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Genotype-Phenotype Correlation - Two Families with *GCH1* Mutations

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Abstract

Dopa-responsive dystonia (DRD), attributed to GTP cyclohydrolase 1 (*GCH1*) mostly, is a clinically and genetically heterogeneous disorder. Our recent study have identified that phenotype may not be identical to genotype, even in the same family. One patient with parkinsonism was found to carry *GCH1* mutation. Why phenotype is not correlated to genotype? Whether *GCH1* is a risk factor for developing Parkinson's disease (PD)? Further genetic and clinical studies are necessary to elucidate these questions.

Keywords: Dopa-responsive dystonia (DRD); *GCH1* gene; *TH* gene; Parkinson's disease (PD)

Introduction

Dopa-responsive dystonia (DRD) was first discovered by Segawa et al. in 1972 [1]. It is a progressive primary dystonia characterized by onset during childhood, marked diurnal fluctuation and a dramatic and long-term response to low doses of levodopa [2]. Mostly, defects in the GTP cyclohydrolase 1 (*GCH1*) gene and the tyrosine hydroxylase (*TH*) gene have been attributed to the pathogenesis of DRD [3]. The characteristics of low CSF homovanillic acid (HVA) levels with low HVA/5-hydroxyindolacetic acid (5-HIAA) ratio were discovered in DRD patients [4]. In our previous study, we found that the clinical phenotypes of patients in one pedigree may be different with the same mutation in one family.

Clinical Phenotype of a Family with *GCH1*(c.550C>T) Mutation

A reported heterozygous mutation of *GCH1* (c.550C>T) was detected in a family [5]. The age of onset of affected patients ranged from 13 to 60 years. Treatment with levodopa results in clinical improvement. However, the dose of levodopa varied from 50 mg twice daily to 100 mg twice daily. The mother of the affected patients was still normal at age 80, who carried the same mutation. The same feature had been reported in previous paper [6-8].

Clinical Phenotype of a Family with *GCH1*(c. IVS2-2A>G) Mutation

In another family, the father/daughter pair carrying the IVS2-2A>G *GCH1* mutation showed different phenotypes [9]. The daughter was diagnosed at age 8 with the symptom of dystonia. She presented excellent response to dopaminergic medications. However, her father was normal before the age of 53, Clinical examination showed asymmetrical bradykinesia, hypomimia, slow gait and poor postural reflexes, actually, more like parkinsonism. He preferred taking L-dopa (100 mg, twice daily), amantadine (100 mg, twice daily) and selegiline (5 mg, daily) to completely control symptoms. The patient was the only one who carried parkinsonian symptoms in our study of DRD patients, which supported the point of view that some *GCH1* coding variants or mutation, like Q110X, V204I, might be associated with Parkinson's disease (PD) [10].

Some Issues need Further Thinking

Here, we show that the clinical phenotypes of DRD patients might be nonspecific. Old age and the symptom of parkinsonism should not be excluded, even with a negative family history. There are a number of issues worth considering. First, why the symptom varied for patients with the same mutation? It might be that apart from the exons, non-coding regions, promotor system, microRNA and other factors may all contributed to this disease [11-13]. Second, is *GCH1* related to PD? Previous studies from Taiwan revealed parkinsonian features were common to DRD in 1996. Later, Shang et al. reported 5 of 16 DRD patients developed parkinsonism symptoms. However, in 2014, it was shown that the frequency of *GCH1* variants was significantly higher in PD cases than in controls by Mencacci et al. (1% and 0.75%, p=0.0001). The authors also presented 4 patients with different *GCH1* mutations fully met the Criteria for definite PD [10]. In 2015, Wang et al. reported a family with a novel *GCH1* variant displayed different phenotypes of PD and DRD. In addition, it was also demonstrated that *GCH1* rs11158026 increased the risk of developing PD [14]. Whether parkinsonism is an atypical symptom of DRD or *GCH1* is a gene responsible for PD?

Conclusion

In further studies, we should do more research on non-coding regions of *GCH1* gene to explain some phenotype variation, thus provide some strategies for new treatment. More *GCH1* screening should be done in subjects with parkinsonism. And apart from gene test, cerebrospinal fluid (CSF) detection and Dopamine transporter imaging are also recommended to help differentiate between PD and DRD [10,15].

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