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TREM2 and Parkinson's Disease

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The finding of a rare non-synonymous variant in *TREM2* (p.R47H, rs75932628-T) confers risk for Alzheimer's disease (AD) (odds ratio 2 to 5),[1, 2] and the finding that rare variants in other AD-related genes confer risk of several other neurodegenerative diseases,[3] prompted us to ask whether R47H confers risk of Parkinson Disease.

Several other observations supported our hypothesis that *TREM2* variation may confer susceptibility to Parkinson Disease. TREM2 is expressed mainly on microglia in the central nervous system and seems to mediate the phagocytosis of apoptotic neurons through TREM2 ligation[4]. Microgliosis has been implicated in the pathogenesis of Parkinson's disease (PD), a neurological disorder characterized by degeneration of dopaminergic neurons in the substantia nigra (SN) pars compacta. Dopaminergic neurons express ligands that interact directly with TREM2[4] and, *TREM2* mRNA levels in the SN are the second highest among all brain regions[1]. In addition, pathological findings of *TREM2* variant carriers have shown the presence of abundant Lewy-bodies[1], the hallmark of PD.

We directly genotyped rs75932628, encoding the R47H variant, in 478 PD patients and 837 healthy individuals from the Washington University in Saint Louis Movement Disorder Clinic[5] as well as in 654 PD patients and 550 controls from the Memory Disorders Unit, Clínica Universidad de Navarra, School of Medicine (Pamplona, Spain)[2]. PD diagnosis was established according to the UK Brain Bank criteria. We found three p.R47H heterozygous carriers among the US PD cases and six among the Spanish PD cases, but in none of the screened controls (Table 1). The p.R47H variant is associated with PD in both the US ($p=0.02$) and in the Spanish sample ($p=0.02$). The combined analysis confirmed the association p.R47H variant with PD ($p=4.7 \times 10^{-3}$). These results suggest that the p.R47H variant not only increases risk for AD but for PD as well.

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Table 1

Association between the rs75932628-T Variant and Parkinson's Disease in two samples with different genetic background

Study	MAF % Cases	MAF % Controls	p value
WU	0.3	0	0.0223¶
Spain	0.45	0	0.0249λ
Combined			0.0047

*Mantel-Haenszel Chi-Square, DF=1 for each series and 4 for the combined analysis

¶WU cases (n=478) and controls (n=837)

λSpanish cases (n=654) and controls (n=550)