GTP cyclohydrolase I gene, dystonia, juvenile parkinsonism, and Parkinson’s disease

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Summary. GTP cyclohydrolase I is the rate-limiting enzyme for the biosynthesis of tetrahydrobiopterin, which is the cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine biosynthesis. We found that dominantly inherited, hereditary progressive dystonia (HPD), first described by Segawa and also called dopa responsive dystonia (DRD), is caused by the mutations of GTP cyclohydrolase I gene, the partial decrease in the enzyme activity, and probably in striatal dopamine level, to less than 20% of the normal values. Juvenile parkinsonism and Parkinson’s disease are also striatal dopamine deficiency, but no mutation in the enzyme has not been found, and they are supposed to be different from HPD/DRD in which no cell death of the nigrostriatal dopamine neurons occurs.

Dystonia, juvenile parkinsonism (JP) and Parkinson’s disease (PD) are the movement disorders accompanied by the dopamine deficiency in the basal ganglia, and are responsive to L-dopa treatment with varying degrees of efficacy. Dopamine is synthesized from L-tyrosine: \( \text{L-tyrosine} \rightarrow \text{L-dopa} \rightarrow \text{dopamine} \). Two dopamine-synthesizing enzymes are required: (1) tyrosine hydroxylase (TH, Nagatsu et al., 1964), aromatic L-amino acid decarboxylase (AADC) (also called dopa decarboxylase, DDC). TH requires a tetrahydrobiopterin as a cofactor, and \((6R)-\text{L-erythro}-5, 6, 7, 8\)-tetrahydrobiopterin \((6R-BH4)\) is the natural cofactor (Kaufman, 1963). \(6R-BH4\) is synthesized in the TH-containing dopamine neurons from GTP: GTP \(\rightarrow\) 7, 8-dihydroleptin triphosphate \(\rightarrow\) 6-pyruvyltetrahydropterin \(\rightarrow\) \(6R-BH4\). Three enzymes are required for \(6R-BH4\) biosynthesis from GTP: (1) GTP cyclohydrolase I, (2) 6-pyruvyltetrahydropterin synthase, and (3) sepiapterin reductase. The first enzyme, GTP cyclohydrolase I is assumed to be the rate-limiting enzyme (Nichol et al., 1985).

In vivo TH activity is considered to be partly regulated by the concentration of \(6R-BH4\) (Kettler et al., 1974; Niwa et al., 1985; Matsuura et al., 1986; Nagatsu et al., 1994), and thus GTP cyclohydrolase I activity may also regulate in vivo TH activity via regulation of \(6R-BH4\) biosynthesis, and ultimately dopamine biosynthesis. Therefore, GTP cyclohydrolase I activity may be
important for the molecular mechanism of dystonia, JP, PD. We have been studying biochemistry and molecular biology of BH4-synthesizing enzymes (Nagatsu et al., 1985; Ichinose et al., 1991; Togari et al., 1992; Nomura et al., 1993). We attempt to examine whether or not BH4-synthesizing enzymes, especially GTP cyclohydrolase I, are related to the dopamine deficiency in the basal ganglia of dystonia, JP, and PD.

GTP cyclohydrolase I gene as the causative gene of hereditary progressive dystonia with marked diurnal fluctuation (HPD) / Dopa responsive dystonia (DRD)

Dystonia refers to a heterogeneous group of movement disorders of unknown etiology. The primary dystonias can be divided into a number of genetic and clinical subtypes. Hereditary progressive dystonia with marked diurnal fluctuation (HPD) is a dystonia, originally described by Segawa et al. (1971, 1986). Clinical onset is mostly in the first decade. The clinical course shows progression in the first two decades, which subsides from the third decade and becomes almost static from the 3rd to 4th decades. Low doses of L-DOPA are essentially curative over the life of the individual without apparent unfavorable side effects. Dopa responsive dystonia (DRD) is a term first proposed by Nygaard et al. (1989, 1991) to describe dystonia responding to L-dopa including dystonia with heterogeneous etiologies. DRD is now considered to be identical to HPD when DRD is diagnosed with strictly defined criteria. HPD/DRD is inherited as autosomal dominant traits with reduced penetrance. Recently the gene for DRD was mapped to chromosome 14q (Nygaard et al., 1993). We have determined the chromosomal localization of GTP cyclohydrolase I to 14q 22.1–q22.2 within the DRD/HPD locus (Ichinose et al., 1994). The GTP cyclohydrolase I gene has six exons (Ichinose et al., 1995a). As we already know the sequences around the exons, we amplified exons, including splicing junctions, from genomic DNA, using polymerase chain reaction (PCR). The antisense primer for the amplification of exon 3 was set in the coding region (19 nucleotides). Amplified DNA fragments were directly sequenced with an automated DNA sequencer. Using our primer sets, we could have determined 97.5% of the nucleotides in the coding region sequence (731 out of 750 nucleotides). We examined four HPD families and a sporadic case and discovered four variations as compared to the control sequence: three single-base changes that predict nonconservative amino acid substitutions (Arg 88 Trp, Asp 134 Val, and Gly 201 Glu) and a two-base insertion (ATG GAG → ATG GG GAG) that shifts the reading frame just after the translational starting methionine (Table 1). All patients were heterozygous in terms of these mutations, and no other mutations were found in the coding region of GTP cyclohydrolase I gene. None of the mutations was found on 108 other chromosomes from unrelated normal Japanese individuals. Both the Arg 88 Trp and Gly 201 Glu substitutions abolished the increase in the GTP cyclohydrolase I activity shown in the wild-type cDNA, demonstrating that these mutations are not simply polymorphisms.