

## Genetic Marker Linking Inflammation with Sporadic Parkinson's Disease

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Parkinson's disease (PD) is a common neurodegenerative disease which frequently leads to neurological disability.<sup>1-3</sup> Medical and surgical therapies ameliorate the symptoms and cellular replacement is a potential therapeutic option.<sup>1-3</sup> Numerous monogenic genes have been associated with familial forms of PD.<sup>4-7</sup> However, these account for only 10% of the PD population. The vast majority of PD patients do not have a family history and the relative contribution of genes and environmental factors in these cases of sporadic PD<sup>4</sup> still remains to be elucidated. A few common genetic risk variants have been found in association with PD but these are unlikely to explain the etiology for all the cases.<sup>7</sup> In the past few years, numerous investigators have utilised the genome-wide association study (GWAS) approach to unravel risk loci for sporadic PD. As GWAS studies are not hypothesis-driven, the identification of genetic markers provide an opportunity for unbiased correlation with known existing pathological processes such as mitochondrial dysfunction, proteasomal impairment, unfolded protein, oxidative stress and abnormal protein accumulation. Thus far, GWASs have provided consistent associations with alpha synuclein (*SNCA*) and tau (*MAPT*).<sup>5,6</sup> However, the most recent GWAS study by Hamza and colleagues<sup>8</sup> has for the first time identified a genetic marker that is linked to inflammation, providing a different perspective to the underlying pathophysiologic mechanism of PD.

This GWAS study was carried out in 3986 American subjects of European ancestry (2000 PD, 1986 control subjects) with more than 800 000 genetic markers being analysed (Fig. 1). Unlike other GWA studies, the long mean disease duration of 8 years at enrollment allowed the investigators to exclude cases which had initially been misdiagnosed, thus improving the accuracy of the phenotype selection. In addition to confirming the 2 known risk loci (*SNCA*, *MAPT*), they identified a new genetic locus in the HLA region (chromosome 6p21.3), which they designated as *PARK18*. Among the genetic markers, rs3129882 in intron 1 of HLA-DRA showed the most robust association with disease, even after differences in population substructure

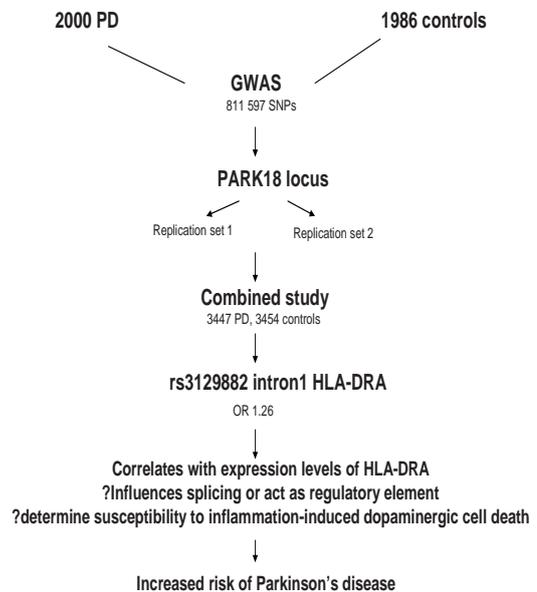


Fig. 1. Identification of an intronic risk variant of HLA-DRA.

were taken into account. This finding was replicated in 2 independent datasets, though this was statistically less robust because of the smaller sample sizes. In the meta-analysis, robust associations were observed in sporadic PD, late-onset PD and specifically in men (Similar demographics were observed in a majority of PD cases.). Interestingly, when the risk alleles in this HLA region were considered together with the other genetic risk regions (*SNCA*, *MAPT*, *GAK*) in their sample, subjects with 4 risk alleles had a 2.5-fold increased risk compared to subjects with 1 or no risk alleles. This risk increased dramatically to 5-fold in those with 6 or more risk alleles.

What kind of important information does identification of this genetic marker at the HLA region indicate? Based on statistical analysis, the most robustly associated marker, rs3129882 is located in the non-coding region of *HLA-DRA*. *HLA-DR* is a major histocompatibility complex, and both

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*HLA-DRA* and *HLA-DRB* encode proteins which are referred to as class II HLA-DR antigens. HLA (human leukocyte antigens) were initially referred to as cell surface antigens that mediate graft-versus-host disease. *HLA-DR* and *HLA-DQ* are closely linked. They have been implicated in autoimmune diseases and are known to modulate susceptibility to various human diseases.<sup>9,10</sup> HLA-DR antigens are expressed by antigen-expressing cells and interact with T-cell receptors. The link with the brain can be seen through the observation that such cells include the microglia. Even though rs3129882 is an intronic marker, it has been shown to correlate with expression levels of *HLA-DRA*. It is possible that rs3129882 influences splicing, or acts as a regulatory element. The other possibility is that this marker is not the actual causative variant but is in linkage disequilibrium with yet to be identified causative genes/loci.

Independent replication remains the litmus test for the validity of genetic association studies. It is well recognised that the genetics of the HLA-DR region is complex and is encoded by several loci and several 'genes' with different function at each locus. It is thus surprising that a single marker at the HLA region could be so strongly linked to PD in a region where various HLA-DR haplotypes are known to exist.<sup>9,10</sup> It remains to be seen whether the present observation could be consistently reproduced not just in subjects with European ancestry but in other ethnic subjects as well. Correction for population structure and detailed haplotype analysis needs to be considered in replication studies, and studies in more genetically homogenous populations would be particularly useful. Gene-environmental interaction is another important consideration since variation in the HLA region may modulate susceptibility to infectious and inflammatory conditions and exposure to environmental agents can complicate this interaction.

Despite some of the caveats, the identification of a HLA genetic marker could increase interest in research on the involvement of neuroinflammation and humoral immunity in the pathophysiology of PD. The cause and effect nature of neuroinflammation of nigral cell loss still remains unanswered. However, studies have suggested that neuroinflammation and microglial activation may be implicated in neuronal degeneration.<sup>11</sup> Microglia have the ability to mediate innate immune responses in response to external pathogens and intrinsic cellular conditions. The resultant outcome of a myriad of pro- and anti-inflammatory responses could decide on the fate of at-risk neurons. Genetic factors may well be essential in determining an individual's susceptibility to inflammation-induced nigral dopaminergic

neuronal cell death. A recent meta-analysis demonstrated a 15% reduction in PD incidence among non-aspirin anti-inflammatory drug users and the protective effect was higher among regular and long-term users.<sup>12</sup> Whether the suggestion that anti-inflammatory drugs can be added to the armamentarium of PD therapeutics will require more research.<sup>13</sup> The latest genetic finding certainly does provide an added impetus in this direction.

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