training and Networking group has strategically developed resources and training opportunities to achieve breadth and impact. As resources, we have developed a free online web-based learning platform (https://training.gp2.org/) dedicated to establishing foundational knowledge in PD genetics and bioinformatics. Tailored training opportunities, ranging from short courses to graduate programs, have been provided to clinicians and scientists from traditionally underrepresented regions in PD research to equip them with research skills and build local research capacity.

Results: 8 courses have been launched on the GP2 Learning Platform thus far; currently accessed by over 800 students. These include: Beginner and Intermediate Bioinformatics, Using Terra for Data Analysis, PD Genetics for Non-Geneticists, Research Methods I and II, Bioinformatics Training Workshop, and Introduction to Python. A course on whole-genome sequencing data analysis in monogenic PD is in development. A Trainee Network, consisting of over 225 members worldwide, has facilitated streamlined training, knowledge exchange, and collaborative data analysis across GP2. Two in-person training workshops in Mexico and India, along with a hybrid Hackathon, involving 80 trainees from over 20 different countries have further enriched the training experience. Over 30 trainees have received support to attend graduate courses in bioinformatics and data science at the Foundation for Advanced Education in the Sciences at the NIH. Furthermore, 11 PhD and 12 master's fellowships have been awarded to individuals in Africa, Asia, Australia and Latin America. Sabbatical training opportunities at GP2 centers have been extended to members of the Trainee Network.

Conclusion: As GP2 continues to gain momentum, our reach will expand to ensure local research capacity is generated and support the expanding network of trainees and researchers worldwide. These efforts contribute significantly to advancing our understanding of the genetic basis of PD.

LBA-2 Clinical-Pathologic Findings in the US-Based Dementia with Lewy Bodies Consortium

P. Patel, LM. Bekris, S. Formica, DW. Tsuang, C. Zabetian, I. Litvan, J. Fleisher, S. Berman, D. Irwin, A. Bozoki, C. Lippa, O. Lopez, D. Galasko (*Cleveland, OH, USA*)

Objective: To examine the clinical and biomarker changes in a cohort of deeply phenotyped Lewy body dementia who have undergone neuropathologic evaluation.

Background: The Lewy body dementias clinically include both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). The Lewy body dementias can be challenging to diagnose accurately, particularly in the mildly symptomatic stage.

Neuropathologic confirmation of the presence of Lewy body pathology can be helpful in confirming the diagnosis of a Lewy body disease process and examining the influence of co-existent neuropathologic changes such as Alzheimer's disease on clinical presentation including imaging and biofluid characteristics. These results can also assist with examining the value of pre-morbid clinical characteristics to improve diagnostic accuracy.

Method: The US-based Dementia with Lewy Bodies Consortium (DLBC) is a NIH/NINDS/NIA funded project, linked to the NINDS Parkinson's Disease Biomarkers Program (PDBP), to annually characterize individuals with either a DLB/MCI-DLB or PDD/PD-MCI diagnosis, including deep clinical phenotyping and collection of imaging and biofluid and to obtain autopsy at the time of death.

Results: In the first 32 autopsied DLBC cases, the average length of time between last evaluation and collection of biofluids was 366 days (median 342 days). Three of the initial 20 cases did not have Lewy body pathology with pathologic diagnoses of LATE, PART and Argyrophilic Grain Disease. In these three cases, the mean MDS-UPDRS part III score was 22.7, MoCA was 19.7. UPSIT, for olfaction, was normal (34 and 35) in two of the non-Lewy body disease cases. For the autopsy confirmed Lewy body disease cases, mean MDS UPDRS III was 32.5, MoCA 18.5 and UPSIT was 13.3. CSF A□ 42/40 was significantly lower in DLBC cases with greater anatomic distribution of amyloid (Thal Stage 4/5, 0.09 versus Thal stages 0-3, 0.14, $p<0.01$) and CSF p-tau was higher in cases with higher staging of neurofibrillary tangle pathology (Braak IV-VI (100.9 pg/ml) versus Braak I-III (64.9 pg/ml).

Conclusion: These findings suggest that in patients with possible Lewy body dementia, impaired olfaction may be useful for differentiating non-Lewy body disease cases from those with Lewy body disease. CSF testing was also useful in determining level of coexistent Alzheimer's disease pathology. Future efforts will include examination of synuclein aggregate assays in CSF from DLBC clinical and autopsy cases, examine the usefulness of dopamine transporter scans, and expand the diversity of the cohort.

LBA-3 Peripheral Nervous System Involvement in CSF1R-Related Disorder – A Transmission Electron Microscopy Study

P. Jiang, W. Lin, DW. Dickson, ZK. Wszolek (*Jacksonville, FL, USA*)

Objective: To assess the peripheral nervous system (PNS) involvement in the CSF1R-Related Disorder (RD).

Background: CSF1R-RD is a hereditary neurodegenerative disease with heterogenous clinical presentation, ranging from inborn multisystem disorder (early-onset CSF1R-RD) to isolated adult-onset neurodegeneration (late-onset CSF1R-RD). As the genetic and phenotypic spectrum of the disorder is expanding, it is possible that other, not yet reported, manifestations of the disease may occur.

Method: We recruited 15 individuals (7 males) with a median age of 49±12 years, including 10 with pathogenic CSF1R mutations and 5 healthy controls. The CSF1R mutations included Gly589Glu, Ala781_Asn783del, Leu786Ser, Gln835X, Ser836Asn, p.Tyr886Ser fs*56, c.1969+115_1969+116del, c.2442+1G>A. Nine mutation carriers were heterozygotes for CSF1R mutations and had a positive family history, whereas one was a CSF1R mutation homozygote with a negative family history for CSF1R-RD. Eight CSF1R mutation carriers were symptomatic with a median disease duration of 5.5 ±12 years. Two symptomatic carriers were treated with hematopoietic stem cell transplantation, and five were participants in an interventional clinical trial (NCT05677659). Skin samples were collected with a 3 mm

punch from a non-dominant forearm and fixed overnight in the 2% glutaraldehyde, 2% paraformaldehyde in 1× PBS. Next, they were treated with 1% OsO4 (1 hour), and 1% uranyl acetate in 50% ethanol (30 minutes), 70%, 80%, 95%, 100% ethanol, and 100% propylene oxide (sequentially, 15 minutes each). Next, the samples were infiltrated with a mixture of propylene oxide/ Epon resin (1 : 1) (overnight), then moved into Epon resin and subsequent polymerization at 60oC degrees (2 days). Lastly, ultrathin sections (70 nm) were cut with Leica Ultramicrotome (UC7) and counterstained with uranyl acetate and lead citrate. The sections were examined with JEM-1400 Flash Transmission EM.

Results: The transmission EM showed similar axonal ultrastructure in skin samples in CSF1R mutation carriers at different disease stages, as well as in healthy controls.

Conclusion: CSF1R-RD mainly affects the central nervous system and spares the PNS. The presence of symptoms related to PNS in individuals with CSF1R mutations should prompt the evaluation for coexisting disorders.

LBA-4 Heterogeneous Contribution of Polygenic Scores to Comorbidities Presentation in Parkinson's Disease Patients

C. Villaman, C. Tejos, G. Repetto, I. Mata, AD. Klein, E. Pérez-Palma (*Santiago, Chile*)

Objective: Our primary goal was to determine whether individual polygenic scores (PGS) for comorbidities commonly found in PD are significantly higher in PD patients who develop the comorbidity compared to those who do not.

Background: In this study, we explored the complex relationship between aggregated common genetic variation, as represented by PGS, and the occurrence of comorbidities in PD patients. Type 2 Diabetes (T2D), Major Depressive Disorder (MDD), Migraine headaches (MH), and Epilepsy (EPI) are comorbidities commonly found in PD. Although most cases of PD are idiopathic and multifactorial, genetic factors play an important role in its development. We aim to provide evidence on the interplay between common genetic factors and the presentation of comorbidities in PD.

Method: We conducted our analysis using data from the UK Biobank dataset, which included 502,367 individuals. We only include in our analysis unrelated individuals from European ancestry. The final dataset consisted of 4,144 PD cases and 370,480 controls. We used GWAS summary statistics (SS) obtained through rigorous meta-analyses using data from 23andMe. We generate PGSs based on the overlap between common SNPs of the UK biobank QC-SNPs and those reported in the SS of each comorbidity GWAS. We evaluated the risk of comorbidities comparing the top distribution with the rest of the population. We used the t-student test to assess the difference between cases and controls.

Results: Individuals with PD and comorbidities exhibited significantly higher PGS values compared to those without comorbidities (Figure 1; T2D p-value 2.06x10-13; MDD p-value 9.98x10-3; MH p-value 0.0469; EPI 9.73x10-3). These findings were consistent for T2D, MDD, MH, and EPI. We identified a higher genetic risk for T2D and EPI in individuals with PD onset between 50-70 years old, suggesting a possible link between genetic predisposition and disease onset (Figure 2). Although PD women exhibited an increased PGS for MDD and epilepsy, males showed a higher risk for T2D (Figure 3).

Conclusion: Our study advances our understanding of the genetic basis of comorbidities presentation in PD patients. We identify genetic contribution to PD presentation and sex-specific risk in comorbidities. By identifying these patterns across multiple comorbidities, our findings contribute to future development of personalized approaches to understand susceptibility and progression of comorbidities in PD patients.

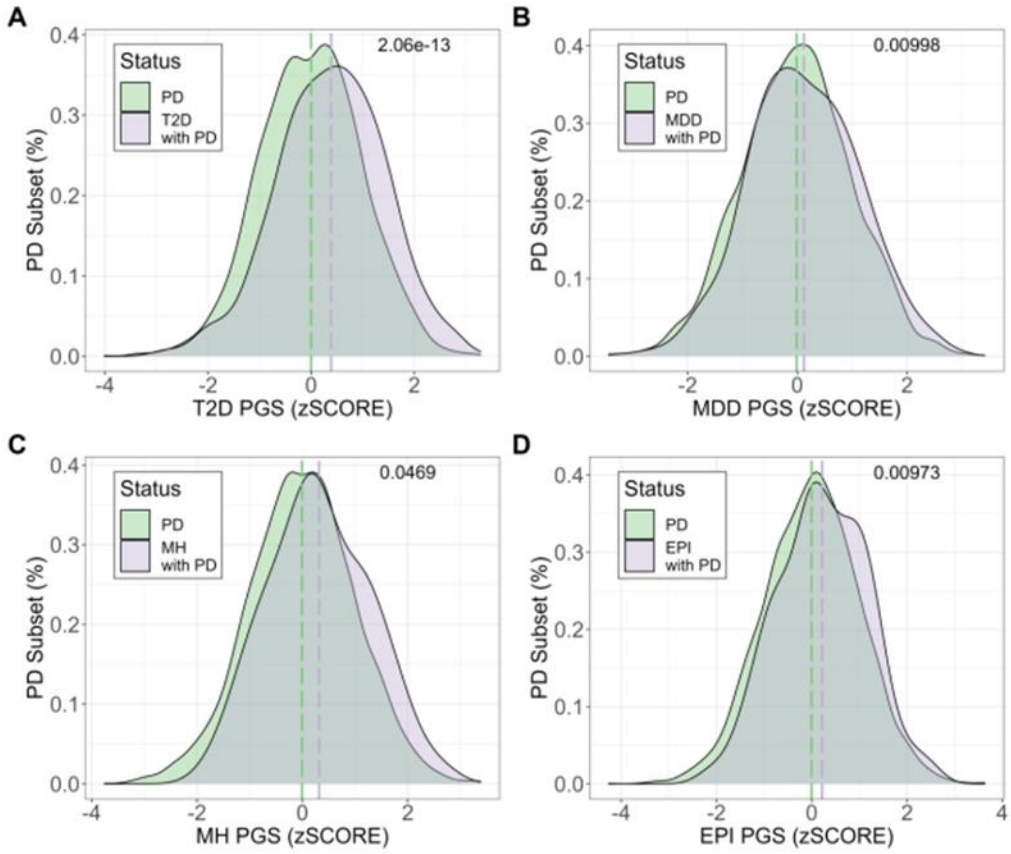

Figure 1. Comorbidity PGS in PD patients from the UK Biobank. (A-D) PGS distribution between the PD subset in green and PD with (A) type 2 diabetes, (B) major depressive disorder, (C) migraine headache, (D) epilepsy in purple. The colored lines indicate the mean for each group. The P-value was calculated with Kolmogorov-Smirnov to compare the normal distribution between groups.

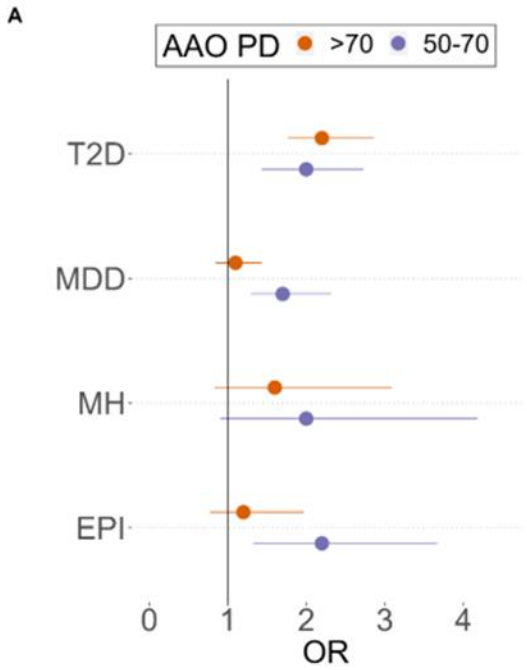

Figure 2. Association of PGS comorbidities with PD onset in individuals from the UK biobank. Shows are the OR and the 95% confidence interval for PD comorbidities in the PD subset), 50-70 (Purple), and >70 (Orange) age at onset. OR was obtained with a logistic regression for comorbidity using age, sex and the first four PC as covariates comparing 20% of high PGS with the rest of the group in each age interval.

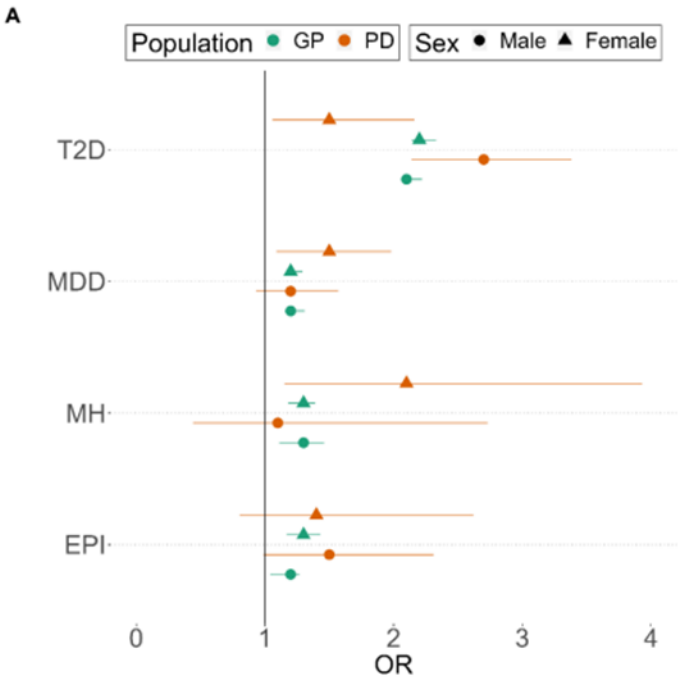

Figure 3. Association of comorbidity PGS with Sex Patterns. (A) Shows are OR and 95% confidence interval, for PD comorbidities in the PD subset (Orange) and the general population (Green) and analyzed by sex (Males as circles and females as triangles). OR was obtained using logistic regression for comorbidities with age, sex and the first four PC as covariates compared to 20% of the high PGS groups.