Genetic Impact on Brain Iron Imbalance in Asian and European Populations (IronGene)

CONTEXT

Restless legs syndrome (RLS) is a neurological disorder characterized by unpleasant sensations in the legs[1] and can occur in association with **Parkinson's disease (PD)**[2]. In patients with RLS, **substantia nigra (SN)** exhibits iron deficiency[1] while in patients with PD, SN exhibits iron augmentation[3]. Brain iron can be quantified using **non-invasive iron-sensitive magnetic resonance imaging (MRI)** techniques such as **quantitative susceptibility mapping (QSM)**[3]. Although the relationship between RLS and its association with PD remains unclear. Neurodegeneration in PD starts before the disease onset. It can be studied in **individuals at risk** in preclinical (**non-manifesting genetic mutation carriers**[4]) and in the presymptomatic phase (**isolated REM sleep behavior disorder**, **iRBD**[5]). Our understanding of spatiotemporal brain iron progression in RLS and its association with PD is very limited. **Genetics** may also contribute to the risk of RLS and PD. **Genome-wide association studies (GWAS)** have identified several genetic variants explaining up to 36% of PD heritability[6] and about 12% of RLS heritability[7,] which can be aggregated into a **polygenic risk score (PRS)**. Exploring genetic determinants of brain iron in the SN could provide precious insights into early mechanisms leading to PD, RLS, and shared pathways. Genetic risk loci may vary between European and non-European populations. To date, non-Europeans remain severely under-represented in RLS and PD GWAS. Enhancing the contribution of non-European ancestry populations to genetic studies of these conditions is extremely important, as it is anticipated to (i) enhance the power to detect genetic associations through cross-ancestry approaches, as shown for other conditions[8], (ii) increase the transportability of clinical applications derived from genetic associations, such as risk prediction through PRS[9]. **To address these gaps, we propose integrating genetic information with neuroimaging markers using population data comprising European and South Asian populations**. **This will offer a unique insight into ancestry-specific understanding of genetic influences on brain iron imbalance across ancestries, encompassing under-represented populations.**

SCIENTIFIC OBJECTIVE

To investigate brain changes in RLS associated with PD (PDRLS+) using multimodal artificial intelligence-driven MRI techniques in Caucasian and South Asian populations. We will also determine the relationships of MRI markers with PRS for PD and RLS, to elucidate the underlying neurodegeneration mechanisms.

JUSTIFICATION FOR THE SCIENTIFIC APPROACH

The iron levels should be regulated rigorously for healthy brain functioning. Therefore, disruption in adequate iron homeostasis may contribute to the risk of developing neurological disorders such as RLS and PD. The iron scarcity in RLS might come from damage to iron acquisition by the nigral neuromelanin cells[10,] as RLS also demonstrates dopaminergic abnormality. Neuromelanin is a pigment found in the dopaminergic neurons of SN and noradrenergic neurons of locus coeruleus (LC)[2,5]. LC plays a critical role in regulating arousal and sleep, implying that LC damage could contribute to sleep disturbances in RLS. A large PD GWAS showed 90 independent genetic risk variants in Europeans[12]. PRS measures the risk of developing a disease by summing up the risk effects of multiple genetic variants obtained from GWAS. PD PRS have shown to influence disease severity[13], cognition and motor progression[14] and cortical thinning[15] but their association with neuromelanin content and brain iron density in the SN is unknown. Studies in other under-represented populations, such as Latinos and East Asians[16,17,] have replicated well-established European PD GWAS signals but have also provided evidence for the existence of ancestry-specific genetic drivers of PD[18]. LRRK2 has been shown to increase the PD risk by two-fold in East Asian population[19]. Neuroimaging studies have demonstrated neuromelanin

decrease and iron increase in **PD patients carrying genetic mutations** like LRRK2[20] and Parkin gene[21], along with free water increase[22] and nigral mean diffusivity decrease in non-manifesting genetic mutation carriers as compared to **healthy volunteers carrying no mutations (HVs)**[23]. We demonstrated regional SN damage in LRRK2 from East Asia[4]. A post-mortem study showed lower melanized nigral neurons in Indians compared to Europeans[24], suggesting a better protective mechanism in Indians. A more comprehensive understanding of population-based neurodegeneration mechanisms and their chronology during the presymptomatic phase is warranted. Eventually, a quantum leap in understanding neurodegenerative mechanisms can only be accomplished through brain imaging genomics by combining analyses of genomic data and brain phenotype data using MRI. Hence, IronGene project will facilitate a deeper understanding of the resilience mechanisms in non-European ancestry populations by investigating the genetic impact on neuroimaging changes.

METHODS

Clinic-based cohorts of Paris Brain Institute of European populations will be used (ICEBERG, NS-PARK, and Neuroprems). Population-based cohorts such as the UK Biobank (UKB, C5)[25] and Lux-GIANT/GAP-India cohort (C6)[26] will be included. The UKB has deep phenotypic and genomic data on roughly half a million individuals with approximately 78,000 individuals of European ancestry who also have brain imaging data such as QSM. Recent UKB update also comprises PD patients. South Asian subjects will be obtained from C6, which comprises 10,200 each PD and HVs. Additionally, the UKB also includes data on the South Asian population. We will compute neuromelanin depigmentation in SN and LC using neuromelanin imaging[27]. We will quantify SN iron using QSM and R2*[28].

COLLABORATIVE ASPECT

French data will be obtained at the Paris Brain Institute. Indian participants will be recruited at the All India Institute of Medical Sciences Delhi (AIIMS, led by Prof. Senthil Kumaran), and artificial intelligence tools will be developed in partnership with Prof. Tapan Kumar Gandhi, Indian Institute of Technology (IIT), Delhi, with funding support of the Integrated Health project, Franco-Indian Campus, Ministry for Europe and Foreign Affairs (MEAE).

REFERENCES

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PROFILE OF THE PHD CANDIDATE

We are seeking a dedicated PhD student to join our MOV'IT research team at the Paris Brain Institute. The ideal candidate should have strong programming skills, preferably with experience in Python or MATLAB. A background in engineering, computer science, or a related computational field is highly desirable. Expertise in artificial intelligence, MRI or image processing will be a plus. The candidate should have a deep passion for clinical neuroscience and genetics research and be eager to contribute to international, interdisciplinary global health projects. Strong analytical thinking, problem-solving skills, and the ability to work collaboratively in a global research environment are essential.