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Parkinson's disease is associated with clonal hematopoiesis with *TET2* mutation

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Kyung Ah Woo[1], Han-Joon Kim[1] ✉, Chan Young Lee[2], Jung Hwan Shin[1], Choonghyun Sun[3], Hogune Im[3], Hongyul An[3], Jiwoo Lim[3], Su-Yeon Choi[4], Youngil Koh[3,5] & Beomseok Jeon[1]

Clonal hematopoiesis of indeterminate potential (CHIP), a premalignant expansion of mutated hematopoietic stem cells, is linked to immune alterations. Given the role of neuroinflammation and immune dysfunction in Parkinson's disease (PD), we hypothesized a connection between CHIP and PD. We analyzed peripheral blood DNA from 341 PD, 92 isolated REM sleep behavior disorder (iRBD) patients, and 5003 controls using targeted sequencing of 24 genes associated with hematologic neoplasms. PD cases were classified by clinical progression mode: fast, slow, and typical. Using multivariable logistic regression models, CHIP prevalence was assessed against controls with a 1.0% variant allele fraction threshold. CHIP with *TET2* mutations was more prevalent in PD than controls (aOR 1.75, 95% CI 1.11–2.77, $p = 0.017$), particularly in the fast motor progression subgroup (aOR 3.19, $p = 0.004$). No distinct associations were observed with iRBD. PD is linked to increased odds of CHIP with *TET2* mutations, suggesting immune dysregulation in PD pathophysiology.

The potential connection between "inflammaging", i.e., chronic inflammation during aging[1], and clonal hematopoiesis of indeterminate potential (CHIP) has emerged as an area of interest, as the link between CHIP and nonmalignant diseases, i.e., atherosclerotic cardiovascular disease, stroke, and most recently, Alzheimer's disease (AD), have been reported[2–4]. CHIP refers to the nonmalignant overgrowth of specific hematopoietic stem cell progeny that carry a cancer-related mutation with a growth advantage[5]. Importantly, CHIP has been linked to an increased risk of cardiovascular death, and experimental evidence suggests that aberrant innate immune responses in CHIP may serve as a common underlying mechanism[6–8].

The inflammatory immune responses play a critical role in the pathogenesis of Parkinson's disease (PD)[9–11]. Alterations in the intestinal microbiota and inflammation, elevated levels of pro-inflammatory cytokines, activation of the innate and adaptive immune systems, and neuroinflammation in the central nervous system (CNS) with activated microglia mark the pro-inflammatory profiles of PD[10]. The presence of mutations in *DNMT3A* and *TET2*, the two most frequently mutated genes in CHIP[5], in the whole-brain DNA of elderly individuals[12] raises the possibility of CNS involvement in CHIP.

Based on these observations, we aimed to investigate the association between CHIP and PD, as well as iRBD as a prodromal entity for Lewy body disorders. We performed targeted sequencing of genes commonly associated with hematologic neoplasms on peripheral blood samples from patients with PD, iRBD, and healthy controls. This included 24 genes, notably *TET2* and *DNMT3A* which together account for two-thirds of CHIP cases and are implicated in inflammation and immune dysfunction. Additionally, utilizing prospectively collected longitudinal data from the PD cohort, we examined whether specific clinical progression subtypes of PD—such as slow-progressing or fast-progressing with prominent motor or cognitive decline—had distinct associations with CHIP.

Results

Clinical characteristics

A total of 341 subjects with PD, 92 with iRBD, and 5003 controls were included in the analysis. Among patients with PD, 95 (27.8%) were classified as Slow PD, 98 (28.7%) as Fast PD, and 148 (43.4%) as Typical PD. The demographic characteristics of the subjects are summarized in Table 1. The patient groups exhibited a higher average age compared to the control groups, and there was a difference in sex distribution between the groups. To address these factors, all subsequent analyses were appropriately adjusted for both sex and age.

[1]Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea. [2]Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea. [3]NOBO Medicine Inc, Seoul, Republic of Korea. [4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Republic of Korea. [5]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea. ✉e-mail: movement@snu.ac.kr

Table 1 | Demographic information of study subjects

	Group		*P* value
	Control	iRBD	
N	3676	92	
Age	57.0 [53.0; 63.0]	69.5 [61.5; 75.0]	<0.001
Sex, M (%)	2578 (70.1)	50 (54.3)	0.002
	Control	**All PD**	
N	5003	341	
Age	54.0 [49.0; 60.0]	66.0 [60.0; 73.0]	<0.001
Sex, M	3644 (72.8)	185 (54.3)	<0.001
	Control	**Slow PD**	
N	5002	95	
Age	54.0 [49.0; 60.0]	63.0 [57.0;70.0]	<0.001
Sex, M	3643 (72.8)	44 (46.3)	<0.001
	Control	**Typical PD**	
N	5001	148	
Age	54.0 [49.0; 60.0]	66.0 [61.0; 72.0]	<0.001
Sex, M	3642 (72.8)	85 (57.4)	<0.001
	Control	**Fast PD**	
N	4360	98	
Age	55.0 [51.0; 62.0]	69.5 [61.0; 74.0]	<0.001
Sex, M	3112 (71.4)	56 (57.1)	0.003

IQR interquartile range, *iRBD* isolated rapid eye movement behavior disorder, *PD* Parkinson's disease.
Information at the time of sample collection is provided, with age presented as mean [IQR].

Association between CHIP, PD, and iRBD

There was no significant difference in the odds of harboring CHIP in any gene between the control group and either the iRBD or PD groups (Fig. 1). However, gene-specific analyses revealed a significant enrichment of CHIP with *TET2* mutations in participants with PD compared to controls (adjusted odds ratio [aOR], 1.75; 95% CI, 1.11–2.77; $p = 0.017$; Fig. 1A). No specific genetic associations were found in iRBD (Fig. 1B).

Association between CHIP and mode of PD progression

For the 341 subjects with PD, the mean follow-up duration after disease onset was 7.42 (SD 3.48) years. Detailed characteristics the PD subgroups with different modes of clinical progression and the criteria can be found in Supplementary Table 1 and the Methods section.

In brief, during an average follow-up of 9.97 (SD 3.08) years after PD onset, 80% of the Slow PD subgroup maintained a Hoehn and Yahr (HY) stage < 3, and the remaining 20% reached HY stage 3 after an average of 10.11 (SD 3.45) years. In contrast, 70% of the Fast PD subgroup reached HY 3 within the follow-up period, with a mean interval of 3.63 (SD 1.92) years between PD onset to HY 3. These participants were subsequently followed for an additional average duration of 2.84 (SD 2.43) years after reaching HY 3, which confirmed the absence of atypical parkinsonism. Additionally, 65 patients met the criteria for fast cognitive decline, with 43 patients classified in the Fast Cognition subgroup and 22 in the Both (Motor & Cognition) subgroup. The average duration from onset to dementia for these patients was 3.07 years (SD 1.78). Of these, 37 patients developed dementia within 3 years. For these individuals, the mean period of additional clinical follow-up was 4.32 years (SD 3.04), during which no exclusion criteria or red flags for PD diagnosis were identified.

Regarding the odds of harboring CHIP, no significant differences were observed when comparing the Fast, Slow, or Typical subgroups of PD with the control group. However, gene-specific analysis revealed the Fast PD subgroup was 2.14 times more likely to harbor a *TET2* clonal mutation (aOR, 2.14; 95% CI, 1.08 – 4.25; $p = 0.030$; Fig. 2A). Such associations were not seen in the Slow PD or Typical PD subgroups (Supplementary Fig. 1). The overall and gene-specific prevalence of CHIP in the Fast, Slow, and Typical PD subgroups are illustrated in Fig. 2B.

To further investigate the clinical aspects of PD associated with CHIP, the Fast PD group was subdivided into three categories based on whether they met criteria related to motor and/or cognition (see Methods): 'Fast Motor,' 'Fast Cognition,' and 'Both' for those meeting both criteria. Those with fast motor decline (55 subjects in the 'Fast Motor' and 'Both' subgroups) reached HY 3 after an average of 3.05 (SD 1.47) years. Individuals with fast cognitive decline (65 subjects in the 'Fast Cognition' and 'Both' subgroups) developed dementia after an average of 3.02 (SD 1.81) years.

Within the Fast PD group, the subjects with fast motor progression had marked enrichment of CHIP with *TET2* mutations compared to controls, with 10 out of 55 subjects being *TET2*-CHIP carriers (aOR, 3.19; 95% CI, 1.46–6.95; $p = 0.004$; Supplementary Table 2). The association remained significant with higher variant allele fraction (VAF) thresholds for CHIP: the adjusted odds ratio was 3.26 (95% CI, 1.38–7.70; $p = 0.007$) at a 1.5% threshold, and 3.63 (1.44–9.16, $p = 0.006$) at a 2.0% threshold. No significant associations were found between cognitive decline and CHIP.

Association of CHIP with *TET2* mutation and PD after propensity score matching

To rigorously verify the association between *TET2*-CHIP and PD, we performed propensity score matching for age and sex and reassessed the significant results compared to the overall control group (Supplementary Tables 3–5). Even after propensity score matching, PD patients ($n = 341$) demonstrated higher odds of CHIP with *TET2* mutations compared to 1:2-matched controls at a VAF ≥ 1.0% threshold (aOR, 1.94; 95% CI, 1.16 – 3.27; $p = 0.012$). The association between the Fast PD group ($n = 98$) and *TET2*-CHIP also remained significant (aOR, 2.41; 95% CI, 1.13–5.15; $p = 0.023$). Specifically, the subgroup of Fast PD patients with fast motor progression ($n = 55$) showed a marked enrichment of *TET2*-CHIP (aOR, 4.07; 95% CI, 1.61–10.29; $p = 0.003$). When applying a VAF ≥ 2.0% threshold, the results for the overall PD and Fast PD groups were not significant; however, the results for the PD with fast motor progression group remained significant ($p = 0.004$).

Discussion

In this cross-sectional cohort study encompassing patients with PD, iRBD, and controls, we observed a 75% higher odds of CHIP with *TET2* mutations in patients with PD compared to controls. This association was particularly evident in the subgroup of PD patients with accelerated motor decline.

Our investigation reveals a novel association between PD and increased odds of TET2 clonal mutation in circulating blood cells. *TET2* encodes the enzyme ten-eleven translocation 2 that catalyzes the conversion of DNA methylation to hydroxymethylation[13]. While mutations in this pivotal epigenetic regulator are frequent in CHIP and myeloid malignancies[5,14], the pathways interconnecting these somatic mutations in the systemic circulation with CNS pathologies demand further exploration. One possible explanation involves microglia, the macrophage population of innate immune cells residing in the brain parenchyma. Evidence suggests that the overactivation of microglia by pathologic α-synuclein in PD contributes to dopaminergic neurodegeneration via phagocytosis, the spread of pathologic α-synuclein, and the initiation of immunologic cascades through antigen presentation and proinflammatory cytokine release[15]. However, it remains uncertain whether marrow-derived macrophages in the systemic circulation can reach the brain parenchyma to partake in these processes[16]. In a murine model, α-synuclein overexpression prompted pro-inflammatory peripheral monocyte infiltration into the substantia nigra, and intervention to block this entry prevented subsequent neurodegeneration[17]. Among CNS macrophage populations in humans, only choroid plexus macrophages are traditionally recognized to partially turnover with blood-borne monocytes[18], and the interactions of these border-

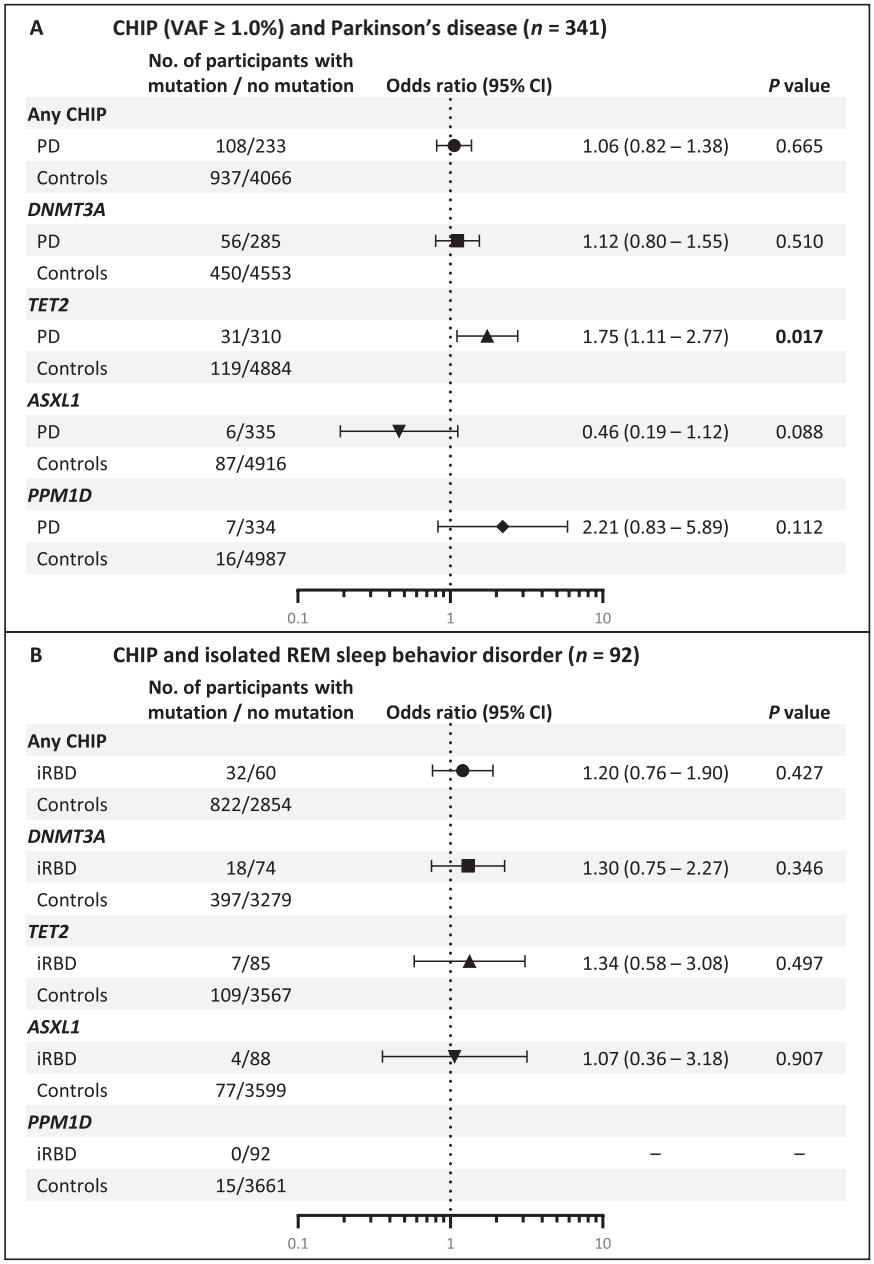


Fig. 1 | Associations between clonal hematopoiesis of indeterminate potential (CHIP), Parkinson's disease, and isolated rapid eye movement (REM) sleep behavior disorder. The forest plots in the panels illustrate the odds ratios for the associations between CHIP and **A** PD and **B** iRBD, as determined by multivariate logistic regression models with age and sex as covariates. *P* values were not adjusted for multiple comparisons. Additional data for 2.0% VAF threshold is provided in Supplementary Fig. 2. vaf variant allele fraction, CI confidence interval.

associated macrophages (BAM) with other CNS compartments remained unknown, although BAMs have been implicated in immunopathological processes, including antigen presentation to circulating lymphocytes[18]. Importantly, recent research on Alzheimer's disease and CHIP provides preliminary evidence that marrow-derived mutant microglia-like cells substantially infiltrate the brain, which may imply a potentially similar role in CNS pathogenesis in PD[4].

An alternate potential mechanism involves the systemic immune dysregulation observed in both *TET2* mutant mice models and PD. Mounting evidence underscores the role of peripheral inflammatory conditions in PD initiation and progression, engaging cytokines and peripheral immune cells[10]. Meta-analyses in PD have reported elevated peripheral cytokine concentrations, including interleukin (IL)-1β, IL-2, IL-6, and IL-10[19]. Similarly, *TET2* dysregulation triggers an immune-active, hyperinflammatory phenotype. Tet2-deficient mice display heightened expression of IL-1β, IL-6, and other inflammatory mediators, accompanied by more pronounced inflammatory responses to endotoxin shock[6,20]. Notably, *TET2*-mutant clonal hematopoiesis is associated with elevated IL-1β secretion in macrophages through nucleotide-binding oligomerization domain-leucine-rich repeat-pyrin domain-containing 3 (NLRP3) inflammasomes[6], suggesting a role for this pathway in *TET2*-CHIP-PD. The NLRP3 inflammasome has a pivotal role in PD pathophysiology by amplifying local inflammation through IL-1β secretion triggered by α-synuclein aggregates[15]; it is also systemically upregulated in immune cells in the blood of PD patients[21,22]. Monocytes could potentially contribute to CHIP-related PD through systemic immune modifications. α-synuclein demonstrates antigenicity for both microglia and monocytes[9]. Activated monocytes are elevated in the periphery of PD patients[23], and monocytes display distinct subpopulation changes and immune-related gene expression patterns in early stages of the disease[9,24].

TET2 dysregulation in neurons has also been linked to PD pathomechanism in the brain via enhanced immune activation, although this may

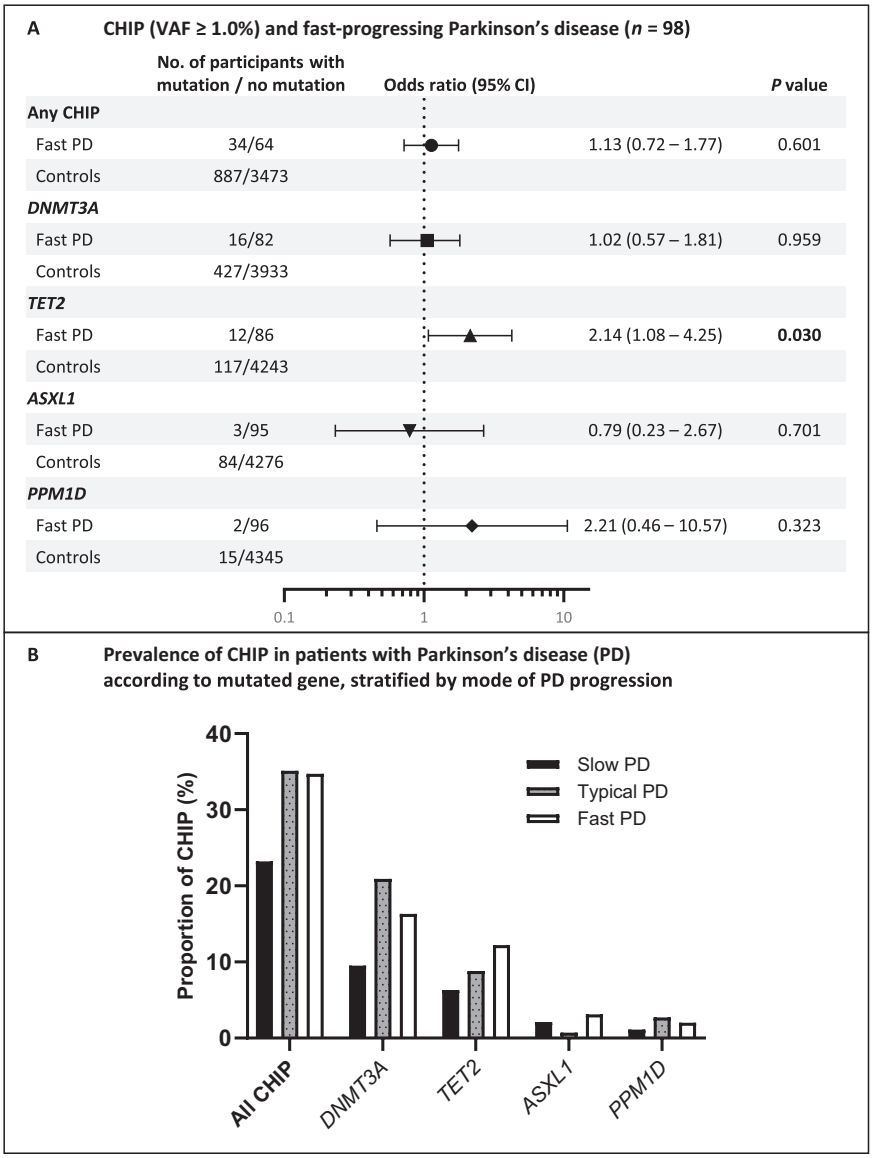


Fig. 2 | Association between CHIP and the mode of PD progression. Panel **A** presents the association between CHIP and fast-progressing PD (Fast PD). *P* values were not adjusted for multiple comparisons. Panel **B** shows the prevalence of overall CHIP and CHIP related to specific genes in each PD subgroup.

not be directly associated with *TET2* somatic mutation in the peripheral circulation. *TET2* transcript levels are significantly upregulated in PD neurons; conversely, i*n vivo* Tet2 inactivation in a mouse model blocked inflammation-induced dopaminergic neurodegeneration. Interestingly, Tet2 knockout mice showed significantly attenuated microglial activation and transcriptional immune responses to inflammatory triggers, suggesting an immune-mediated contribution of neuronal *TET2* to PD pathogenesis[25]. This diverges from the findings in the periphery, where Tet2 deficiency in bone marrow cells is linked to a hyperinflammatory state[6]. Nevertheless, taken together, these findings imply that *TET2* could play a role in PD pathogenesis through a certain mechanism, despite the specific site and directionality of this contribution remaining to be clarified.

The link between *TET2*-CHIP and the accelerated motor decline observed in our PD cohort is intriguing. Plasma IL-1β levels, which are elevated in *TET2*-CHIP, exhibit a positive correlation with motor severity in PD patients[21]. *TET2* is also engaged in the differentiation of CD4+ helper T cells[26], and emerging evidence indicates that peripheral inflammation, marked by an elevated neutrophil-to-lymphocyte ratio due to reduced lymphocyte count, aligns with parkinsonian motor severity and striatal dopaminergic denervation[27]. Taken together, our findings may imply that *TET2*-CHIP and associated immune alterations primarily exert a detrimental effect on the central dopaminergic system, potentially resulting in early parkinsonian motor decline.

Our study found no significant association between CHIP and iRBD, despite potential immune implications in iRBD. For example, blood monocytes in iRBD show elevated expression of CD11b and CCR2 involved in tissue adhesion and infiltration, similar to changes in early PD[28]. Also, toll-like receptor 4 expression on iRBD monocytes correlates with nigral immune activation and dopaminergic degeneration[28]. Meanwhile, the peripheral pro-inflammatory cytokine profile in iRBD might differ from that assumed in *TET2*-CHIP-PD. In multiple iRBD studies, alterations in IL-1β have not been observed, while serum TNF-α is elevated and predicts earlier phenoconversion to synucleinopathies[29,30]. Microglia-secreted TNF-α contributes to CNS neuronal death[31]; TNF-α is also produced in the intestinal epithelium[32]; peripheral neutralization of soluble TNF alleviates dopaminergic neurodegeneration in rodents[33]. The link between chronic anti-TNF therapy and reduced PD odds in inflammatory bowel diseases suggests the role of TNF-α in the gut-brain inflammatory pathogenesis of PD[34], and possibly, iRBD. In essence, *TET2*-CHIP and iRBD may connect to PD through distinct systemic immune mechanism changes. Nonetheless, the shared and synergistic biological activities of IL-1 and TNF-α[35] may lead to a common inflammatory outcome. Additionally, a study reported that Tet2-mutant clonal hematopoiesis is favored in a chronic TNF-α exposure

environment, which may imply a possible active cross-talk between the two mechanisms[36].

Several limitations in the present study require attention. Firstly, the VAF cutoff for CHIP was empirically set at 1.0%. While multiple studies set the CHIP threshold at 2.0, varying thresholds such as 1.0%, 2.0%, and 5.0% are also utilized depending on the disease context, testing facility, and cohort characteristics[5]. In our analysis of the entire PD or iRBD participants, thresholds of 1.5% or 2.0% did not yield significant outcomes, possibly due to sample size constraints, as higher thresholds result in fewer CHIP-positive patients. Nevertheless, the results of the subgroups that exhibited a strong enrichment of *TET2*-CHIP, specifically the group with fast motor decline, remained significant with the 1.5% and 2.0% thresholds. One concern is that the statistics might be influenced by the smaller size of the PD subsets. We speculate that replication of the findings in a larger PD cohort in the future will be useful to confirm the association between *TET2*-CHIP and PD. Additionally, it is important to note that information on medical comorbidities, including coronary heart disease and type 2 diabetes, was not collected in the present study. Given the reported associations between these conditions and CHIP and the role of inflammatory mediators in these links[2,5], as well as the suggested relationships between PD and these systemic diseases[37,38], the possibility that they may have acted as potential confounding factors should be considered in future studies. Lastly, the mode of PD progression was determined based on the onset of dementia or postural instability, which are presentations of advanced-stage PD. Milder clinical features or quantitative scales, if available, could allow for a more sensitive evaluation of the association between CHIP and PD progression.

To summarize, our findings demonstrate the association between PD and increased odds of TET2-related CHIP, especially in PD patients with accelerated motor decline. Inflammatory dysregulation may play a critical role in this relationship.

Methods

Study participants

The DNA samples of patients diagnosed with PD or iRBD at the Movement Disorders Clinic of Seoul National University Hospital between 2013 and 2020 who provided informed consent for the DNA repository database were included. The diagnosis of PD was established by a movement disorders specialist (HJK) based on the Movement Disorders Society clinical diagnostic criteria for PD[39]. iRBD was diagnosed according to the third edition of the International Classification of Sleep Disorders with video polysomnography.

The control group comprised of an institutional cohort, called the "GENIE" cohort, of healthy subjects who voluntarily underwent a routine health screening program provided by Seoul National University Hospital Healthcare System Gangnam Center and provided informed consent to be included in the DNA repository database.

The demographic profiles of the subjects with PD, iRBD, and controls were collected. Additionally, for PD subjects, regular follow-up observations were conducted at 3- to 4-month intervals to ensure the reliability of PD diagnosis (i.e., to exclude the possibility of atypical parkinsonism) and to track changes in the HY stage and the occurrence of dementia after sample collection in the outpatient clinic. The criteria for diagnosing dementia were set as a Mini-Mental Status Examination (MMSE) score of 24 or below or a Montreal Cognitive Assessment (MoCA) score of 22 or below. Based on this, the PD subject group was categorized according to clinical progression patterns. Those progressing to HY stage 3 or higher, or developing dementia within 6 years of onset, were classified as fast-progressing PD (Fast PD). Patients who remained stable, showing unilateral motor involvement for 5 years after onset, or a HY stage of 2.0 or below for 10 years without dementia, were categorized as the Slow PD group. The Typical PD group included patients with onset in or before 2020, regardless of severity or rate of progression, to represent PD patients commonly encountered in outpatient settings.

To address the potential age differences between the control and patient groups, comparative analyses were performed by selecting control cohort samples within the age range of each patient group. Specifically, for the comparison with iRBD, subjects from the GENIE cohort aged between 50 and 85 years, matching the age range of the iRBD patient group, were chosen as the control group. Likewise, for the comparison with PD, control subjects aged between 40 and 86 years, corresponding to the age range of the PD patient group, were selected.

The study protocol was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 2106-116-1227, H-1908-121-1056), and informed consent was waived by the board.

Sample preparation and analysis

Participants' genomic DNA extracted from peripheral blood mononuclear cell was used for targeted sequencing for twenty-four genes frequently involved in CHIP (Supplementary Table 6). Twist target enrichment panel (Twist Bioscience, USA) and DNBSEQ-G400 Dx (MGI Tech, China) were used with 2 × 100 bp paired-end reads with a minimum coverage of 970x (average coverage 1,724x; 960x ~ 3100x). Detailed methods for CHIP variant calling are described below.

CHIP variant calling

Data preprocessing and quality control. Targeted sequencing reads for peripheral blood mononuclear cell samples were demultiplexed using Illumina's bcl2fastq (v2.17.1.14) to generate FASTQ files. We used SeqPrep for adapter trimming (default settings) and Sickle (v1.33) for low BQV base trimming (minimum average base quality value [BQV] = 20). Subsequently, trimmed FASTQ files were submitted to GATK best practice pipeline, which includes alignment to the hg19 reference with BWA-MEM (v0.7.10). For all samples, duplicate marking and sorting were performed using PICARD (v1.94) MarkDuplicates, followed by indel realignment and base quality score recalibration using GATK Light (v2.3.9). This was followed by duplicate marking again, resulting in a final coordinate-sortedm analysis-ready BAM file for each sample. Duplication metrics and BAM quality metrics were computed using PICARD (v1.94; MarkDuplicates, CalculateHsMetrics, CollectGcBiasMetrics).

CHIP-Negative cohort. To filter out artifactual variants, we generated CHIP-negative cohort data ($n = 209$, age 20–30 years) for the CHIP variant calling filtering process. Putative CHIP variants with VAF ≥ 0.1% were collected and organized as variant frequency tables.

CHIP mutation calling and filtering. Analysis-ready BAM files for the analyzed cohort and CHIP-negative cohort were qualified based on depth of coverage (average DOC > 700x), ensuring a 2% VAF limit of detection. These BAM files were processed through a somatic variant calling pipeline, which includes VarDict[40], Mutect2 (v4.1.4.1)[41], SNVer (v0.4.1)[42], for calling single nucleotide variants (SNVs), insertions, and deletions. To achieve comprehensive somatic variant calling, we enforced a union approach among the variant callers. The criteria for positive SNVs/Indels were as follows: total reads ≥ 20, alternative reads ≥ 10 (with at least 5 positive and 5 negative), and VAF between 1.5% and 30%. We further filtered out common germline variants with a minor allele frequency (MAF) > 0.1% in gnomAD. Additionally, we excluded a subset of artifactual calls with a MAF > 2% in somatic variants on the negative cohort data that do not exist in COSMIC hematological criteria. Final variants were curated by IGV review to filter out potential artifacts driven by PCR, highly homologous regions, and repeat regions.

CHIP threshold. While CHIP has been defined by VAF of at least 2.0%[43], several studies have reported an association of hematopoietic clones with VAF < 2% with cardiovascular disease[44,45]. We sought to minimize false negatives by applying a more sensitive method with a cut-off of 1.0% VAF. Thus, all non-synonymous variants with a VAF of 1.0% to 30% were considered CHIP variants. Common germline variants with

gnomAD allele frequency ≥ 0.1% were excluded unless previously reported to be somatic and involved in COSMIC hematologic malignancies. We filtered a subset of artifactual calls with MAF > 2% in somatic variants on 20–year CHIP-negative cohort data, which do not exist in COSMIC hematological criteria. Final variants were curated by IGV review to filter out potential artifacts driven by PCR, highly homologous regions, and repeat regions.

Among the twenty-five genes sequenced, individuals with mutations in the four most frequently mutated genes in CHIP, namely *DNMT3A*, *TET2*, *ASXL1*, and *PPM1D*, were additionally specified according to the mutated gene.

Variant annotation. All dependable non-synonymous variants associated with malignancy were annotated as CHIP-driving mutations in accordance with the criteria: (1) any truncating mutations; (2) any somatic variants previously reported on at least 20 occasions with solid malignancy or on 10 occasions with hematopoietic malignancy in the COSMIC database v83.

Statistical analysis

Continuous variables are represented as mean and interquartile range or standard deviation, or as the median with range. Categorical data is presented as percentages (%). For comparing continuous variables, we employed either an independent *t*-test or the Mann–Whitney U test. Categorical variables were compared using the $\chi 2$ test or Fisher's exact test. Multivariate logistic regression, adjusted for age and sex, was utilized to identify independent risk factors for CHIP with a VAF threshold of 1.0% in both PD and iRBD. Statistical analyses were conducted using R statistical software version 4.0.2 (http://www.r-project.org).

Propensity score matching. To verify the significant findings by rigorously balancing age and sex between groups, we further performed propensity score matching using the MatchIt package in R. Age and sex was included in the propensity score model as covariates. A nearest-neighbor matching algorithm with a patient-to-control ratio of 1:2 or 1:4 was applied. The quality of matching was visually inspected using propensity score histograms to ensure a balanced distribution of propensity scores. The balance of covariates after matching was assessed using the independent t-test. The matching ratio that best eliminated statistically significant differences in age and sex was selected for each comparison. The matched dataset was then used for further multivariate logistic regression, adjusted for age and sex, to confirm the association between CHIP and PD or iRBD.

Data availability

The data is available from the corresponding author upon reasonable request.

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Author contributions

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique. KAW: 1B, 1C, 2A, 2B, 3A. HJK: 1A, 1B, 1C, 2C, 3A, 3B. CYL: 1B, 1C. JHS: 2C, 3B. CS, HI, HA, JL: 1B, 1C, 2A, 2B, 3B. SYC: 1C. YIK: 1A, 1B, 2C, 3B. BJ: 2C, 3B.

Competing interests

CS, HI, HA, JL, and YIK are employed in NOBO Medicine Inc. CS, HI, HA, and YIK are stockholders of NOBO Medicine Inc.

Additional information

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Correspondence and requests for materials should be addressed to Han-Joon Kim.

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