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NATIONAL VA PARKINSON'S DISEASE CONSORTIUM
Education · Collaboration · Advocacy

THE TRANSMITTER

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Article Reviews

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Genome-Wide Association and Meta-Analysis of Age at Onset in Parkinson Disease: Evidence From the COURAGE-PD Consortium

Parkinson's disease (PD) is one of the fastest-growing neurodegenerative diseases globally, with an estimated 30.9% increase in the number of PD patients in 2019 as compared to 2010. An earlier age of onset (AAO) of PD is an essential contributor to overall burden of the disease. ~95% of cases are sporadic with predominantly late age of onset. Genome-wide association studies (GWAS) have identified genetic variants at 78 loci for sporadic PD. Prior studies led to identification of two loci, SNCA and TMEM175, as risk factors for an earlier AAO. Both of these loci are known to play a role in alpha-synuclein-linked mechanisms. The COURAGE-PD (Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease) is a world-wide consortium comprising 35 PD study cohorts. The present study aims to perform an AAO GWAS in COURAGE-PD and to investigate the validity of previously observed loci by conducting one of the largest meta-analyses of PD AAO GWAS to date by combining previous International Parkinson's Disease Genomics Consortium (IPDGC) AAO GWAS (n = 17, 415) with newly generated COURAGE-PD AAO GWAS (n = 8,535), resulting in a combined dataset of 25,950 patients with PD.

The average AAO in the COURAGE-PD dataset was 58.9 $\pm$ 11.6 (SD) years, with an under-representation of females (40.2%). No major influence of gender or ethnicity on AAO was noted. The meta-analysis of COURAGE-PD and IPDGC datasets led to the identification of two loci that reached genome-wide significance. The SNCA variant, rs983361, was the most strongly associated SNP, with the presence of allele T (frequency = 0.204) leading to an average delay in AAO by 0.72 years. An independent locus, BST1, on the fourth chromosome, showed similar effects in COURAGE-PD and IPDGC datasets, resulting in the identification of a novel genome-wide significant BST1 locus for AAO. The rs4698412 allele A (frequency = 0.562) at the locus led to an average earlier AAO of 0.526 years in PD patients. There was an inverse association between PD polygenic risk score (PRS) and AAO of PD. PRS explained only 0.59% of the genetic proportion of PD heritability.

This study further refines the genetic architecture of chromosome 4 underlying through the identification of BST1 as a novel AAO PD locus. These findings open a new direction for the development of treatments to delay the onset of PD.

Grover S, Kumar Sreelatha AA, Pihlstrom L, et al. Genome-wide Association and Meta-analysis of Age at Onset in Parkinson Disease: Evidence From the COURAGE-PD Consortium. Neurology. 2022;99(7):e698-e710. doi:10.1212/WNL.0000000000200699

Six Action Steps to Address Global Disparities in Parkinson Disease: A World Health Organization Priority

The Global Burden of Disease study identified PD as the fastest growing neurological disorder between 1990 and 2016 in terms of death and disability. This calculation was based on a global evaluation with estimates of prevalence, deaths, and disability-adjusted life-years (DALYs) in 195 countries and territories. Current estimates suggest that in 2019, PD resulted in 5.8 million DALYs, increasing by 81% since 2000. Moreover, it is estimated that PD caused 329,000 deaths in 2019, an increase of more than 100% since 2000. The rise in cases is thought to be multifactorial and is likely affected by factors such as aging populations, improved research methods, advanced technologies, better education, and an increased awareness of the disease. Higher prevalence rates could also be a result of increasing life expectancy. According to the World Health Organization (WHO) Atlas for Neurological Disorders, the available resources for neurological disorders, including PD, within most countries are grossly insufficient, with large inequalities existing across regions, income levels, and countries. This assertion has been reinforced by a recent study demonstrating the consistent scarcity and unaffordability of PD therapies and resources in most African countries. Likewise, in low-income countries, the total neurological workforce is 0.1 per 100,000 population compared with a global median of 3 per 100,000. A strong recognition of the growing effect, high numbers, and contrasting lack of resources and treatment for people with PD needs to be addressed.

In April 2021, a multidisciplinary, sex-balanced, international WHO workshop identified 6 workable avenues for action with emerging themes and a focus on low- and middle-income countries (LMICs) and resource limited settings. Among the topics and strategies that emerged from these discussions are the domains of disease burden; advocacy and awareness; prevention and risk reduction; diagnosis, treatment, and care; caregiver support; and research. Six major challenges were identified and their proposed solutions included in the action plan. The first challenge is a lack of quality epidemiological data to determine disease burden. It was proposed to generate better-standardized epidemiological and economic data, with equitable representation (by race, ethnicity, geography, sex, and gender). The second challenge is lack of awareness and advocacy for PD in general. It is suggested to improve public education and training of health workforce as well as change in legislation and policy to address PD. The third challenge is lack of risk reduction and prevention strategies. The action plan proposes to generate harmonized approaches for PD risk reduction based on existing evidence, with both individual and population level interventions. The fourth challenge is lack of access to diagnosis, treatment, and care, creating a huge treatment gap. It is proposed to develop culturally and socioeconomically acceptable models of care that are interdisciplinary, replicable, affordable, and accessible to those who need them most, and to integrate a continuum of services to include wellness, neurorehabilitation, and palliative care at the earliest stages of diagnosis through the implementation of universal health coverage. The fifth challenge is lack of caregiver support. Action plan proposes to provide an accurate and timely diagnosis, accompanied by training and education to caregivers as well as psychosocial, financial, and community-based support. Finally, the sixth challenge is lack of research coordination and investment in PD research. It is suggested to improve coordination, reduce redundancies, provide appropriate funding to conduct and implement PD research. This action plan proposes six workable avenues for action in the domains of disease burden, in order to create a global, collaborative effort to address the global disparities in PD care.

Schiess N, Cataldi R, Okun MS, et al. Six Action Steps to Address Global Disparities in Parkinson Disease: A World Health Organization Priority [published online ahead of print, 2022 Jul 11]. JAMA Neurol. 2022;10.1001/jamaneurol.2022.1783. doi:10.1001/jamaneurol.2022.1783

Dysautonomia and REM Sleep Behavior Disorder Contributions to Progression of Parkinson's Disease Phenotypes

Non-motor symptoms in PD have been noted to precede motor manifestations, particularly rapid eye movement sleep behavior disorder (RBD) and autonomic dysfunction. Both RBD and dysautonomia are noted to have high rates of phenoconversion to manifest neurodegenerative synucleinopathies such as PD, dementia with Lewy bodies, or multiple system atrophy. On the other hand, a significant proportion of manifest PD patients have no RBD or significant autonomic dysfunction. Therefore, the presence or absence of these non-motor symptoms may indicate different trajectories and possibly disparate pathogenesis of PD. Hence, this investigation was conducted to analyze the role of RBD and autonomic dysfunction as distinctive traits for PD subtypes and analyze the interaction of these two classifiers to in PD severity and progression.

Data from the Parkinson's Progression Marker's Initiative (PPMI) study cohort were utilized, including 423 subjects with PD diagnosis with 3 years of follow-up. Scores from the multiple rating scales were considered including Movement Disorder Society-Unified PD Rating scale (MDS-UPDRS), Hoehn and Yahr scale (H&Y), University of Pennsylvania smell identification test (UPSIT), Montreal cognitive assessment (MoCA), Scales for Outcomes in PD-Autonomic dysfunction (SCOPA-AUT), REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), Epworth Sleepiness Scale (ESS), Geriatric depression scale (GDS), State-Trait Anxiety Inventory (STAI), heart rate (HR), and blood pressure (SBP). It was observed that at baseline the majority (64%) of PD subjects reported symptoms of autonomic dysfunction. By year 3, 76% of subjects reported dysautonomia. This analysis showed that 44% of subjects at baseline had positive pRBD score, which increased to 53% at year 3.

To further assess the role of RBD and dysautonomia symptoms in identifying PD subtypes, PD cohorts were divided based on dysautonomia status (DysA+ or DysA−) and pRBD status (pRBD+ or pRBD−) at baseline into four groups: DysA+/pRBD+, DysA+/pRBD−, DysA−/pRBD+, and DysA−/pRBD−. The subgroup with both dysautonomia and pRBD symptoms (DysA+/pRBD+) presented with a more severe pattern of motor and non-motor symptoms. Pairwise multiple comparisons between groups confirmed a significant difference in non-motor symptoms, particularly between the DysA+/pRBD+ vs. DysA−/pRBD− groups. With comparisons among all groups, a statistically significant difference was more frequently present when groups were discordant for dysautonomia (i.e., DysA+ vs. DysA− groups) than when discordant for pRBD. Hence, it was concluded that dysautonomia symptoms predict severe progression of motor and non-motor symptoms better than RBD symptoms across the 3-year follow-up period. It was noted that dysautonomia is associated with a more severe PD phenotype, possibly corresponding to a distinct neuropathological subtype with more widespread involvement across peripheral and central nervous system locations. These observations have important prognostic value for the counseling of patients presenting to the clinic and for stratification of subjects for observational and therapeutic studies.

Riboldi, G.M., Russo, M.J., Pan, L. et al. Dysautonomia and REM sleep behavior disorder contributions to progression of Parkinson's disease phenotypes. npj Parkinsons Dis. ***8****, 110 (2022).*
https://doi.org/10.1038/s41531-022-00373-0

Committee Activities

Clinical Care Committee

- **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The Southwest PADRECC leads the committee for September/October. The committee meets via conference call the first Tuesday of the month at 12pm (EST)
- **Standardize and Optimize Clinical Care:** The committee continues to discuss treatment strategies, new medications and other procedures, and other clinical issues to improve patient care and outcomes across the national PADRECCs service area.. It also serves to provide clinical support to the consortium network by focusing on procedures and measures to standardize clinical care across the PADRECC network.
- Recent agenda items have included:

1. Discussion of COVID 19 era operational modifications at various PADRECCs, sharing of new practices
2. Evaluation of strengths and weaknesses of clinical services at various PADRECCs
3. Future planning to enhance clinical service provision at PADRECCs : Suggestions and Strategies

Education Committee

- **PADRECC/EES Movement Disorder Series-Webinars:** knowledge-based webinars to provide VHA healthcare professionals with current practice standards and emerging trends in the treatment of Parkinson's disease and other movement disorders. CEs are typically provided for the live webinars. Check out the following link for a list of past webinars and if you are interested in receiving a recording of a past webinar please email Gretchen.glenn@va.gov and list the date/topic of interest: https://www.parkinsons.va.gov/Consortium/Presentations/Audio_Conference/MDS.asp

  - **REGISTRATION NOW OPEN!**
    Movement Disorders Series Part II-Webinar **October 13, 2022**- 9am-1pm PST / 12pm-4pm EST

  - **National VA PD Newsletter:** newsletter is available for viewing: **The VA Parkinson Report**

- **VHA/PADRECC & The Parkinson's Foundation Partnership:** Goal of the partnership is to improve the care and quality of life for Veterans living with PD through collaborative education, research and services. This committee spearheads many of the projects for this partnership. Please check out the Transmitter email for current partnership offerings/activities
- **National Website Maintenance:** The committee performs periodic maintenance checks of the National Website to ensure information is current and up-to-date.
- **PADRECC Transmitter:** This committee continues to assemble and distribute this *e*-newsletter every other month.
- **Resources available on the National Website:**
  - **Patient Education Brochures-** https://www.parkinsons.va.gov/patients.asp
    - Exercise and Physical Activity
    - Fall Prevention
    - Motor Symptoms
    - Non-Motor Symptoms
    - Agent Orange and Toxic Exposures and PD

- **PADRECC Support/Education Groups:** The PADRECCs are now holding virtual groups open to Veterans and care partners interested in attending. Please check out the National Website for listing of dates/times and contact person to register for the groups and please share with your patients/care partners: https://www.parkinsons.va.gov/patients.asp
- **My Parkinson's Story-**https://www.parkinsons.va.gov/patients.asp
  A series of short videos prepared by the VA PADRECCs addressing various aspects of Parkinson's disease.
- **Suggested Education Essentials for Veterans with PD**
  - **Digital version:** https://www.parkinsons.va.gov/patients.asp
  - **Printer friendly version:** 

Suggested Education Essentials