Abstract of Presentation

Presentation Title:

Association study for Parkinson's disease

Abstract :

Parkinson's disease (PD), one of the most common neurodegenerativedisease, is caused by multiple genetic and enviromental factors. Although several causal genes for Mendelian inherited PD have recently been identified, strong genetic factors that influence idiopathic PD have not yet been identified. Firstly, to identify susceptibility genes for sporadic PD, we have done case-control analysis by using SNPs in multiple candidate genes. We selected candidate genes from the viewpoints of familial PD, dopaminergic neurons, trophic factors, oxidative stress, mitochondria, apoptosis, ubiquitin-proteasome, autophagy, etc. For initial screening, we genotyped 190 patients and 190 controls for 267 SNPs in 122 candidate genes by Invader method. We confirmed these associations by increasing the number of samples to nearly 900 for patients and 900 for controls. We established *α-synuclein* as the first definite susceptibility gene for sporadic PD (P=1.7x10^{-11}). SNCA is a major component of Lewy bodies, the pathological hallmark of PD. Aggregation of SNCA is thought to play a crucial role in PD. *SNCA* expression levels tended to be positively correlated to the number of the associated allele in autopsied frontal cortices.

Further, we found *calbindin 1 (CALB1)* showed association (P=7.1x10^{-5}). When the analysis was stratified relative to the *SNCA* genotype, the odds ratio of *CALB1* tended to increase according to the number of protective alleles in *SNCA*. CALB1 is a calcium-binding protein that widely is expressed in neurons. A relative sparing of CALB1-positive dopaminergic neurons is observed in PD brains, compared with CALB1-negative neurons. Our genetic analysis suggests that *CALB1* is associated with PD independently of *SNCA*.

Secondly, we performed a Genome-Wide Association Study of PD, using Illumina HumanHap550. Array. Subjects were 1,012 PD patients and 2,573 RIKEN controls of Japanese ancestry. After SNP QC filter, high quality genotypes of 438,886 common SNPs were obtained. We excluded the samples with the cryptic duplicate and relatedness (MZ twin and 1-2 degree) through computing IBS probabilities, and the individuals who seemed to have non-Japanese ancestry were also excluded using multidimensional scaling. After these exclusions, 988 cases and 2,521 controls remained for the analysis. Genomic control method indicated that there was little evidence of any general inflation of the test statistics (genomic inflation factor λ =1.05). We assessed each SNP for association with PD using a Cochran-Armitage trend test. A total of 127 SNPs were significant at the P<10^{-4}. The most significant SNP was rs11931074 (P=6.17x10^{-13}) and its neighbors, located in the 7 kb downstream - intron4 of α -synuclein. The *MAPT* locus was not identified significant in our study, because, unlike Caucasian, risk SNPs in the *MAPT* locus were monomorphic in the Japanese population, suggesting genetic heterogeneity of PD among races. Replication analysis of top-hit SNPs is underway with another set of samples. Our finding will play an important role in clarification of the etiology of PD.

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