Check for updates

Editorial: Genetic and molecular diversity in Parkinson's disease

Nor Azian Abdul Murad[1], Siti Aishah Sulaiman[1], Azlina Ahmad-Annuar[2], Norlinah Mohamed Ibrahim[3]*, Wael Mohamed[4], Shahrul Azmin Md Rani[3] and Kin Ying Mok[5,6,7]*

[1]UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia (UKM), Kuala Lumpur, Malaysia, [2]Department of Biomedical Science, Faculty of Medicine, University of Malaya (UM), Kuala Lumpur, Malaysia, [3]Neurology Unit, Department of Medicine, Faculty of Medicine, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia (UKM), Kuala Lumpur, Malaysia, [4]Kulliyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, [5]Department of Neurodegenerative Disease, University College London (UCL) Institute of Neurology, University College London, London, United Kingdom, [6]State Key Laboratory of Molecular Neuroscience, Division of Life Science, Molecular Neuroscience Center, The Hong Kong University of Science and Technology, Hong Kong, Hong Kong SAR, China, [7]Hong Kong Center for Neurodegenerative Diseases, Hong Kong Science Park, Hong Kong, Hong Kong SAR, China

Editorial on the Research Topic
Genetic and molecular diversity in Parkinson's disease

For various reasons, most genetic studies including those related to Parkinson's disease (PD), are primarily performed with populations of European ancestry (Schumacher-Schuh et al., 2022). The insufficient representation of Asian populations in these studies could lead to missed opportunities in novel gene discoveries, drug development, and the advancement of care in multi-ethnic Asian populations. Population-specific differences in PD have been observed in various aspects. For example, epidemiological findings from most studies involving subjects of European ancestry consistently reported a male predominance in PD (Haaxma et al., 2007; GBD 2016 Parkinson's Disease Collaborators, 2018). However, this gender difference is either not apparent or reversed in East Asian studies (Ma et al., 2014; Abbas et al., 2018; Song et al., 2022; Yoon et al., 2022; Zhou et al., 2022).

Similarly, genetic studies have highlighted differences in both monogenic and complex PD between populations. The LRRK2 G2019S variant is more common in Ashkenazi Jewish, North African, and European populations, but extremely rare in East Asian populations, whereas the G2385R variant is only found in East Asian populations (Shu et al., 2019; Simpson et al., 2022). These two variants belong to different functional domains of the LRRK2 protein (Rudenko et al., 2012). While PD pathogenicity may not be related to kinase activity, PD treatment that targets LRRK2 will have to be different in East Asian populations (with a carrier rate of 6–11%) compared to other populations (Simpson et al., 2022). Because of the discrepancy in prevalence across populations, an

understanding of variant effects has to be drawn from local populations (Liang et al., 2018; Wang et al., 2022a,b). The GBA gene also poses similar issues. Where there are variants that are only found in one ethnic group but not others (Zhang et al., 2018), there is significant variation (3-31%) in the carrier frequency of GBA gene mutation across populations (Menozzi and Schapira, 2021). The R163Q variant, for example, is regarded as "benign" but mainly exists in East Asian populations. Therefore, in this case, studies confirming the role of pathogenicity should only be conducted in East Asia.

Population variations also play a role in sporadic PD. In one of the largest East Asian genome-wide association studies (GWAS) on PD, Foo et al. replicated some of the same results as studies on European ancestry populations. More importantly, the authors found two novel loci which had not been reported in the European-ancestry GWAS (Foo et al., 2020). The functional significance is yet to be determined, but the findings again point to the need to have a diversity of studies to complete the jigsaw of PD pathogenicity. The same concern applies to atypical Parkinson's disease and other neurological diseases. Taken together with local data, the polygenic risk score may be one such way forward (Sia et al., 2021).

Large GWAS in other Asian populations, particularly people from South East Asia (SEA), is still lacking. A previous meta–genome-wide association study in Asian populations (including SEA Singaporeans and Malaysians), reports similarities and differences in genetic risk factors between Asian and European individuals in the risk for PD, though the study was focused on Han Chinese and South Korean populations (Foo et al., 2020). In fact, a systematic review of all PD publications showed that SEA populations only account for 3% of the total investigated (Schumacher-Schuh et al., 2022). The lack of such underrepresented populations may result in missed opportunities, including the discovery of novel genetic associations for complex traits.

Similarly to East Asian populations, discrepancies in genetic variants associated with PD are observed in SEA populations when compared to people of European and Ashkenazi Jewish ancestry. The LRRK2 G2385R and R1628P are common variants found in East Asia, particularly among the Han Chinese. The G2385R, but not the R1628P variant, is common among Japanese and Korean populations, though the reverse is true for those of Thai ethnicity (Zhang et al., 2017). In Malaysia, both the G2385R and R1628P variants were associated with an increased risk of PD in the Malay and Chinese ethnic groups (Gopalai et al., 2014). More importantly, the N551K variant was protective against PD in Malay individuals (Gopalai et al., 2019), although this finding needs to be replicated in Malay populations from neighboring SEA countries such as Indonesia and the Philippines. Several GBA variants were investigated in multi-ethnic Malaysian populations consisting of Malay, Chinese, and Indian people. The most common variant was L483P, though three novel variants were also identified: P71L, L411P, and

L15S. The common European risk variants, E365K, T408M, and N409S, were not detected (Lim et al., 2022). Another study involving only the Malay ethnic group reported that GBA variants may be associated with PD and may modify age of onset amongst the population (Mohamad Pakarulrazy et al., 2020), and this observation was also observed in Thai populations (Pulkes et al., 2014).

Ethnic differences may also play a role in recessive forms of genetic PD. The PINK1 L347P variant, which has not been reported in other populations, had a higher carrier frequency in Filipino people (Rogaeva et al., 2004). A similar observation was also reported recently in Malay ethnic groups (Tan et al., 2020), and two patients of Indian descent in Malaysia (Lim et al., 2021), supporting the pathogenicity of the L347P variant. Another example of population differences is the PINK1 variant identified in Vietnamese individuals with PD, in which the A340T variant was higher in early-onset PD (EOPD, OR = 5.704) (Ton et al., 2020); an opposite association was observed in Han Chinese populations (Wang et al., 2006). Although these findings highlight genetic diversity, most of the studies utilized a small sample size. Thus, larger studies are needed to elucidate the genetic architecture of PD in SEA populations.

In this Research Topic, the need for diversity in PD studies is well-demonstrated. Two EOPD studies in eastern China provide additional information on EOPD in the region. Müller-Nedebock et al. demonstrate an important and interesting point, that even the same mitochondrial DNA variations may have different effects if they are "out of place" of their usual haplotypes. This adds a further dimension of potential variation that scientists and clinicians should study. Besides diversifying genetic studies on PD to complete the jigsaw of PD as far as possible, Akbar et al. also rightly point out that management is also affected by genetics, and discussions and a roadmap on how to address this are needed.

To tackle this missing diversity, a few consortiums were formed in different parts of the world including Africa (Rizig et al., 2021), Central Asia, East Asia (Mok, 2021), Latin America (Zabetian and Mata, 2017), and South Asia (Rajan et al., 2020). Their main aim is to investigate the genetic cause of PD in different populations (Global Parkinson's Genetics Program, 2021). More importantly, these consortiums have started growing from a purely genetic collaboration into a platform for researchers to form new collaborations and address important clinical questions. Ultimately, the better we understand PD, the better our patients will be managed. We should welcome more diversity in the research of PD, and we should actively promote this in the wider community to gain better support.

Author contributions

NA and SS wrote the manuscript draft. AA-A, NM, WM, and SM reviewed the final manuscript draft. KM wrote and reviewed

the manuscript draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Abbas, M. M., Xu, Z., and Tan, L. C. S. (2018). Epidemiology of Parkinson's disease-east versus west. *Mov. Disord. Clin. Pract.* 5, 14–28. doi: 10.1002/mdc3.12568

Foo, J. N., Chew, E. G. Y., Chung, S. J., Peng, R., Blauwendraat, C., Nalls, M. A., et al. (2020). Identification of risk loci for parkinson disease in Asians and comparison of risk between Asians and europeans: a genome-wide association study. *JAMA Neurol.* 77, 746–754. doi: 10.1001/jamaneurol.2020.0428

GBD 2016 Parkinson's Disease Collaborators. (2018). Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 17, 939–953. doi: 10.1016/s1474-4422(18)30295-3

Global Parkinson's Genetics Program. (2021). GP2: the global parkinson's genetics program. *Mov. Disord.* 36, 842–851. doi: 10.1002/mds.28494

Gopalai, A. A., Lim, J. L., Li, H. H., Zhao, Y., Lim, T. T., Eow, G. B., et al. (2019). LRRK2 N551K and R1398H variants are protective in Malays and Chinese in Malaysia: a case-control association study for Parkinson's disease. *Mol Genet Genomic Med* 7, e604. doi: 10.1002/mgg3.604

Gopalai, A. A., Lim, S.-Y., Chua, J. Y., Tey, S., Lim, T. T., Mohamed Ibrahim, N., et al. (2014). LRRK2 G2385R mutations are associated with an increased risk of Parkinson's disease in the Malaysian population. *Biomed. Res. Int.* 2014, 867321. doi: 10.1155/2014/867321

Haaxma, C. A., Bloem, B. R., Borm, G. F., Oyen, W. J., Leenders, K. L., Eshuis, S., et al. (2007). Gender differences in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 78, 819–824. doi: 10.1136/jnnp.2006.103788

Liang, D., Shu, L., Pan, H., Xu, Q., Guo, J., Yan, X., et al. (2018). Clinical characteristics of PD patients with LRRK2 G2385R and R1628P variants. *Neurosci. Lett.* 685, 185–189. doi: 10.1016/j.neulet.2018.08.015

Lim, J. L., Lohmann, K., Tan, A. H., Tay, Y. W., Ibrahim, K. A., Abdul Aziz, Z., et al. (2022). Glucocerebrosidase (GBA) gene variants in a multi-ethnic Asian cohort with Parkinson's disease: mutational spectrum and clinical features. *J. Neural Transm.* 129, 37–48. doi: 10.1007/s00702-021-02421-0

Lim, S.-Y., Ahmad-Annuar, A., Lohmann, K., Tan, A. H., Tay, Y. W., Lim, J. L., et al. (2021). Parkinson's disease with homozygous PINK1 p.Leu489Pro mutations in two Indian sisters. *Neurol. Asia* 26, 167–173.

Ma, C. L., Su, L., Xie, J. J., Long, J. X., Wu, P., and Gu, L. (2014). The prevalence and incidence of Parkinson's disease in China: a systematic review and meta-analysis. *J. Neural Transm.* 121, 123–134. doi: 10.1007/s00702-013-1092-z

Menozzi, E., and Schapira, A. H. V. (2021). Exploring the genotype-phenotype correlation in GBA-Parkinson disease: clinical aspects, biomarkers, and potential modifiers. *Front. Neurol.* 12, 694764. doi: 10.3389/fneur.2021.694764

Mohamad Pakarulrazy, N. F., Syafruddin, S. E., Ab Mutalib, N. S., Ahmad-Annuar, A., Lim, S.-Y., Jamal, R., et al. (2020). Glucocerebrosidase genetic variants in Malays with early and late-onset Parkinson's disease. *Neurol. Asia* 25, 39–46.

Mok, K. Y. (2021). The East Asian Parkinson disease genomics consortium. *Lancet Neurol.* 20, 982. doi: 10.1016/S1474-4422(21)00373-2

Pulkes, T., Choubtum, L., Chitphuk, S., Thakkinstian, A., Pongpakdee, S., Kulkantrakorn, K., et al. (2014). Glucocerebrosidase mutations in Thai patients with Parkinson's disease. *Parkinsonism Relat. Disord.* 20, 986–991. doi: 10.1016/j.parkreldis.2014.06.007

Rajan, R., Divya, K. P., Kandadai, R. M., Yadav, R., Satagopam, V. P., Madhusoodanan, U. K., et al. (2020). Genetic architecture of Parkinson's disease in the indian population: harnessing genetic diversity to address critical gaps in Parkinson's disease research. *Front. Neurol.* 11, 524. doi: 10.3389/fneur.2020.00524

Rizig, M., Okubadejo, N., Salama, M., Thomas, O., Akpalu, A., and Gouider, R. (2021). The international Parkinson disease genomics consortium Africa. *Lancet Neurol.* 20, 335. doi: 10.1016/S1474-4422(21)00100-9

Rogaeva, E., Johnson, J., Lang, A. E., Gulick, C., Gwinn-Hardy, K., Kawarai, T., et al. (2004). Analysis of the PINK1 gene in a large cohort of cases with Parkinson disease. *Arch. Neurol.* 61, 1898–1904. doi: 10.1001/archneur.61.12.1898

Rudenko, I. N., Kaganovich, A., Hauser, D. N., Beylina, A., Chia, R., Ding, J., et al. (2012). The G2385R variant of leucine-rich repeat kinase 2 associated with Parkinson's disease is a partial loss-of-function mutation. *Biochem. J.* 446, 99–111. doi: 10.1042/BJ20120637

Schumacher-Schuh, A. F., Bieger, A., Okunoye, O., Mok, K. Y., Lim, S. Y., Bardien, S., et al. (2022). Underrepresented populations in Parkinson's genetics research: current landscape and future directions. *Mov. Disord.* 37, 1593–1604. doi: 10.1002/mds.29126

Shu, L., Zhang, Y., Sun, Q., Pan, H., and Tang, B. (2019). A comprehensive analysis of population differences in LRRK2 variant distribution in Parkinson's disease. *Front. Aging Neurosci.* 11, 13. doi: 10.3389/fnagi.2019.00013

Sia, M. W., Foo, J. N., Saffari, S. E., Wong, A. S., Khor, C. C., Yuan, J. M., et al. (2021). Polygenic risk scores in a prospective Parkinson's disease cohort. *Mov. Disord.* 36, 2936–2940. doi: 10.1002/mds.28761

Simpson, C., Vinikoor-Imler, L., Nassan, F. L., Shirvan, J., Lally, C., Dam, T., et al. (2022). Prevalence of ten LRRK2 variants in Parkinson's disease: a comprehensive review. *Parkinsonism Relat. Disord.* 98, 103–113. doi: 10.1016/j.parkreldis.2022.05.012

Song, Z., Liu, S., Li, X., Zhang, M., Wang, X., Shi, Z., et al. (2022). Prevalence of Parkinson's disease in adults aged 65 years and older in China: a multicenter population-based survey. *Neuroepidemiology* 56, 50–58. doi: 10.1159/000520726

Tan, A. H., Lohmann, K., Tay, Y. W., Lim, J. L., Ahmad-Annuar, A., Ramli, N., et al. (2020). PINK1 p.Leu347Pro mutations in Malays: prevalence and illustrative cases. *Parkinsonism Relat. Disord.* 79, 34–39. doi: 10.1016/j.parkreldis.2020.08.015

Ton, N. D., Thuan, N. D., Thuong, M. T. H., Ngoc, T. T. B., Nhung, V. P., Hoa, N. T. T., et al. (2020). Rare and novel variants of PRKN and PINK1 genes in Vietnamese patients with early-onset Parkinson's disease. *Mol. Genet. Genomic Med.* 8, e1463. doi: 10.1002/mgg3.1463

Wang, F., Feng, X., Ma, J., Zou, H., and Chan, P. (2006). A common A340T variant in PINK1 gene associated with late-onset Parkinson's disease in Chinese. *Neurosci. Lett.* 410, 121–125. doi: 10.1016/j.neulet.2006.09.080

Wang, P., Cui, P., Luo, Q., Chen, J., Tang, H., Zhang, L., et al. (2022a). Penetrance of Parkinson disease LRRK2 G2385R-associated variant in the Chinese population. *Eur. J. Neurol.* 29, 2639–2644. doi: 10.1111/ene.15417

Wang, P., Pan, J., Luo, Q., Chen, J., Tang, H., Chen, S., et al. (2022b). A 10-Year Community-based study of leucine-rich repeat kinase 2 G2385R carriers' conversion to Parkinson's disease. *Mov. Disord.* 37, 1767–1772. doi: 10.1002/mds.29127

Yoon, S. Y., Park, Y. H., Lee, H. J., Kang, D. R., and Kim, Y. W. (2022). Lifestyle factors and Parkinson disease risk: Korean nationwide cohort study with repeated health screening data. *Neurology* 98, e641–e652. doi: 10.1212/WNL.0000000000012942

Zabetian, C. P., and Mata, I. F. (2017). LARGE-PD: examining the genetics of Parkinson's disease in Latin America. *Mov. Disord.* 32, 1330–1331. doi: 10.1002/mds.27081

Zhang, Y., Shu, L., Sun, Q., Zhou, X., Pan, H., Guo, J., et al. (2018). Integrated genetic analysis of racial differences of common GBA variants in Parkinson's disease: a meta-analysis. *Front. Mol. Neurosci.* 11, 43. doi: 10.3389/fnmol.2018.00043

Zhang, Y., Sun, Q., Yi, M., Zhou, X., Guo, J., Xu, Q., et al. (2017). Genetic analysis of LRRK2 R1628P in Parkinson's disease in Asian populations. *Parkinsons. Dis.* 2017, 8093124. doi: 10.1155/2017/8093124

Zhou, X., Liu, Z., Zhou, X., Xiang, Y., Zhou, Z., Zhao, Y., et al. (2022). The Chinese Parkinson's Disease Registry (CPDR): study design and baseline patient characteristics. *Mov. Disord.* 37, 1335–1345. doi: 10.1002/mds.29037