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# BIOMDB: Database of Mutations Causing Tetrahydrobiopterin Deficiencies

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## Introduction

GTPCH, PTPS, SR, PCD/DCoH, and DHPR are each encoded by single genes (*GCH1*, *PTPS*, *SPR*, *PCBD*, and *QDPR*), and the corresponding loci are mapped to chromosomes 14q21-q22.2, 11q22.3-q23.3, 2p13, 10q22, and 4p15.3, respectively (see Chapters 2.2). BH<sub>4</sub> deficiencies, a group of rare inherited neurological diseases with catecholamines and serotonin deficiency, may present phenotypically with or without hyperphenylalaninemia (HPA) [1]. BH<sub>4</sub> deficiency presenting with hyperphenylalaninemia can be caused by mutations in genes encoding the enzymes involved in its biosynthesis (GTPCH and PTPS) [2] or regeneration (PCD/DCoH and DHPR) [3, 4]. The mutations are all inherited autosomal-recessively. Biochemical, clinical, and DNA data of patients with BH<sub>4</sub> deficiencies are tabulated in the BIODEF and BIOMDB databases and are available via the internet ([www.bh4.org](http://www.bh4.org)). BIOMDB is a locus-specific database with detailed records of disease-producing allelic variations and natural polymorphic markers. It was founded and designed according to the recommendations of the HUGO Mutation Database Association, and fits the proposals of the Working Group of Nomenclature, and Locus-specific Databases. Details of these proposals can be obtained at URL: <http://www.gene.ucl.ac.uk/nomenclature/>.

The autosomal-dominantly inherited form of GTPCH deficiency (*adGTPCH*; Dopa-responsive dystonia; DRD), initially described as Segawa's disease [5], together with the recently described autosomal-recessive SR deficiency [3] present both without elevated plasma phenylalanine levels in infancy, and thus, in contrast to classical BH<sub>4</sub> deficiencies, cannot be detected through newborn screening for phenylketonuria (PKU). For a more detailed summary of BIOMDB mutations see review article by Thöny and Blau [6].

## GCH1

A total of 90 mutations are distributed across all 6 exons and 5 introns (Figure 1). Among patients with HPA four were found to be homozygotes (R184H, M211I, M211V, and M213T) and one was compound heterozygote (Q110X, second allele not defined). Two patients with homozygous mutations (P199A and R249S) presented without HPA. All other mutations occurred in heterozygous state and were associated with DRD: 52 missense

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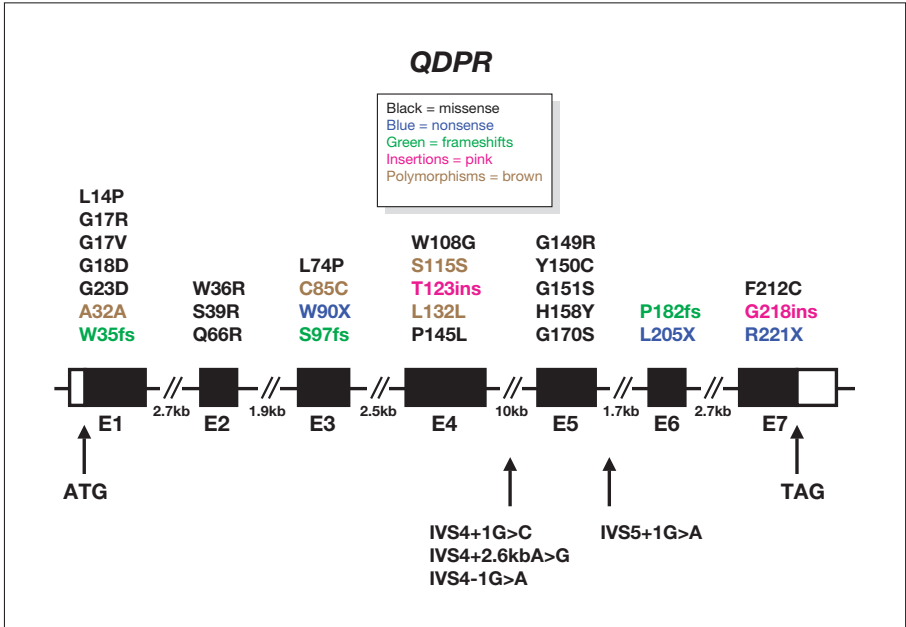


Figure 5: Genomic structure and location of mutations in human *QDPR* gene.

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