A ROLE FOR ALTERED GCH1 EXPRESSION IN AUTOSOMAL DOMINANT DOPA-RESPONSIVE DYSTONIA AND IN IDIOPATHIC PARKINSON'S DISEASE

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Autosomal dominant Dopa-responsive Dystonia (AD-DRD) is characterized by a marked dopamine deficiency in the striatum primarily due to mutations in the GCH1 gene ($GCH1$). Here we describe the identification and characterization of a novel 24 kb deletion spanning exon 1 and 5' regulatory region of $GCH1$ causing a wide spectrum of clinical presentations of AD-DRD in a large Belgian family due to loss of transcript. As is the case for DRD, decreased levels of dopamine in the brain are also found in Parkinson disease (PD) patients. It is therefore not surprising that a substantial number of PD patients also present with dystonia. Additionally, a large number of DRD patients carrying $GCH1$ mutations develop classical parkinsonism, either later in the course of the disease or as solitary symptom. $GCH1$ is therefore a perfect suspect as a risk factor for PD. Here we report the first comprehensive mutation analysis of $GCH1$, including both sequencing and copy number detection of all exons and regulatory regions, in an extended population consisting primarily of sporadic (84%) PD patients. We did not identify coding or copy number variations linked to PD, in accordance with previous smaller studies in primarily familial PD patients, but we did identify a remarkable number of expression regulating variants. The exact role of these regulatory variants in PD pathogenesis needs further study but it is to be expected that genetic variation in the $GCH1$ promoter or other regulatory sequences affecting the expression of GCH1, are involved in the development of PD.