BDNF rs6265 and Response to Dopaminergic Therapy in PD

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Research Abstract

Project Summary Oral levodopa (L-dopa) has become the mainstay pharmacotherapy for Parkinson’s disease (PD). Although generally effective in treating the motor symptoms of PD, the clinical response is highly variable. We contend that the efficacy of oral L-dopa may be influenced by subject genotype. Indeed, response to antidepressant and antipsychotic pharmacotherapy is influenced by the Bdnf gene coding for brain-derived neurotrophic factor

(BDNF), specifically the single nucleotide polymorphism (SNP) rs6265. The Bdnf SNP rs6265 is relatively common with a 40.6% prevalence of carrying the minor Met66 allele (Val/Met or Major/Minor = 35.4%, Met/Met or Minor/Minor = 5.2%, allelic frequency assuming Hardy-Weinberg). Presence of the Met allele disrupts packaging and release of activity-dependent BDNF. We recently genotyped early-stage PD patients who were treated with either deep brain stimulation of the subthalamic nucleus (DBS) or optimized drug therapy (ODT, predominantly oral L-dopa) and enrolled in the Vanderbilt DBS in Early Stage PD clinical trial (NCT00282152). The trial occurred over a period of 24 months. Five of 15 subjects (33%) and 6 of 13 subjects (46%) in the DBS and ODT treatment arms, respectively, carried the Met allele of the Bdnf SNP rs6265. At baseline, all clinical endpoints were statistically similar across Bdnf genotype ($p > 0.05$). However, Met allele carriers in the ODT arm exhibited significantly higher (worse) UPDRS scores ON medications at 18 ($p = 0.017$) and 24 months ($p = 0.019$) and significantly higher PDQ-39 scores at 12 ($p = 0.033$) and 24 months ($p = 0.018$, compared to ODT subjects with the most common genotype Val/Val). In contrast, no significant differences were observed due to Met allele status in subjects receiving DBS at any time point with any clinical metric ($p > 0.05$). Our discovery cohort results suggest that possession of the Met66 allele of the SNP rs6265 confers a treatment-specific, suboptimal response to dopaminergic PD medication that emerges over long treatment intervals. Validation in a larger cohort of early PD subjects treated with dopaminergic medication is warranted to establish whether our phenomenon is truly generalizable to the PD population as a whole. Our ultimate goal is to determine whether genotyping for the Bdnf SNP rs6265 could be used as a precision medicine approach for the treatment of PD by either medical or surgical interventions as well as a method for stratification of subjects enrolled in clinical trials for more efficient and effective clinical trial design.

Further information available at:

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