Results

Drinking behavior

SSCP analysis demonstrated three different banding patterns, each of which corresponded to a single base pair variation (1510 G/A) on direct PCR sequencing (Figure 1). Because of the good agreement between the SSCP analysis and direct sequencing data, we used SSCP analysis to determine the ALDH2 genotypes of the 93 PD patients and 297 control subjects.

Neither the genotype distributions nor the allele frequencies of the ALDH2 gene differed significantly between the two groups (χ^2=2.43, p=0.119) (Table 3). However, the alcohol consumption of each genotypic group differed significantly between PD patients and control subjects (*ALDH2*1/ALDH2*1*; PD: 431.1±728.7, Controls: 792.6±712.0, t=3.08, p=0.002. *ALDH2*1/ALDH2*2*, PD: 155.9±413.7, Controls: 568.7±562.9, t=4.22, p<0.001. *ALDH2*2/ALDH2*2*, PD: 4.0±6.2, Controls: 107.9±195.0, t=1.29, p=0.215). Also, a significant difference was observed for alcohol consumption between both genders (Males: *ALDH2*1/ALDH2*1*; PD: 799.2±915.4, Controls: 1160.7±752.4, t=1.96, p= 0.053. *ALDH2*1/ALDH2*2*, PD: 303.8±619.2, Controls: 901.5±605.7, t=3.35, p<0.002. *ALDH2*2/ALDH2*2*, PD: 6.0±8.5, Controls: 192.5 ±282.2, t=0.89, p=0.409. Females: *ALDH2*1/ALDH2*1*; PD: 107.3±226.2, Controls: 341.8±258.4, t=4.07, p< 0.001. *ALDH2*1 /ALDH2*2*, PD: 67.1±180.4, Controls: 242.2±233.2, t=3.31, p=0.001. *ALDH2*2 /ALDH2*2*, PD: 3.0±6.0, Controls: 44.5±54.9, t=1.47, p=0.170) (Table 4).

Personality

Table 5 shows the mean values for each of the subcategorizes of the TPQ test for the PD patient group, compared to the control subjects. The PD

patient group showed a lower total NS score (PD: 12.4±3.0, Controls: 13.7±3.2, t=2.6, p=0.012), particularly in the "Exploratory" (PD: 2.6±1.4, Controls: 3.7±1.4, t=4.7, P<0.0001) and "Dramatic" (PD: 0.5±0.7, Controls: 0.8±1.0, t=2.1, P=0.036) subcategory. The total score for the HA dimension for patients with PD was notably higher than that obtained for the control group (PD: 20.0±5.1, Controls: 15.7±6.5, t=-4.2, P<0.0001), and the scores within the subcategorizes of "Anticipatory worry and pessimism" (PD: 5.2±2.1, Controls: 3.9±2.2, t=3.5, P=0.001), as well as for "Fatigability and asthenia" (PD: 5.2±2.0, Controls: 2.8±2.4, t=6.2, P<0.0001), were significantly higher in the PD patient group than in the control group. The only gender interaction to immerge from the analysis was in the "Persistence" subcategory (PD: males 4.9±2.1, females 5.6±1.6, Controls: males 5.8±1.6, females 5.2±2.0, F=4.1, p=0.046).

Table 6 compares the mean scores in the TPQ for the anti-depressant drug-treated PD patients versus the PD patients that did not receive anti-depressant drugs. Patients treated with anti-depressant drugs scored significantly higher on the HA dimension than the non-anti-depressant treated patients (Treated patients: 22.4±4.7, Non-treated patients: 18.8±5.0, t=2.8, P=0.007). In addition, the scores obtained for the subcategorizes "Shyness with strangers" (Treated patients: 4.4±1.6, Non-treated patients: 3.5±1.6, t=5.3, P=0.025), and "Fatigability and asthenia" (Treated patients: 6.1±1.9, Non-treated patients: 4.7±2.0, t=6.5, P=0.013) were significantly higher in the PD patients treated with anti-depressant drugs.

L-dopa Induced Hallucination

The PCR products of the promoter and coding region of the CCK gene were screened by SSCP for the detection of variations within the DNA sequence obtained from 116 patients with PD and from 95 control subjects.

Four polymorphic sites were identified in the two groups. They appeared at nucleotide number -196G and - 45C in the promoter region, at 1270C in intron 1, and at 6662C in intron 2 (Figure 2). Complete linkage disequilibrium was observed between the -45 and 1270 loci in patients and controls (Table 7). In addition, a possible linkage disequilibrium was found between the -45 locus and the -196 locus for PD patients (delta value =0.168, D' value =0.680, $p<0.000001$) and for controls (delta value =0.166, D' value =0.700 , $p<0.000001$).

The distribution of genotypes and allelic frequencies for these polymorphic locus in the CCK gene were compared between PD patients and control subjects. The genotypic distribution deviated significantly from Hardy-Weinberg equilibrium ($\chi^2=8.84$, $p<0.02$).

A significant difference was found in the distributions of the three genotypes, namely *CC*, *CT*, *TT* at the -45 locus when compared between PD patients and control subjects ($\chi^2=7.95$, $p=0.018$; $p=0.054$ after Bonferroni correction for multiple comparisons of three loci) (Table 8). Alternatively, the genotypic distribution at the 1270 locus was also significantly different between both groups. Major symptoms, age, age of onset, period of administration and daily dosage of L-dopa were not different amongst the three genotypic groups at the -45 locus (*CC*, *CT*, *TT*), and also at the -196 locus (*A A*, *GA*, *GG*) in PD patients.

In contrast, a significant difference was found in the distributions of the three genotypes at the -45 locus between the drug-treated PD patients experiencing hallucinations and those who did not experience hallucinations as shown in Table 9 ($\chi^2=8.08$, $p=0.018$). However no significancy was obtained after Bonferroni correction for multiple comparisons using 7 tests (three locus, diskinesia, wearing-off, hallucination, and a total of PD; $p=0.144$). Note that no significant differences were observed in the -

196G/A genotypes between these two groups.

Finally, we analyzed the three genotypes at both the -45 and the -196 loci as a function of the age of onset of the disease. Statistical (ANOVA) analysis indicated that there was no significant difference of the onset age for both loci (-45 locus; $F = 0.14$, $p = 0.872$, -196 locus; $F = 1.49$, $p = 0.230$).