

The rs6971 TSPO polymorphism does not influence disease presentation or progression in Parkinson's disease

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Mitochondrial translocator protein (TSPO) PET imaging is widely used to study neuroinflammation in vivo. TSPO, located on the outer mitochondrial membrane, is upregulated in microglia in association with neuroinflammation¹, with increased binding observed in Parkinson's disease (PD)². The first-generation TSPO ligand [¹¹C]PK11195 has important limitations due to low signal-to-noise ratio, and a high production failure rate. Second generation TSPO ligands (e.g. [¹¹C]PBR28 / [¹⁸F]DPA714) offer improved binding affinity, specificity and bioavailability³, making them valuable in clinical studies as an index of brain inflammation. Since chronic neuroinflammation emerges early in PD and potentially drives disease progression⁴, TSPO-PET imaging can help evaluate the effectiveness of anti-inflammatory therapies and support the development of disease-modifying therapies.

However, second generation TSPO ligands are sensitive to a single nucleotide polymorphism in the TSPO gene (rs6971 Ala147Thr) producing high (HAB), mixed (MAB) and low (LAB) affinity binders⁵. LABs, (approximately 10% of Europeans⁶), have lower signal to noise ratios, challenging scan interpretation, often leading to their exclusion from studies utilising these ligands, potentially introducing selection bias and limiting generalisability.

A previous PD study reported the rs6971 polymorphism did not affect baseline demographics but HABs progressed to dyskinesia faster⁷. This study was limited by a relatively small sample size (n=150) and short follow-up period. We aimed to further explore the impact of TSPO genotype on disease progression and clinical outcomes in PD.

393 participants (98.5% Caucasian) with idiopathic PD from two incident population-representative cohorts (Parkinsonism: Incidence and Cognitive Heterogeneity in Cambridgeshire (PICNICS)) and *Cambridgeshire Parkinson's Incidence from GP to Neurologist* (CamPaIGN) were genotyped and underwent at least 12 years of follow up with regular clinical assessments (Supplementary Methods). The frequencies of HABs (46.6%), MABs (44.8%) and LABs (8.6%) matched prior European data⁶. No statistical difference was seen between the genotypic groups in terms of baseline characteristics including sex, age at diagnosis, Levodopa Equivalent Daily Dose, Beck Depression Inventory, Mini Mental State Examination (MMSE) and MDS-UPDRS part III scores (Supplementary Table 1).

Kaplan–Meier survival analysis showed no difference in progression to dyskinesia, dementia, postural instability or death between the genotypic groups (Figure 1). Cox proportional hazard regression models confirmed rs6971 was not a significant predictor of these outcomes (Supplementary Table 2).

Line plots with locally estimated scatterplot smoothing were used to visualise longitudinal changes in MDS-UPDRS part III, MMSE and Addenbrookes Cognitive Examination Revised (ACE-R) scores between the genotypic groups (Supplementary Figure 1). Linear mixed effects models of longitudinal MDS-UPDRS part III and MMSE scores confirmed that rs6971 was not a predictor of motor or cognitive progression and was the first variable removed via AIC-based backward selection (Supplementary Tables 3–4). The MMSE model demonstrated a poor fit due to ceiling effects and non-normal data distribution. An alternative model using ACE-R scores also found no significant effect of rs6971 on cognitive decline (Supplementary Table 5).

Our results indicate that the rs6971 genetic polymorphism is not associated with baseline clinical characteristics or disease progression in PD, supporting the continued exclusion of LABs from studies using second generation TSPO-PET ligands without compromising generalisability.

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Authors Roles

B.P conceived the study under the supervision of C.H.W-G. B.P. completed all genotyping and performed the statistical analysis. J.R.E, D.P.B, T.F., S.L.M, G.C., R.W, B.P., M.C., R.A.B and C.H.W-G., collected the clinical data. B.P wrote the first draft of the manuscript and this was critiqued and reviewed by all authors.

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