Introduction

GTPCH, PTPS, SR, PCD/DCoH, and DHPR are each encoded by single genes (GCH1, PTS, 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). BH₄ deficiencies, a group of rare inherited neurological diseases with catecholamines and serotonin deficiency, may present phenotypically with or without hyperphenylalaninemia (HPA) [1]. BH₄ 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 BH₄ deficiencies are tabulated in the BIODEF and BIOMDB databases and are available via the internet (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 BH₄ 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
mutations, 13 nonsense mutations, 17 frameshift mutations, 12 splice-site mutations, 6 deletions, one insertion, and two located in the 3’-promotor region (Figure 1).

**Figure 1:** Genomic structure and location of mutations in human GCH1 gene.

**PTS**

A total of 43 mutations are distributed across all 6 exons and the first 3 introns (Figure 2). Two mutations, N52S and P87S, appear to be relatively frequent in the Asian population. Among the exonic mutations there are, besides the 34 substitutions, 1 insertion and 5 deletions. The 3 splice-site mutations are distributed in the first 3 introns, and two of them lead to skipping of exon 3. The E81E mutation is not a polymorphism, but rather leads to a splicing defect and skipping of exon 4.
Four different disease-causing alleles are known that are all located in exon 2, one deletion and 3 substitutions. Whereas 2 of the 4 mutations cause premature stop codons, the other 2 generate an amino acid exchange (Figure 3). One intronic mutation (IVS2-2A>G) was found to be frequent in the Maltese population [7].
Figure 3: Genomic structure and location of mutations in human SPR gene.

**PCBD**

So far 9 different mutations were detected in patients with PCD deficiency, most of them located in exon 4 (Figure 4). All these mutations are associated with a benign form of BH$_4$ deficiency (primapterinuria), characterized by excretion of 7-substituted biopterin (primapterin) and transient HPA.
33 different mutations are tabulated in the BIOMDB database: 17 missense mutations, three nonsense mutations, three frameshift mutations, four splice-site mutations, insertions, and four polymorphisms (Figure 5). Two mutations were found to be associated with a mild form of DHPR deficiency (G151S, F212C).
Figure 5: Genomic structure and location of mutations in human QDPR gene.

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References


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