Latourelle and colleagues re-evaluated data from two genome wide association studies for genetic factors modulating age at onset in PD. Twenty-four SNPs selected from the meta-analysis of these studies were used for additional confirmation in a large replication study. No age at onset modulating factor with genome-wide significance was found based on meta-analysis of all three samples. Two SNPs revealed evidence for a genetic effect under a recessive model leading to a later (chromosome 11) or earlier (chromosome 2) age at onset in homozygous carriers. Since both genes encode proteins that may be linked to endocytosis and lysosomal function, the authors speculate that mechanisms involved in these biological functions may be relevant for modulation of disease onset.

This is an interesting report on whole genome association studies in different cohorts of PD patients and controls. Genetic association studies are a potent tool to detect predisposing alleles in candidate genes. Concerning the quality of the association study the authors provide sufficient accuracy and the data presented are convincing enough to support most of the conclusions, however, some points still need to be addressed:

The authors describe an association of age at onset with a SNP in the AAK1 gene on chromosome 2p14 and refer to the PARK3 locus. This is not correct, because the PARK3 locus was assigned to 2p13 (Gasser et al., 1998) and should be corrected.

In their meta-analysis the authors refer to two large studies in index patients from families with PD (GenePD and Progeni). Thus it would be of major interest, whether the identified SNPs, that modulate age at disease onset, also contribute to the variation of the age at onset in the respective families. This should be included in the results and/or discussion section.

The growing information due to computational genetic approaches defining risk SNPs for neurodegenerative diseases contrasts with the paucity of direct clues to the pathogenesis. Therefore the discussion section should include a paragraph, where the authors define, which should be the next steps to draw biological conclusions from their genetic association data. What mechanism the authors would suggest for a biological factor that modulates age at onset, i.e. in contrast to a 'pure' disease causing variant? What does the poor overlap between both approaches in GWAS analyses (susceptibility vs. age at onset) mean for
molecular mechanisms involved in neurodegeneration versus normal ageing? These issues need to be addressed to overcome the rather descriptive level of genetic association studies.

In the methods section the authors state that SNPs were excluded based on a minor allele frequency less than 0.01. However in the statistical section they report an exclusion of SNPs with a minor allele frequency less than 0.1. This needs to be stated.

Page 6: the fact that ‘many’ cases were genotyped for known mutations in PD is not informative and needs to be specified (n=?) for the respective PD genes.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.