

MUTATION UPDATE

Mutations in Human Monoamine-Related Neurotransmitter Pathway Genes

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Biosynthesis and metabolism of serotonin and catecholamines involve at least eight individual enzymes that are mainly expressed in tissues derived from the neuroectoderm, e.g., the central nervous system (CNS), pineal gland, adrenal medulla, enterochromaffin tissue, sympathetic nerves, and ganglia. Some of the enzymes appear to have additional biological functions and are also expressed in the heart and various other internal organs. The biosynthetic enzymes are tyrosine hydroxylase (TH), tryptophan hydroxylases type 1 and 2 (TPH1, TPH2), aromatic amino acid decarboxylase (AADC), dopamine beta-hydroxylase (DβH), and phenylethanolamine N-methyltransferase (PNMT), and the specific catabolic enzymes are monoamine oxidase A (MAO-A) and catechol O-methyltransferase (COMT). For the TH, DDC, DBH, and MAOA genes, many single nucleotide polymorphisms (SNPs) with unknown function, and small but increasing numbers of cases with autosomal recessive mutations have been recognized. For the remaining genes (TPH1, TPH2, PNMT, and COMT) several different genetic markers have been suggested to be associated with regulation of mood, pain perception, and aggression, as well as psychiatric disturbances such as schizophrenia, depression, suicidality, and attention deficit/hyperactivity disorder. The genetic markers may either have a functional role of their own, or be closely linked to other unknown functional variants. In the future, molecular testing may become important for the diagnosis of such conditions. Here we present an overview on mutations and polymorphisms in the group of genes encoding monoamine neurotransmitter metabolizing enzymes. At the same time we propose a unified nomenclature for the nucleic acid aberrations in these genes. New variations or details on mutations will be updated in the Pediatric Neurotransmitter Disorder Data Base (PNDDDB) database (www.bioPKU.org). Hum Mutat 29(7), 891–902, 2008. © 2008 Wiley-Liss, Inc.

KEY WORDS: monoamine neurotransmitter; serotonin; catecholamine; dopamine; epinephrine; norepinephrine; psychiatric and neurological disorders; SNPs; haplotypes

INTRODUCTION

Mendelian mutations affecting monoamine neurotransmitter pathway genes encoding enzymes that metabolize serotonin and the catecholamines appear to be extremely rare. On the other hand, nucleotide polymorphisms or defined combinations of polymorphisms (i.e., haplotypes) may be risk factors for development of several motor or neuropsychiatric disturbances. However, despite intensive investigations during the past decades, it is still unclear whether such variants are causally involved in common human disorders. We consider that developments of a unified, systematic nomenclature of mutations, as well as easily accessible, informative databases are prerequisites for further progress in this field. For an overview of the metabolism of serotonin and the catecholamines and for some characteristics of the metabolizing enzymes see Fig. 1 and Table 1.

Serotonin, also known as 5-hydroxytryptamine (5-HT), is synthesized from tryptophan via 5-hydroxytryptophan (5HTP) by the subsequent action of tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (AADC). For TPH, two individual isoforms with distinct function and localization exist, a peripheral subtype termed TPH1, and the neuronal subtype TPH2 [McKinney et al., 2005; Walther and Bader, 2003]. Degradation of serotonin to 5-hydroxyindolacetic acid involves monoamine

oxidase (mainly MAO-A) in combination with aldehyde dehydrogenase (ALDH). Most of the serotonin is found in the intestinal wall (over 80%), but it has also important functions in the central nervous system (CNS) and in blood vessels [Gershon, 2003]. Serotonin plays numerous roles as a neurotransmitter or hormone and controls appetite, sleep, memory and learning, body temperature, mood, sexual behavior, cardiovascular function, muscle contraction hemostasis, and endocrine functions [Lucki, 1998]. Serotonin acts via many different serotonin receptors and intracellular signaling pathways, some of which have been

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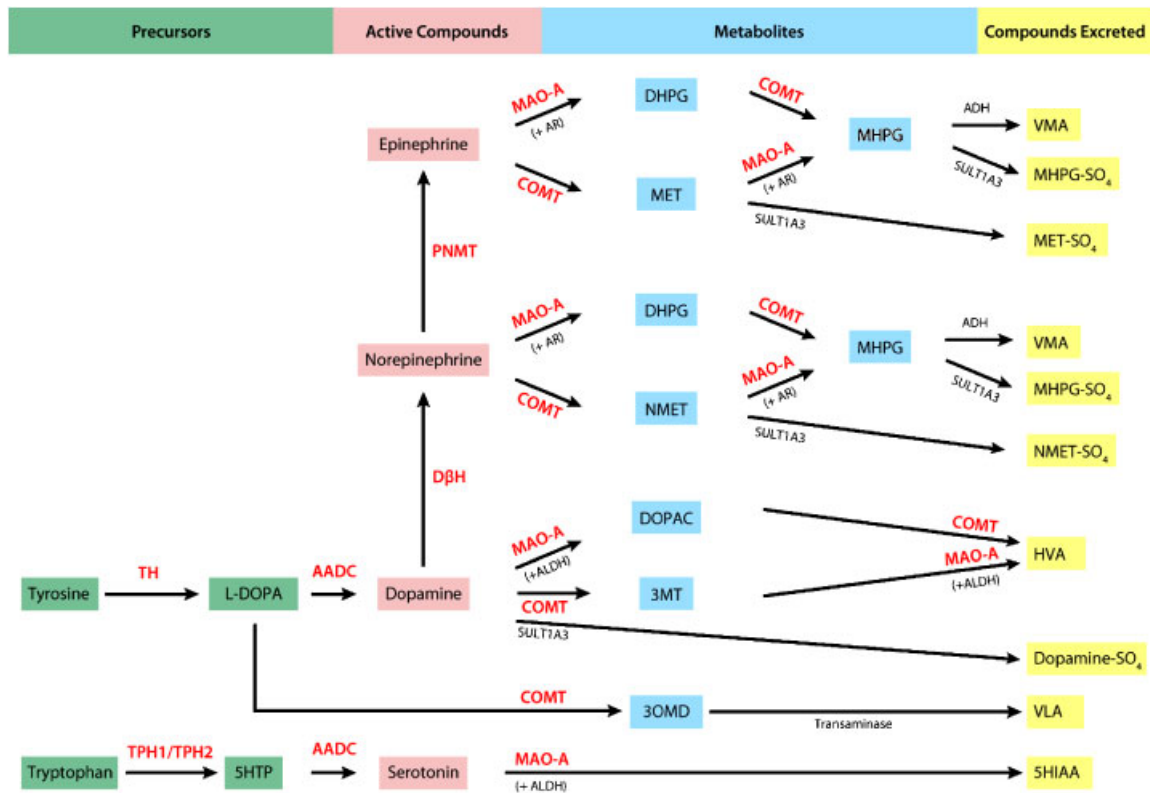


FIGURE 1. Pathways of biosynthesis and metabolism of catecholamines and serotonin. Abbreviations for enzymes: TH, tyrosine 3-hydroxylase or tyrosine 3-monooxygenase; TPH1, tryptophan 5-hydroxylase isoform 1 or tryptophan 5-monooxygenase isoform 1; TPH2, tryptophan 5-hydroxylase isoform 2 or tryptophan 5-monooxygenase isoform 2; AADC, aromatic L-amino acid decarboxylase; D β H, dopamine beta-hydroxylase; PNMT, phenylethanolamine N-methyltransferase; MAO-A, monoamine oxidase A; ALDH, aldehyde or aldose dehydrogenase/oxidoreductase; AR, aldehyde or aldose reductase; ADH, alcohol dehydrogenase; COMT, catechol O-methyltransferase; SULT1A3, sulfotransferase type 1A3. All metabolites are shown in boxes; abbreviations: DHPG, 3,4-dihydroxyphenylglycol; DOPAC, dihydroxyphenylacetic acid; 5HTP, 5-hydroxytryptophan; 5HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; L-DOPA, 3,4-dihydroxyphenylalanine; MET, metanephrine; MHPG, 3-methoxy-4-hydroxyphenylglycol; 3MT, 3-methoxytryptamine; 3OMD, 3-O-methyldopa; NMET, normetanephrine; SO₄, sulfate; VMA, vanillylmandelic acid; VLA, vanillic acid. Note: whereas catecholamine synthesis is a single pathway, metabolism of catecholamines involves multiple alternative pathways and the present scheme is a simplification. Furthermore, whereas only for enzymes printed in red the corresponding mutations are tabulated and discussed here, putative gene polymorphisms for enzymes in black are discussed to some extent in the text but are not tabulated, as possible contributions of gene variants to human disease or variation in response to metabolism remain unclear.

reviewed recently [D'Souza and Craig, 2006]. The regulation of these signaling systems adds another level of complexity to the physiological function and control of the serotonin system.

Metabolism of catecholamines is a highly complex, tissue-type specific, and dynamic process, and involves some of the same enzymes as for serotonin, including the biosynthetic enzyme AADC and the catabolic enzyme MAO (plus aldehyde or aldose reductase [AR] and aldehyde or aldose dehydrogenase/oxidoreductase [ALDH] [Eisenhofer et al., 2004]). The committing step is the conversion of tyrosine to 3,4-dihydroxyphenylalanine (L-Dopa) by tyrosine hydroxylase (TH). The neurotransmitters dopamine, norepinephrine, and epinephrine are subsequently synthesized by AADC, dopamine beta-hydroxylase (D β H), and the final enzyme in the catecholamine synthesizing cascade phenylethanolamine-N-methyltransferase (PNMT), respectively. Degradation of these catecholamine compounds requires the combined action of catechol O-methyltransferase (COMT), MAO-A and either AR for the catecholamines norepinephrine and epinephrine, or ALDH for dopamine and serotonin (see also Fig. 1 for details) [Eisenhofer et al., 2004; Goldstein et al., 1996]. Note that deamination of norepinephrine and epinephrine leads primarily to production of the metabolite dihydroxyphenylglycol

(DHPG) with very little 3,4-dihydroxymandelic acid being formed (not shown in Fig. 1). Formation of vanillylmandelic acid (VMA) from 3-methoxy-4-hydroxyphenylglycol (MHPG) requires the action of alcohol dehydrogenase (ADH). Furthermore, the sulfotransferase (SULT) isoenzyme 1A3 catalyzes the sulfate conjugation of catecholamines, i.e., dopamine, NMET, MET, and MHPG, which are cleared by urinary excretion as dopamine-3-O-sulfate, normetanephrine sulfate (NMET-SO₄), metanephrine sulfate (MET-SO₄), and MHPG-SO₄, respectively [Eisenhofer et al., 1999; Thomae et al., 2003].

Dopamine is not only produced in several regions of the brain, but also in the adrenal glands and in the gastrointestinal tract. The latter produces a substantial amount of dopamine in the body that is not converted to norepinephrine or epinephrine (for references on gastrointestinal production of dopamine see [Aneman et al., 1995; Eisenhofer et al., 1995, 1997, 1999; Mezey et al., 1999]). In the CNS, dopamine is primarily synthesized in the substantia nigra, striatum, and the ventral tegmental area, where it acts as neurotransmitter activating the five types of dopamine receptors, D1–D5. Furthermore, dopamine functions as a neurohormone released by the hypothalamus to inhibit the release of prolactin from the pituitary gland. Dopamine influences multiple brain

TABLE 1. Overview on Human Enzymes Involved in Biosynthesis and Metabolism of Catecholamines and Serotonin

Enzyme ^a	E.C. number	OMIM number	Gene symbol	Number of exons (amino acids) ^b	Chromosome location	Figure number	Supplementary table number
TH	1.14.16.2	191290 or 605407 (Segawa syndrome)	TH	14 (TH-4, 528 aa) 13 (TH-1, 497 aa) 13 (TH-2, 501 aa) 14 (TH-3, 524 aa)	11p15.5	2	S1
TPH1	1.14.16.4	191060	TPH1	11 (444 aa)	11p15.3-p14	3	S2
TPH2 (NTPH)	1.14.16.4	607478	TPH2	11 (490 aa)	12q15	4	S3
AADC	4.1.1.28	608643 (gene 107930)	DDC (or AADC)	15 (480 aa)	7p11	5	S4
DβH	1.14.17.1	223360 (gene 609312)	DBH	12 (603 aa)	9q34	6	S5
PNMT	2.1.1.28	171190	PNMT (or PENT)	3 (282 aa)	17q21-q22	7	S6
MAO-A	1.4.3.4	309850 or 300615 (Brunner syndrome)	MAOA	15 (527 aa)	Xp11.4-p11.3	8	S7
COMT	2.1.1.6	116790	COMT	6 (MB-COMT, 271 aa) 6 (S-COMT, 221 aa)	22q11.21-q11.23	9	S8
SULT1A3	2.8.2.1	600641	SULT1A3/4	9 (275 aa) or 10 (295 aa)	16p11.2 (SULT1A3)	None	None

^aAll three aromatic amino acid hydroxylases contain Fe²⁺ and use as cosubstrates O₂ and tetrahydrobiopterin (BH₄), whereas AADC is a pyridoxal phosphate dependent enzyme, DβH is an oxidoreductase belonging to the copper type II ascorbate-dependent monooxygenase, and MAO-A is a flavin monoamine oxidase.

TH, tyrosine 3-hydroxylase or tyrosine 3-monoxygenase; TPH1, tryptophan 5-hydroxylase isoform 1 or tryptophan 5-monoxygenase isoform 1, classical form expressed in peripheral organs like gut, pineal gland, spleen, and thymus; TPH2, tryptophan 5-hydroxylase isoform 2 or tryptophan 5-monoxygenase isoform 2, also termed neuronal tryptophan hydroxylase (NTPH), neuronal or brain type expressed predominantly in brain stem (central nervous system); AADC, aromatic L-amino acid decarboxylase; wide expression in neuronal but also nonneuronal tissues; an exon 3 deleted splice variant with only 442 amino acids is widely expressed but results in an inactive AADC isoform; gene symbol DDC: dopa decarboxylase (old gene symbol synonym is AADC); DβH, dopamine beta-hydroxylase; PNMT, phenylethanolamine N-methyltransferase; MAO-A, monoamine oxidase A; the oxidase activity is accompanied by aldehyde/aldose reductase (AR) an aldehyde/aldose dehydrogenase/oxidoreductase (ALDH) that metabolizes various unstable aldehyde intermediates; for details see Eisenhofer et al. [2004]; COMT, catechol O-methyltransferase; SULT1A3: sulfotransferase 1A3; the same SULT1A3 protein is expressed from the two genes, duplicated on chromosome 16p, SULT1A3 and SULT1A4 (also see Metabolism of Serotonin and Catecholamines for more details).

^bFor TH, there are four splicing variants in intron 1 resulting in combinations of TH-1 with 497 aa (exon 1 with 30 aa), TH-2 with 501 aa (extended exon 1 with 34 aa), TH-3 with 524 aa (exon 1 with 30 aa and exon 2 with 27 aa), and TH-4 with 528 aa (extended exon 1 with 34 aa and exon 2 with 27 aa; for details see Grima et al. [1987] and Kaneda et al. [1987]). Note that mutations in Supplementary Table S1 are based on TH-4 with 14 exons and a total of 528 aa, and in parentheses on TH-1 with 13 exons and a total of 497 aa. For COMT there is one single gene that codes for a soluble COMT with 221 amino acids (S-COMT) and a membrane-bound COMT with 271 amino acids (MB-COMT; for details see Lundström et al. [1995] and Mannisto and Kaakkola [1999]). The SULT1A3 protein is published as a protein of 295 aa by Aksoy and Weinsilboum [1995] and Thomae et al. [2003] under accession number P50244, and as a protein isoform of 275 aa by Hildebrandt et al. [2004] under REFSEQ accession number NP_001014999.1.

functions, including reward response, motivation, and pleasure, but also modulates skeletal muscle contraction via the extrapyramidal motor system. Thus, dopamine is critical to the control of voluntary movements, and dopamine depletion in the nigrostriatal pathway can cause Parkinson's disease. In other brain regions depletion can lead to reduced activities of memory, attention, and problem-solving functions. Disturbances in dopamine and/or norepinephrine function have also been implicated in affective, psychotic, or attention-deficit/hyperactivity disorder [Biederman and Faraone, 2005; Nutt, 2006].

Norepinephrine and epinephrine are physiologically important hormones and neurotransmitters with profound influences on the activity of the cardiovascular system. Norepinephrine is released from the liver and mesenteric organs, i.e., gastrointestinal tract, pancreas, and spleen [Aneman et al., 1995], but also from adrenal glands, and sympathetic nerves [Eisenhofer et al., 2004]. Norepinephrine has also neurotransmitter function in the locus ceruleus in the CNS. Similar to serotonin, it has also been implicated in depression as norepinephrine reuptake inhibitors have antidepressant activity. Epinephrine is a hormone released particularly by the adrenal medulla, but small amounts are also found in the CNS. Epinephrine plays a central role as a stress hormone in the short-term stress reaction, e.g., by increasing heart rate, stroke volume, and conversion of glycogen to glucose in the liver. Epinephrine is also used as a drug to treat cardiac arrest and other cardiac dysrhythmias, as well as circulatory shock and anaphylaxis.

Until recently, only a small number of recessive mutations have been described in the genes encoding TH, AADC, DBH, and MAO-A and B, and they typically present as neurometabolic diseases with altered levels of specific metabolites in cerebrospinal fluid (CSF) and/or urine [Blau et al., 2005]. In contrast, for the genes encoding TPH1, TPH2, PNMT, COMT, and SULT1A3, mainly single nucleotide polymorphisms (SNPs) or other polymorphisms with potential association with different psychiatric

symptomatology have been described. Figs. 2–9 with corresponding Supplementary Tables S1–S8 (available online at <http://www.interscience.wiley.com/jpages/1059-7794/suppmat>) list the known mutations and all polymorphisms that have been described in the coding region of the genes (see also Table 1). In accordance with our proposal to use a unified nomenclature for the nucleic acid and amino acid codon aberrations, the numbering of all cDNAs (or mRNAs) for the genes that are presented here start with 1 at the A of the ATG start codon, and of the protein with 1 at the starting methionine (Met). The following websites, databases and programs were used for approval of gene symbols and correct reference sequences at www.genenames.org/index.html, for mutation nomenclature at www.hgvs.org/mutnomen, including the nomenclature checklist at www.hgvs.org/mutnomen/checklist.html, and for checking sequence variant descriptions the Mutalyzer program using the “batch mode” at www.LOVD.nl/mutalyzer [Wildeman et al., 2008].

For a recent review on polymorphisms of monoamine related transporters and receptors we refer to the *Mutation Update* in this journal by D'Souza and Craig [2006], and for a more extensive summary of murine models available for inherited monoaminergic neurotransmitter disorders see the recent article by Thöny and Gibson [2006].

Aromatic Amino Acid Hydroxylases

The phenylalanine hydroxylase (PAH), TH, and TPHs constitute a small family of closely related tetrahydrobiopterin cofactor-dependent aromatic amino acid hydroxylases [Fitzpatrick, 2000]. Although the conversion of PAH to tyrosine in dog liver was demonstrated in 1913 [Embden and Baldes, 1913], the first mammalian PAH was characterized around 1960. Similarly, the conversion of tyrosine to L-DOPA as the first step in catecholamine biosynthesis was postulated in 1939, but TH was first purified in 1964 [Nagatsu et al., 1964], the same year as the

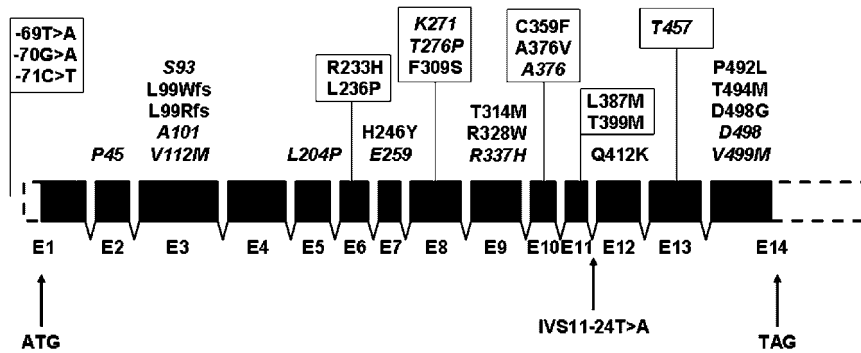


FIGURE 2. Genomic structure and location of mutations in human *TH* gene. Reference sequences: transcript ENST00000324155 (or NM_199292.2 for variant TH-4 with 528 aa, and NM_000360.3 for variant TH-1 with 497 aa), gene ENSG00000180176, Swiss Prot P07101, MIM# 191290, 605407. Mutations in italics are cited as SNPs (in the Ensembl v43 Database; see also Supplementary Table S1).

role of TPH in brain serotonin production was described [Grahame-Smith, 1964]. Mammalian genomes contain a single copy of *TH* and *PAH* genes, but two structurally related *TPH* genes (*TPH1* and *TPH2*). The latter enzymes have also been referred to as peripheral TPH and the central or neuronal form of TPH (NTPH), respectively (Table 1). The mammalian *PAH*, *TH*, and *TPH1* genes were cloned during the 1980s, but *TPH2* escaped attention until recently [Walther and Bader, 2003]. The structure and variations in the human *PAH* gene have been well characterized and the *PAH* Locus Knowledgebase (*PAHdb* databank; www.pahdb.mcgill.ca) currently contains more than 500 different mutations, most of which cause phenylketonuria/hyperphenylalaninemia. Many of these enzyme variants have been expressed and characterized in vitro [Waters, 2003]. In contrast, few mutations have been reported for *TH*, *TPH1*, and *TPH2*, and, particularly for the latter enzymes, their relationship to human disease is still not clarified. This might seem curious, as the size and structure of the *TH*, *PAH*, and *TPH* genes are very similar, and the mutation rates should also be comparable. However, the *PAH* gene occupies a rather unique position in human clinical genetics, as *PAH* deficiency produces a well-defined clinical and biochemical phenotype, and well organized newborn screening programs have been implemented for many years to search for the mutant enzymes [Blau, 2006].

Mutations Within the *TH* Gene

Given the importance of *TH* in the synthesis of catecholamine neurotransmitters, it was early suspected that a lack of this enzyme could be associated with neurological and/or psychiatric symptoms [Mallet, 1999]. Several related neurological phenotypes of *TH* deficiency have been described, i.e., L-DOPA-responsive dystonia (DRD) [Ludecke et al., 1995], juvenile parkinsonism [Ludecke et al., 1996], and progressive infantile encephalopathy with L-DOPA-nonresponsive dystonia [Hoffmann et al., 2003], all inherited in a recessive manner. This autosomal recessive form of DRD is different from the more frequent dominant form of DRD (dominant Segawa syndrome) due to GTP cyclohydrolase I mutations [Ichinose et al., 1994; Thöny and Blau, 2006]. Thus far, several deletion and missense mutations, more than 20 noncoding SNPs, and various synonymous coding and nonsynonymous coding SNPs, a splice junction mutation, and at least three promoter mutations have been reported in the *TH* gene (Supplementary Table S1). Expression analysis and biochemical characterization of the missense mutant enzymes have revealed that they have either normal or decreased enzymatic activity (V_{max}) in vitro, but all seem to have decreased thermal stability in

vitro [Knappskog et al., 1995; Ludecke et al., 1996; Royo et al., 2005], similar to what has been found for the “mild” variants of *PAH* associated with PKU (www.pahdb.mcgill.ca).

In addition to the mutations that have been documented in patients with neurological disorders, *TH* has been examined as a candidate gene in several psychiatric disorders. Thus, a micro-satellite that has five to 10 repetitions of the motif TCAT in the first intron of the *TH* gene has been identified and proposed to be associated with schizophrenia in a French population. However, as the genetic findings and functional studies have been inconsistent, it is still not settled whether mutations in the *TH* gene are directly involved in psychiatric disorders [reviewed in D’Souza and Craig, 2006].

Mutations Within the *TPH1* and *TPH2* Genes

Based on early observations of low brain levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA) in patients involved in suicidal acts [Asberg et al., 1976] and the indirect pharmacological relationship between low serotonin levels and symptoms of depression, *TPH* was early identified as a potential candidate gene for depression and other psychiatric conditions. Recently, many genetic studies have been performed, trying to establish a relationship between the *TPH* genes and various mental disorders. Many investigators have examined intronic variants of the *TPH1* gene, but after the discovery of *TPH2*, most attention has shifted to the latter enzyme.

A single *TPH1* missense mutation, V177I, has been reported in a patient suffering from a neurodevelopmental syndrome (see Supplementary Table S2 and Fig. 3) [Ramaekers et al., 2001]. In vitro characterization of the mutant enzyme showed that its molecular properties were indistinguishable from the wild type (McKinney, unpublished observations), and it is still unclear whether this mutation is causally involved in the reported syndrome. Besides this nonsynonymous coding mutation in exon 5 of *THP1*, two more synonymous coding alterations in exon 6 are compiled as SNPs in the Ensembl database with unknown effect (p.F241 and p.F263).

A rare *TPH2* missense mutation (R441H) has been reported to be associated with unipolar depression in a small American clinical sample [Zhang et al., 2005]. The corresponding protein p.R441H appeared to have reduced activity compared to the wild type when stably expressed in PC12 cells. Recently, it was found that the pure enzyme had intact kinetic properties, but decreased thermal stability and an increased rate of aggregation in vitro, supporting a role of this mutation in the clinical phenotype [Winge et al., 2007]. More recently, another rare missense mutation (p.P206S)

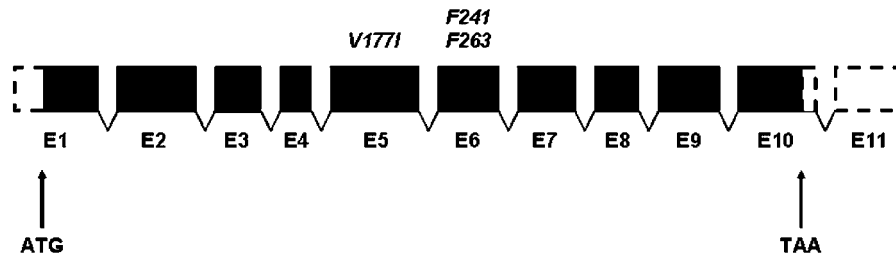


FIGURE 3. Genomic structure and location of SNPs in human *TPH1* gene. Only SNPs in the coding region of the *TPH1* gene are depicted (see also Ensembl v43 Database and Supplementary Table S2). Reference sequences: transcript ENST00000250018 (NM_004179.1), gene ENSG00000129167, Swiss Prot P17752, MIM# 191060.

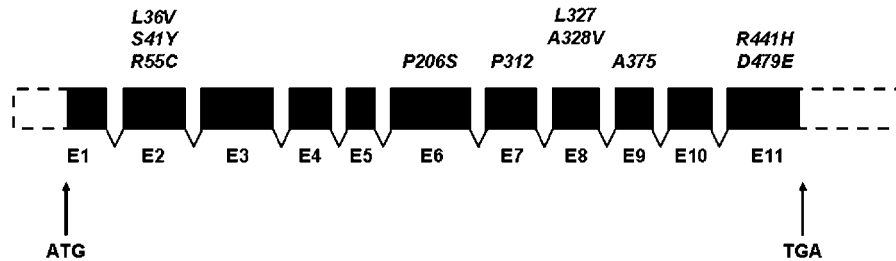


FIGURE 4. Genomic structure and location of mutations in human *TPH2* gene. Only SNPs in the coding region of the *TPH2* gene are depicted (see also Ensembl v43 Database and Supplementary Table S3). Reference sequences: transcript ENST00000333850 (NM_173353.2), gene ENSG00000139287, Swiss Prot Q81WU9, MIM# 607478.

has been reported to be associated with unipolar and bipolar depression in different populations [Cichon et al., 2008; Zhou et al., 2005b]. Molecular characterization of this mutation revealed that the enzyme behaved similar to the wild type, but had a moderately reduced thermal stability and increased rate of aggregation in vitro [Cichon et al., 2008]. The other coding nonsynonymous

SNPs and synonymous SNPs in *TPH2* have so far not been associated with any particular phenotype (see Supplementary Table S3 and Fig. 4).

In addition to these coding variants, several SNPs in the intronic or untranslated regions (UTRs) of the *TPH1* and *TPH2* genes have been reported to be associated with psychiatric symptoms such as depression, bipolar disorder, suicidality, or attention deficit/hyperactivity disorder, although with somewhat conflicting results [reviewed in Zhang et al., 2006b]. In *TPH1*, the common intronic SNPs A218C and A779C have been studied the most, while in the *TPH2* gene several different 5'-UTR or intronic variants have been reported to be associated with various psychiatric symptoms [Cichon et al., 2008; Scheuch et al., 2007; Van Den Bogaert et al., 2006; Zhou et al., 2005b]. There is also evidence that polymorphisms in the 5' regulatory regions of these genes affect gene expression both in vivo and in vitro, but these results should be considered as preliminary, as the mechanisms underlying the findings are not known and the promoter regions of the *TPH1* and *TPH2* genes are only superficially characterized.

Mutations Within the *DDC* Gene

AADC catalyzes the decarboxylation of both L-DOPA and 5HTP to produce the neurotransmitters dopamine and serotonin, respectively (Fig. 1) [Lovenberg et al., 1962]. Both reactions are pyridoxal phosphate (PLP)-dependent. In nonneuronal tissue, including liver, kidney, spleen, intestine, and different cell types, AADC is probably involved in additional metabolic functions

[Bertoldi and Borri Voltattorni, 2003; Christenson et al., 1972]. For diagnostic purposes AADC activity can be measured in plasma [Hyland and Clayton, 1992].

The human *DDC* gene is over 85 kbp in length and is composed of 15 exons (Fig. 5). Full-length cDNAs from a pheochromocytoma library have been cloned and characterized [Ichinose et al., 1989; Sumi-Ichinose et al., 1992]. There are two forms of human AADC mRNA that differ only in their 5'-UTRs. These encode an identical amino acid sequence of 480 amino acid residues, with a molecular mass of 53.9 kDa. The different 5' UTRs are encoded by two distinct exons (N1 for the neuronal type and L1 for the nonneuronal type) [Albert et al., 1992; Krieger et al., 1991].

AADC deficiency is associated with severe developmental delay, oculogyric crises, and autonomic dysfunction. The disease was described in 1992 by Hyland et al. [1992]. Diagnosis was done by identification of very low levels of the neurotransmitter metabolites homovanillic acid (HVA) and 5HIAA, and high levels of 3-O-methyl-DOPA (3OMD), L-DOPA, and 5HTP in cerebrospinal fluid. Vanillic acid (VLA) was increased in urine and AADC activity was absent in plasma of two patients. Since that description, several patients have been reported [Abdenur et al., 2006; Chang et al., 2004; Fiumara et al., 2002; Korenke et al., 1997; Pons et al., 2004; Swoboda et al., 2003].

Almost 30 mutations have been detected in patients with AADC deficiency, including missense mutations, a splice-site mutation in intron 6, and two deletions, with one of the deletions in the 5' UTR (see Supplementary Table S4 and Fig. 5). In addition, several noncoding SNPs were reported. Kinetic analysis was performed only for the G102S recombinant protein and it was shown that the mutant protein exhibits a 60-fold decreased affinity for L-DOPA [Chang et al., 2004]. In some patients with bipolar affective disorder, two frequent sequence variations in the coding region of the *DDC* gene were found; a 1-bp deletion in the promoter (not shown in Supplementary Table S4) and a 4-bp deletion in the untranslated exon 1 [Borglum et al., 1999; Chang et al., 1998]. Using additional genetic markers, several groups have

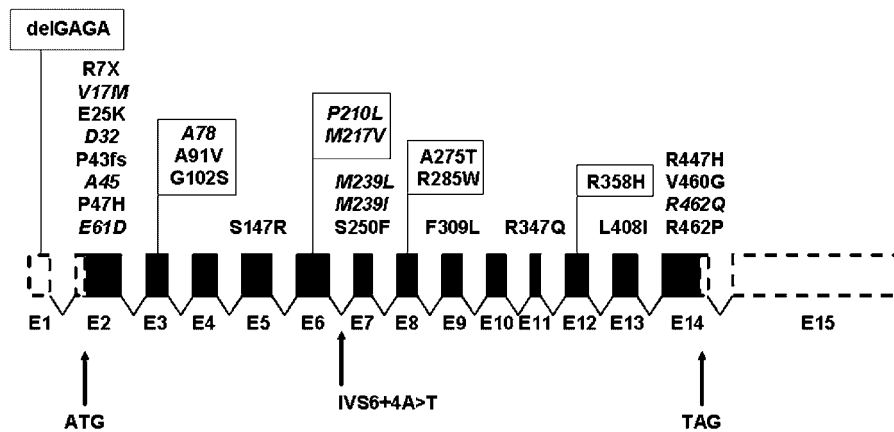


FIGURE 5. Genomic structure and location of mutations in human *DDC* gene. Only SNPs in the coding region of the *DDC* gene are depicted. Reference sequences (see also footnotes in Supplementary Table S4): ENST00000340197 (NM_000790.3), gene ENSG00000132437, Swiss prot P20711, MIM# 608643. Mutations in italics are cited only as SNPs (in the Ensembl v39 Database; see also Supplementary Table S4).

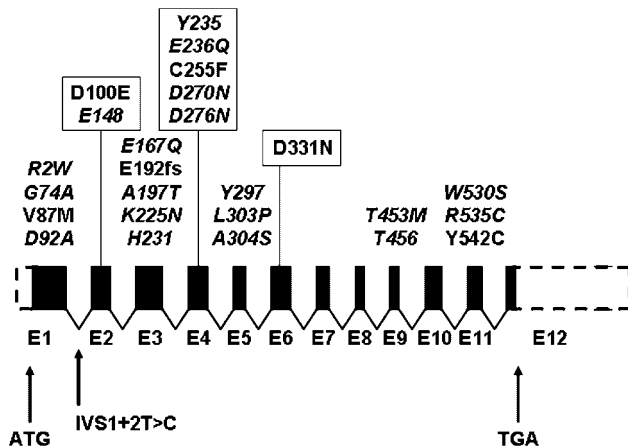


FIGURE 6. Genomic structure and location of mutations in human *DBH* gene. Reference sequences: ENST00000263611 (or NM_000787.2), gene ENSG00000123454, Swiss Prot P09172, MIM# 223360. Mutations in italics are cited as SNPs (only in coding region; see also Ensembl v43 Database and Supplementary Table S5).

recently reported positive association findings with ADHD and nicotine dependence, indicating that altered *DDC* function could be involved in several neuropsychiatric disturbances [Ribases et al., in press; Zhang et al., 2006a].

Mutations Within the *DBH* Gene

Dopamine- β -hydroxylase (DBH) is a copper-containing mono-oxygenase that catalyzes the conversion of dopamine to norepinephrine using molecular oxygen as additional substrate and vitamin C (ascorbate) as cofactor. It is a glycoprotein with a molecular weight of 290 kDa and consists of four identical subunits, each with a single type II copper atom. DBH exists in both a soluble and membrane-bound form within vesicles and as a constituent of their membranes with its active site directed inward. DBH is localized in noradrenergic and adrenergic neurons of CNS, sympathetic ganglia, and adrenal medulla chromaffin cells.

Two cDNA variants (types A and B), which are derived from the human *DBH* gene, were isolated from a pheochromocytoma cDNA library. Type A (2.7 kb) and B (2.4 kb) cDNAs encode the same sequence of 603 amino acids. The type A cDNA contains a

3'-extension of 300 bp at the end of type B cDNA [Kobayashi et al., 1989].

Autosomal recessive DBH deficiency is a rare form of primary autonomic failure characterized by a complete absence of norepinephrine and epinephrine in plasma, together with increased levels of dopamine and low serum DBH activity [Biaggioni and Robertson, 1987; Man in 't Veld et al., 1987; Senard and Rouet, 2006]. These patients present with severe orthostatic hypotension and episodic hypoglycemia and hypothermia. Oral administration of dihydroxyphenylserine restores plasma norepinephrine and increases blood pressure. Patients with Menkes disease, a neurodegenerative disorder of copper metabolism, exhibited secondary DBH deficiency because the enzyme requires copper to catalyze the conversion of dopamine to norepinephrine [Kaler et al., 1993]. Very few mutations, besides a number of polymorphisms, were reported in patients with DBH deficiency, with at least five missense mutations, one single-base pair deletion, and two synonymous coding splice-site mutations (Supplementary Table S5 and Fig. 6). No functional analysis is available for these mutant DBHs. Variations in the *DBH* gene were further reported in patients with Gilles de la Tourette syndrome, ADHD, and schizophrenia [Kopeckova et al., 2006; Ozbay et al., 2006; Park et al., 2007].

Mutations Within the *PNMT* Gene

Phenylethanolamine *N*-methyltransferase (PNMT) methylates in an *S*-adenosylmethionine-dependent reaction norepinephrine to form epinephrine, which is the last step of catecholamine biosynthesis. PNMT is present in many tissues throughout the body, with particularly high concentrations in the adrenal medulla and the left atrium of the heart [Ziegler et al., 2002]. Its product epinephrine plays an important role for adrenergic control of stress, metabolic function, and energy metabolism [Goldstein, 1995]. Analysis of stroke-prone spontaneously hypertensive rats indicated that genes in a conserved group syntenic to human chromosome 17q are involved in blood pressure regulation in the rat [Hilbert et al., 1991; Jacob et al., 1991; Julier et al., 1997]. A functionally relevant candidate at this locus is the *PNMT* gene, which contains 3 exons, predicts a protein of 282 amino acids, and is subject to multiple regulatory mechanisms at the transcriptional and post-transcriptional levels [Wong et al., 2004]. It was expected that due to the central function of epinephrine in controlling metabolism

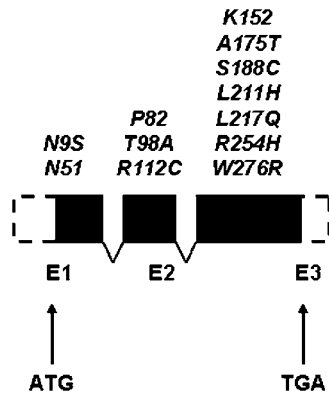


FIGURE 7. Genomic structure and location of SNPs in human PNMT gene. Only SNPs are reported in the coding region of the PNMT gene (see also Ensembl v43 Database and Supplementary Table S6). Reference sequences: transcript ENST00000269582 (NM_002686.3), gene ENSG00000141744, Swiss Prot P11086, #MIM 171190.

and energy homeostasis, and its influence on the activity of the cardiovascular system, mutations may lead to early lethality. However, thus far neither a distinct metabolic or clinical phenotype with potential dysfunction of PMNT, nor a candidate mutation for the PMNT has been reported, except for gene variations or polymorphisms with association to diseases. Besides studies on rats, mouse models were investigated for elucidating the physiological function of PMNT, and it was reported that ablation of PNMT-producing cell populations from the adrenal medulla and retina resulted in abnormalities in the adrenal medulla, eye, and testis [Quaife et al., 1994], but PMNT knockout mice with concomitant loss of epinephrine were viable and fertile with no apparent developmental defects [Ebert et al., 2004]. Regarding human gene variations, several publications plus the Ensembl Database report various synonymous coding and nonsynonymous coding SNPs in the coding region of the PNMT gene (see Fig. 7 and Supplementary Table S6). In addition, at least five different SNPs in the 5' gene upstream, four SNPs in intron 1, and 2 SNPs in the 3' UTR were reported (not shown in Fig. 7 and in Supplementary Table S6) [Ji et al., 2005; Kepp et al., 2007; Mann et al., 2001; Peters et al., 2003]. The various promoter mutations exhibited different activities in reporter gene studies [Ji et al., 2005], and some of them were reported to have association with early-onset Alzheimer Disease [Mann et al., 2001], or to be predictive of weight loss in obese women [Peters et al., 2003]. However, upon reinvestigating several of the SNPs in the 5' upstream region, in intron 1 and in exon 2 (p.K152 and p.A175T), none of these nucleotide variations showed significant differences in allelic frequency between hypertensive and normotensive subjects, indicating that the difference in PMNT expression among population samples are not determined by these polymorphisms [Kepp et al., 2007].

Metabolism of Serotonin and Catecholamines

For a schematic overview of serotonin and the catecholamines metabolism see Fig. 1. Serotonin degradation to 5HIAA, which is found in CSF and in urine, is a two-step pathway with a 5-hydroxyindolacetic aldehyde intermediate (not shown), and involves the consecutive action of the two enzymes MAO-A and ALDH. The product of TH, L-DOPA, can be degraded by COMT to the 3OMD intermediate and by transamination to VLA as a final metabolite that is excreted in the urine. Dopamine is degraded either

via 3-methoxytryptamine (3MT), or via dihydroxyphenylacetic acid (DOPAC) to HVA, or to dopamine sulfate by SULT1A3. Enzymatic degradation of catecholamines involves methylation and oxidation reactions catalyzed by COMT, MAO-A (plus AR), ADH, and SULT1A3 (unstable aldehyde intermediates are not shown in Fig. 1). The MHPG-SO₄, NMET-SO₄, MET-SO₄, and VMA are excreted in the urine, with VMA as the major urinary metabolite of norepinephrine and epinephrine. More detailed information on the contribution of the different pathways for the metabolism of norepinephrine and epinephrine can be found in Eisenhofer et al. [2005, 2004]. The metabolites DOPAC, 3MT, MET, NMET, and, most importantly, HVA, VMA, and MHPG are all found in CSF and are used for differential diagnosis of the various defects (for details see Blau et al. [2005]).

The activities of at least three distinct enzymes, MAO, COMT, and SULT1A3, have an important role in the homeostasis, inactivation, and clearance of monoamine neurotransmitters. For the MAO, two isoforms exist, i.e., MAO-A and MAO-B, which are encoded by separate genes closely linked in opposite orientation on the X-chromosome and expressing proteins with 70% amino acid identity. The MAOA gene is split into 15 exons (similar the MAOB gene) and encodes a single protein with a subunit length of 527 amino acids. Although dopamine is a substrate for both MAO-A and MAO-B, the two isoenzymes have distinct roles in the metabolism based on their substrate selectivity and inhibitor sensitivity, and to some extent also due to distinct tissue localization. Furthermore, knockout mice cannot compensate for an apparent absence of either MAO-A or MAO-B, and studies with MAO-A-deficient men and mice knockouts have shown distinct differences in behavior and neurotransmitter metabolism, including elevated brain levels of serotonin, dopamine, and norepinephrine [Shih, 2004]. MAO-A exhibits a higher affinity for serotonin and norepinephrine, and is thus important for serotonin and catecholamine metabolism, although in the brain it is predominantly found in catecholaminergic neurons. MAO-B has a higher preference for metabolism of phenylethylamine and is predominantly abundant in serotonergic and histaminergic neurons and glial cells [Shih et al., 1999]. MAO activity is always accompanied by AR or ALDH that metabolizes unstable aldehyde intermediates [Eisenhofer et al., 2004].

COMT catalyzes the transfer of the methyl group from S-adenosylmethionine to catecholamine substrates such as L-DOPA, dopamine, epinephrine, and norepinephrine. Besides its role in catecholamine neurotransmitter degradation, it is important in the detoxification of xenobiotics and metabolism of catechol drugs, which are used for the treatment of hypertension, asthma, and Parkinson's disease [Mannisto and Kaakkola, 1999]. The human gene COMT has an unusual organization as it contains six exons with the two first exons being noncoding. Furthermore, its expression is controlled by two distinct promoters, P2 located in exon 1 and P2 in exon 3 that produces two different transcripts. The larger transcript can code for both a membrane-bound COMT (MB-COMT) with 271 amino acids and a soluble COMT (S-COMT) with 251 amino acids, whereas the shorter transcript can only code for S-COMT [for details see Lundström et al., 1995; Mannisto and Kaakkola, 1999]. Most tissues contain both forms of COMT, but brain dominantly expresses the MB-COMT. The latter has a much higher affinity for its substrates and might therefore metabolize also low concentrations of catecholamines.

The SULT isoenzyme SULT1A3 is mainly localized in the upper gastrointestinal tract and carries out extraneuronal detoxification by sulfate conjugation of circulating dopamine, NMET, MET, and MHPG (and other related drugs), and is a final and quantitatively

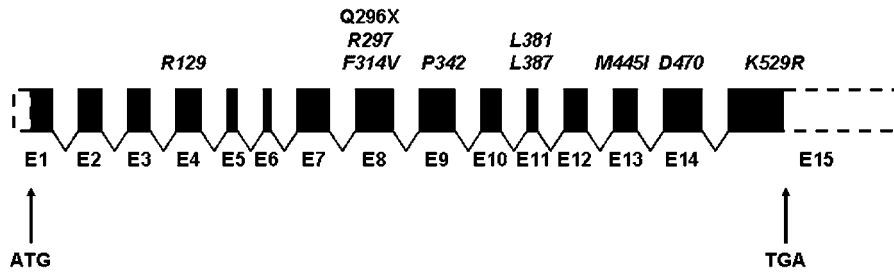


FIGURE 8. Genomic structure and location of SNPs in human MAOA gene. Reference sequences: transcript ENST00000338702 (or NM_000240.2), gene ENSG00000189221, Swiss prot P21397, MIM# 309850, 300615 (see also Ensembl v43 Database and Supplementary Table S7).

important metabolic step before urinary clearance of sulfonated catecholamines [Eisenhofer et al., 1999; Thomae et al., 2003]. The *SULT1A3* gene is one member of the 11 or 12 members of the human *SULT* gene family, and is located in a cluster of the three genes *SULT1A1–1A3* with the *1A3* gene copy on chromosome 16p11.2 apparently duplicated at 16p12.1 as *SULT1A4*. The duplicated *SULT1A3/1A4* genes are 99.8% identical, but express the same *SULT1A3* proteins [Hildebrandt et al., 2004]. The gene organization is further complicated by the 100% identity of three 5'-noncoding exons of *SULT1A3/4* overlapping with three coding exons of region MGC5178. The *SULT1A3/1A4* genes contain each 10 exons, besides the additional four "intercalated" exons, with seven coding and at least three alternatively-spliced 5'-noncoding exons [Aksoy and Weinshilboum, 1995]. Several studies based on a single copy of *SULT1A3* identified a number of DNA variants, but the discovery of a two-gene, four-allele system led to the identification of more than 20 polymorphisms in this system of alternative introns/exons and overlapping two-gene cluster, among them at least four nonsynonymous SNPs (p.P101L, p.P101H, p.R144C, and p.K234N) with varying activity when expressed in COS-1 cells [Hildebrandt et al., 2004; Raftogianis et al., 1997; Thomae et al., 2003]. This intricate situation is further complicated by both overlapping copies of *SULT1A3/1A4* being transcriptionally active with unclear regulation.

As the possible contribution of *SULT1A3/1A4* gene variants to human disease or variation in response to catecholamine sulfonation remains unclear, at this stage we did not include a summary on the polymorphisms for *SULT1A3* (for an overview see Hildebrandt et al. [2004]). Furthermore, the gene variants in the relevant AR, aldehyde or aldose dehydrogenase/oxidoreductase (ALDH) and ADH are limited for the metabolism of catecholamines and serotonin, or episodically reported (see for instance Buervenich et al. [2005]), and are also not covered in this *Mutation Update*.

Mutations Within the MAOA Gene

The earliest observations of MAOA deletions were from patients with severe mental retardation due to X-chromosomal deletions including MAOA, MOAB as well as the *Norrie disease* gene. Selective MAO-A deficiency observed in males from a Dutch family revealed relatively mild symptoms associated with impulsive aggression (for more details on the different phenotypes of these patients see Brunner et al. [1993]; Lenders et al. [1996]; and Shih et al. [1999]). Furthermore, MAOA deficient knockout mice manifested a distinct behavioral disturbances, including enhanced aggression in males, and aggression was normalized by restoring MAOA expression [Cases et al., 1995; Shih and Thompson, 1999]. In the Dutch family, MAO-A deficiency was diagnosed based on

urinary metabolites like elevated NMET and tyramine, low 5HIAA, VMA and HVA, as well as mutation analysis of the MAOA gene. All affected males carried the same MAOA-mutant allele p.Q296X, i.e., an early termination codon in exon 8 leading to nonfunctional protein truncation. Still, only these few male patients from the Dutch family have been reported with a distinct MAO-A deficiency. However, low MAO-A activity due to tandem repeat polymorphism in the promoter was reported to be associated with antisocial behavior in selectively maltreated children [Caspi et al., 2002]. Mutations in the variation database in the coding region are several SNPs in various exons, including synonymous and nonsynonymous substitutions, with no approved functional role (see Supplementary Table S7 and Fig. 8). More variations in the MAOA gene with debatable functionality are reviewed in D'Souza and Craig [2006]. For instance, allelic variations of the MAOA gene are considered to be candidates for alcohol dependence susceptibility, among them are several alleles including, e.g., a 30-bp repeat polymorphism of the MAOA-*uVNTR* gene, a variable number of tandem repeats located upstream of the promoter (not shown in Table S7 and Fig. 8), and the *EcoRV* polymorphism for SNP p.D470 [Huang et al., 2007]. Other studies have found no association between alcoholism and the MAOA gene (see references in Huang et al. [2007]). Furthermore, the MAOA-*uVNTR* promoter mutation was reported by various authors to be associated with the pineal MAO-A activity in Alzheimer's diseases [Wu et al., 2007], with symptoms of depression and sleep quality [Brummett et al., 2007], and with a significant risk factor for aggressive behavior [Frazzetto et al., 2007]. Another recent study reported no significant association of this promoter mutation between aggressive and nonaggressive patients [Fresan et al., 2007]; for discussion see also Rosenberg et al. [2006].

Mutations Within the COMT Gene

Studies with a complete COMT knockout mouse revealed apparently physical healthy and fertile animals with no gross abnormalities of dopaminergic neurons but minor, sexually dimorphic changes in catecholamine levels and behavior [Gogos et al., 1998]. Most surprising were the findings that residual levels of HVA were detected in the brain, and that the ratio of HVA/DOPAC as a measure of COMT activity was not changed in various brain regions of knockout animals compared to wild type. As one possible interpretation, an alternative compensatory but yet unidentified methyltransferase may exist. Human patients with COMT gene deficiency have not been described. Nevertheless, the genetic variant p.V158M with low thermal stability and low COMT activity is a well established polymorphism that could contribute to various neuropsychiatric manifestations (for more details see also D'Souza and Craig [2006] and Mannisto and

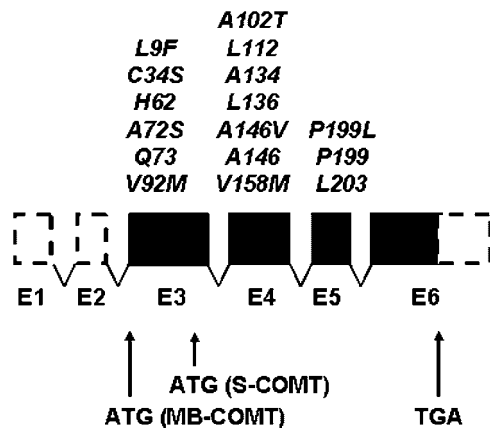


FIGURE 9. Genomic structure and location of SNPs in human *COMT* gene. The human *COMT* gene codes for a soluble protein with 221 amino acids (S-COMT) and a membrane bound protein with 271 amino acids (MB-COMT). Only SNPs in the coding region of the *COMT* gene are depicted (see also Ensembl v43 Database and Supplementary Table S8). Reference sequences: transcript ENST00000207636 (NM_000754.2 for MB-COMT mRNA; NM_007310.1 for S-COMT mRNA), gene ENSG00000093010, Swiss prot P21964 (NP_000745.1 for MB-COMT with 271 aa; NP_009294.1 for S-COMT with 221 aa), MIM# 116790.

Kaakkola [1999]). Furthermore, the nonsynonymous A72S polymorphism was associated with reduced COMT enzyme activity and with a risk for schizophrenia [Lee et al., 2005]. More recently, three major haplotypes formed by four SNPs, one in the S-COMT promoter region (rs6296; not shown in Supplementary Table S8) and three in the S- and MB-COMT coding region (p.H62, p.L136, and p.V158M), were associated with differences in pain sensitivity and the likelihood of developing a chronic musculoskeletal pain condition [Nackley et al., 2006]. It was shown that these haplotypes modulate protein expression by altering mRNA secondary structure, thus stressing the functional significance of synonymous variations and importance of haplotypes. In the light of these findings, the results of previous association studies of behavioral phenotypes with different synonymous and nonsynonymous *COMT* variants may have to be reconsidered. The *COMT* p.V158M polymorphism also appears to influence cognitive function. The association between the p.V158M polymorphism and cognitive function has been addressed in many studies, albeit with variable results. It has been suggested that the low-activity M158 allele allows for better performance on cognitive tasks that have a working memory component [Savitz et al., 2006]. The same polymorphism is associated with bipolar disorder and may influence neurocognitive performance [Burdick et al., 2007]. Besides these substitutions, several more nonsynonymous and synonymous mutations in three coding exons of the human *COMT* gene are reported in the variation database with unknown function (see Supplementary Table S8 and Fig. 9).

SUMMARY AND OUTLOOK

With the present *Mutation Update* on metabolic enzymes for serotonin and catecholamine biosynthesis and metabolism, we have attempted to provide a comprehensive summary of mutations and polymorphisms that have been reported to affect these genes. As heritable DNA variations for neurometabolic diseases that directly cause or predispose to the development of clinical syndromes are rare but are increasingly diagnosed or confirmed by mutation analysis, our proposition for a unified nomenclature of

gene structure and nucleic acid aberrations will make it easier to report on new mutations or haplotypes that modulate expression or enzyme activities. Our compilation of mutations will be updated and kept accessible in the Pediatric Neurotransmitter Disorder Data Base (PNDDDB; www.bioPKU.org) to help the scientific community identify and interpret the effects of mutations. For a better understanding of the relation between neurometabolic abnormalities, DNA variations, and clinical syndromes, further research is needed, but molecular testing may become an even more important diagnostic tool in the future. Furthermore, the genotype–phenotype information derived from these rare monogenic disorders will be extremely useful for the elucidation of their role in the more common neuropsychiatric disturbances.

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REFERENCES

- Abdenur JE, Abeling N, Specola N, Jorge L, Schenone AB, van Cruchten AC, Chamoles NA. 2006. Aromatic L-amino acid decarboxylase deficiency: unusual neonatal presentation and additional findings in organic acid analysis. *Mol Genet Metab* 87:48–53.
- Aksoy IA, Weinshilboum RM. 1995. Human thermolabile phenol sulfotransferase gene (STM): molecular cloning and structural characterization. *Biochem Biophys Res Commun* 208:786–795.
- Albert VR, Lee MR, Bolden AH, Wurzbarger RJ, Aguanno A. 1992. Distinct promoters direct neuronal and nonneuronal expression of rat aromatic L-amino acid decarboxylase. *Proc Natl Acad Sci USA* 89:12053–12057.
- Aneman A, Eisenhofer G, Fandriks L, Friberg P. 1995. Hepatomesenteric release and removal of norepinephrine in swine. *Am J Physiol* 268 (Pt 2):R924–R930.
- Asberg M, Traskman L, Thoren P. 1976. 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? *Arch Gen Psychiatry* 33:1193–1197.
- Bertoldi M, Borri Voltattorni C. 2003. Reaction and substrate specificity of recombinant pig kidney Dopa decarboxylase under aerobic and anaerobic conditions. *Biochim Biophys Acta* 1647:42–47.
- Biaggioni I, Robertson D. 1987. Endogenous restoration of noradrenaline by precursor therapy in dopamine-beta-hydroxylase deficiency. *Lancet* 2:1170–1172.
- Biederman J, Faraone SV. 2005. Attention-deficit hyperactivity disorder. *Lancet* 366:237–248.
- Borglum AD, Bruun TG, Kjeldsen TE, Ewald H, Mors O, Kirov G, Russ C, Freeman B, Collier DA, Kruse TA. 1999. Two novel variants in the DOPA decarboxylase gene: association with bipolar affective disorder. *Mol Psychiatry* 4:545–551.
- Brautigam C, Steenbergen-Spanjers GC, Hoffmann GF, Dionisi-Vici C, van den Heuvel LP, Smeitink JA, Wevers RA. 1999. Biochemical and molecular genetic characteristics of the severe form of tyrosine hydroxylase deficiency. *Clin Chem* 45:2073–2078.
- Brummett BH, Krystal AD, Siegler IC, Kuhn C, Surwit RS, Zuchner S, Ashley-Koch A, Barefoot JC, Williams RB. 2007. Associations of a regulatory polymorphism of monoamine oxidase-A gene promoter (MAOA-uVNTR) with symptoms of depression and sleep quality. *Psychosom Med* 69:396–401.
- Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. 1993. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* 262:578–580.
- Buervenich S, Carmine A, Galter D, Shahabi HN, Johnels B, Holmberg B, Ahlberg J, Nissbrandt H, Eerola J, Hellstrom O, Tienari PJ, Matsuura T, Ashizawa T, Wüllner U, Klockgether T, Zimprich A, Gasser T,

- Hanson M, Waseem S, Singleton A, McMahon FJ, Anvret M, Sydow O, Olson L. 2005. A rare truncating mutation in ADH1C (G78Stop) shows significant association with Parkinson disease in a large international sample. *Arch Neurol* 62:74–78.
- Burdick KE, Funke B, Goldberg JF, Bates JA, Jaeger J, Kucherlapati R, Malhotra AK. 2007. COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. *Bipolar Disord* 9:370–376.
- Cases O, Seif I, Grimsby J, Gaspar P, Chen K, Pournin S, Muller U, Aguet M, Babinet C, Shih JC, De Maeyer E. 1995. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. *Science* 268:1763–1766.
- Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. 2002. Role of genotype in the cycle of violence in maltreated children. *Science* 297:851–854.
- Chang YT, Mues G, McPherson JD, Bedell JA, Marsh JL, Hyland K. 1998. Mutations in the human aromatic l-amino acid decarboxylase gene. *J Inherit Metab Dis* 21(Suppl 2):4.
- Chang YT, Sharma R, Marsh JL, McPherson JD, Bedell JA, Knust A, Brautigam C, Hoffmann GF, Hyland K. 2004. Levodopa-responsive aromatic l-amino acid decarboxylase deficiency. *Ann Neurol* 55:435–438.
- Christenson JG, Dairman W, Udenfriend S. 1972. On the identity of DOPA decarboxylase and 5-hydroxytryptophan decarboxylase (immunological titration-aromatic l-amino acid decarboxylase-serotonin-dopamine-norepinephrine). *Proc Natl Acad Sci USA* 69:343–347.
- Cichon S, Winge I, Mattheisen M, Georgi A, Karpushova A, Freudenberg J, Freudenberg-Hua Y, Babadjanova G, Van Den Bogaert A, Abramova LI, Kapiletti S, Knappskog PM, McKinney J, Maier W, Jamra RA, Schulze TG, Schumacher J, Propping P, Rieselmeier M, Haavik J, Nöthen MM. 2008. Brain-specific tryptophan hydroxylase 2 (TPH2): a functional Pro206Ser substitution and variation in the 5'-region are associated with bipolar affective disorder. *Hum Mol Genet* 17:87–97.
- D'Souza UM, Craig IW. 2006. Functional polymorphisms in dopamine and serotonin pathway genes. *Hum Mutat* 27:1–13.
- De Lonlay P, Nassogne MC, van Gennip AH, van Cruchten AC, Billatte de Villemeur T, Cretz M, Stoll C, Launay JM, Steenbergen-Spanje GC, van den Heuvel LP, Wevers RA, Saudubray JM, Abeling NG. 2000. Tyrosine hydroxylase deficiency unresponsive to L-dopa treatment with unusual clinical and biochemical presentation. *J Inherit Metab Dis* 23:819–825.
- de Rijk-Van Andel JF, Gabreels FJ, Geurtz B, Steenbergen-Spanjers GC, van Den Heuvel LP, Smeitink JA, Wevers RA. 2000. L-dopa-responsive infantile hypokinetic rigid parkinsonism due to tyrosine hydroxylase deficiency. *Neurology* 55:1926–1928.
- Deinum J, Steenbergen-Spanjers GC, Jansen M, Boomsma F, Lenders JW, van Ittersum FJ, Huck N, van den Heuvel LP, Wevers RA. 2004. DBH gene variants that cause low plasma dopamine beta hydroxylase with or without a severe orthostatic syndrome. *J Med Genet* 41:e38.
- Dhondt, J-L. 2006. Laboratory diagnosis of phenylketonuria. In: Blau N, editor. PKU and BH4: advances in phenylketonuria and tetrahydrobiopterin. Heilbronn: SPS Verlagsgesellschaft. p 161–179.
- Diepold K, Schutz B, Rostasy K, Wilken B, Hougaard P, Guttler F, Romstad A, Birk Moller L. 2005. Levodopa-responsive infantile parkinsonism due to a novel mutation in the tyrosine hydroxylase gene and exacerbation by viral infections. *Mov Disord* 20:764–767.
- Ebert SN, Rong Q, Boe S, Thompson RP, Grinberg A, Pfeifer K. 2004. Targeted insertion of the Cre-recombinase gene at the phenylethanolamine n-methyltransferase locus: a new model for studying the developmental distribution of adrenergic cells. *Dev Dyn* 231:849–858.
- Eisenhofer G, Aneman A, Hooper D, Holmes C, Goldstein DS, Friberg P. 1995. Production and metabolism of dopamine and norepinephrine in mesenteric organs and liver of swine. *Am J Physiol* 268(Pt 1): G641–G649.
- Eisenhofer G, Aneman A, Friberg P, Hooper D, Fandriks L, Lonroth H, Hunyady B, Mezey E. 1997. Substantial production of dopamine in the human gastrointestinal tract. *J Clin Endocrinol Metab* 82:3864–3871.
- Eisenhofer G, Coughtrie MW, Goldstein DS. 1999. Dopamine sulphate: an enigma resolved. *Clin Exp Pharmacol Physiol Suppl* 26:S41–S53.
- Eisenhofer G, Kopin IJ, Goldstein DS. 2004. Catecholamine metabolism: a contemporary view with implications for physiology and medicine. *Pharmacol Rev* 56:331–349.
- Eisenhofer G, Huysmans F, Pacak K, Walther MM, Sweep FC, Lenders JW. 2005. Plasma metanephrines in renal failure. *Kidney Int* 67:668–677.
- Emden G, Baldes K. 1913. Über den Abbau des Phenylalanins im tierischen Organismus (on the degradation of phenylalanine in animal organisms). *Biochem Z* 55:301–322.
- Fitzpatrick PF. 2000. The aromatic amino acid hydroxylases. *Adv Enzymol Relat Areas Mol Biol* 74:235–294.
- Fiumara A, Brautigam C, Hyland K, Sharma R, Lagae L, Stoltenberg B, Hoffmann GF, Jaeken J, Wevers RA. 2002. Aromatic l-amino acid decarboxylase deficiency with hyperdopaminuria. Clinical and laboratory findings in response to different therapies. *Neuropediatrics* 33:203–208.
- Frazzetto G, Di Lorenzo G, Carola V, Proietti L, Sokolowska E, Siracusano A, Gross C, Troisi A. 2007. Early trauma and increased risk for physical aggression during adulthood: the moderating role of MAOA genotype. *PLoS ONE* 2:e486.
- Fresan A, Camarena B, Apiquian R, Aguilar A, Urraca N, Nicolini H. 2007. Association study of MAO-A and DRD4 genes in schizophrenic patients with aggressive behavior. *Neuropsychobiology* 55:171–175.
- Furukawa Y, Graf WD, Wong H, Shimadzu M, Kish SJ. 2001. Dopa-responsive dystonia simulating spastic paraplegia due to tyrosine hydroxylase (TH) gene mutations. *Neurology* 56:260–263.
- Gershon MD. 2003. Plasticity in serotonin control mechanisms in the gut. *Curr Opin Pharmacol* 3:600–607.
- Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, Karayiorgou M. 1998. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. *Proc Natl Acad Sci USA* 95:9991–9996.
- Goldstein DS. 1995. Stress, catecholamines, and cardiovascular disease. New York: Oxford University Press.
- Goldstein DS, Lenders JW, Kaler SG, Eisenhofer G. 1996. Catecholamine phenotyping: clues to the diagnosis, treatment, and pathophysiology of neurogenetic disorders. *J Neurochem* 67:1781–1790.
- Grahame-Smith DG. 1964. Tryptophan hydroxylation in brain. *Biochem Biophys Res Commun* 16:586–592.
- Grattan-Smith PJ, Wevers RA, Steenbergen-Spanjers GC, Fung VS, Earl J, Wilcken B. 2002. Tyrosine hydroxylase deficiency: clinical manifestations of catecholamine insufficiency in infancy. *Mov Disord* 17:354–359.
- Grima B, Lamouroux A, Boni C, Julien JF, Javoy-Agid F, Mallet J. 1987. A single human gene encoding multiple tyrosine hydroxylases with different predicted functional characteristics. *Nature* 326:707–711.
- Harvey M, Shink E, Tremblay M, Gagne B, Raymond C, Labbe M, Walther DJ, Bader M, Barden N. 2004. Support for the involvement of TPH2 gene in affective disorders. *Mol Psychiatry* 9:980–981.
- Hilbert P, Lindpaintner K, Beckmann JS, Serikawa T, Soubrier F, Dubay C, Cartwright P, De Gouyon B, Julier C, Takahashi S, Vincent M, Ganten D, Georges M, Lathrop GM. 1991. Chromosomal mapping of two genetic loci associated with blood-pressure regulation in hereditary hypertensive rats. *Nature* 353:521–529.
- Hildebrandt MA, Salavaggione OE, Martin YN, Flynn HC, Jalal S, Wieben ED, Weinshilboum RM. 2004. Human SULT1A3 pharmacogenetics: gene duplication and functional genomic studies. *Biochem Biophys Res Commun* 321:870–878.
- Hoffmann GF, Assmann B, Brautigam C, Dionisi-Vici C, Haussler M, de Klerk JB, Naumann M, Steenbergen-Spanjers GC, Strassburg HM, Wevers RA. 2003. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. *Ann Neurol* 54 (Suppl 6):S56–S65.
- Hotamisligil GS, Breakefield XO. 1991. Human monoamine oxidase A gene determines levels of enzyme activity. *Am J Hum Genet* 49:383–392.
- Huang SY, Lin WW, Wan FJ, Chang AJ, Ko HC, Wang TJ, Wu PL, Lu RB. 2007. Monoamine oxidase-A polymorphisms might modify the association between the dopamine D2 receptor gene and alcohol dependence. *J Psychiatry Neurosci* 32:185–192.
- Hyland K, Clayton PT. 1992. Aromatic l-amino acid decarboxylase deficiency: diagnostic methodology. *Clin Chem* 38:2405–2410.
- Hyland K, Surtees RA, Rodeck C, Clayton PT. 1992. Aromatic l-amino acid decarboxylase deficiency: clinical features, diagnosis, and treatment of a new inborn error of neurotransmitter amine synthesis. *Neurology* 42:1980–1988.

- Hyland K. 2005. Disorders of neurotransmitter metabolism. In: Blau N, Duran M, Blaskovics ME, Gibson KM, editors. *Physician's guide to the laboratory diagnosis of metabolic diseases*. 2nd edition. Berlin: Springer Verlag. p 106–122.
- Ichinose H, Kurosawa Y, Titani K, Fujita K, Nagatsu T. 1989. Isolation and characterization of a cDNA clone encoding human aromatic L-amino acid decarboxylase. *Biochem Biophys Res Commun* 164:1024–1030.
- Ichinose H, Ohye T, Takahashi E, Seki N, Hori T, Segawa M, Nomura Y, Endo K, Tanaka H, Tsuji S, Fujita K, Nagatsu T. 1994. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. *Nat Genet* 8:236–242.
- Ishiguro H, Arinami T, Saito T, Akazawa S, Enomoto M, Mitushio H, Fujishiro H, Tada K, Akimoto Y, Mifune H, Shiozuka S, Hamaguchi H, Toru M, Shibuya H. 1998. Systematic search for variations in the tyrosine hydroxylase gene and their associations with schizophrenia, affective disorders, and alcoholism. *Am J Med Genet* 81:388–396.
- Jacob HJ, Lindpaintner K, Lincoln SE, Kusumi K, Bunker RK, Mao YP, Ganten D, Dzau VJ, Lander ES. 1991. Genetic mapping of a gene causing hypertension in the stroke-prone spontaneously hypertensive rat. *Cell* 67:213–224.
- Janssen RJ, Wevers RA, Haussler M, Luyten JA, Steenbergen-Spanjers GC, Hoffmann GF, Nagatsu T, Van den Heuvel LP. 2000. A branch site mutation leading to aberrant splicing of the human tyrosine hydroxylase gene in a child with a severe extrapyramidal movement disorder. *Ann Hum Genet* 64(Pt 5):375–382.
- Ji Y, Salavaggione OE, Wang L, Adjei AA, Eckloff B, Wieben ED, Weinshilboum RM. 2005. Human phenylethanolamine N-methyltransferase pharmacogenomics: gene re-sequencing and functional genomics. *J Neurochem* 95:1766–1776.
- Julier C, Delepine M, Keavney B, Terwilliger J, Davis S, Weeks DE, Bui T, Jeunemaitre X, Velho G, Froguel P, Ratcliffe P, Corvol P, Soubrier F, Lathrop GM. 1997. Genetic susceptibility for human familial essential hypertension in a region of homology with blood pressure linkage on rat chromosome 10. *Hum Mol Genet* 6:2077–2085.
- Kaler SG, Goldstein DS, Holmes C, Salerno JA, Gahl WA. 1993. Plasma and cerebrospinal fluid neurochemical pattern in Menkes disease. *Ann Neurol* 33:171–175.
- Kaneda N, Kobayashi K, Ichinose H, Kishi F, Nakazawa A, Kurosawa Y, Fujita K, Nagatsu T. 1987. Isolation of a novel cDNA clone for human tyrosine hydroxylase: alternative RNA splicing produces four kinds of mRNA from a single gene. *Biochem Biophys Res Commun* 146:971–975.
- Kepp K, Juhanson P, Kozich V, Ots M, Viigimaa M, Laan M. 2007. Resequencing PNMT in European hypertensive and normotensive individuals: no common susceptibility variants for hypertension and purifying selection on intron 1. *BMC Med Genet* 8:47.
- Kim CH, Zabetian CP, Cubells JF, Cho S, Biaggioni I, Cohen BM, Robertson D, Kim KS. 2002. Mutations in the dopamine beta-hydroxylase gene are associated with human norepinephrine deficiency. *Am J Med Genet* 108:140–147.
- Knappskog PM, Flatmark T, Mallet J, Ludecke B, Bartholome K. 1995. Recessively inherited L-DOPA-responsive dystonia caused by a point mutation (Q381K) in the tyrosine hydroxylase gene. *Hum Mol Genet* 4:1209–1212.
- Kobayashi K, Kurosawa Y, Fujita K, Nagatsu T. 1989. Human dopamine beta-hydroxylase gene: two mRNA types having different 3'-terminal regions are produced through alternative polyadenylation. *Nucleic Acids Res* 17:1089–1102.
- Kopeckova M, Paclt I, Goetz P. 2006. Polymorphisms and low plasma activity of dopamine-beta-hydroxylase in ADHD children. *Neuro Endocrinol Lett* 27:748–754.
- Korenke GC, Christen HJ, Hyland K, Hunneman DH, Hanefeld F. 1997. Aromatic L-amino acid decarboxylase deficiency: an extrapyramidal movement disorder with oculogyric crises. *Eur J Paediatr Neurol* 1: 67–71.
- Krieger M, Coge F, Gros F, Thibault J. 1991. Different mRNAs code for dopa decarboxylase in tissues of neuronal and nonneuronal origin. *Proc Natl Acad Sci USA* 88:2161–2165.
- Lee SG, Joo Y, Kim B, Chung S, Kim HL, Lee I, Choi B, Kim C, Song K. 2005. Association of Ala72Ser polymorphism with COMT enzyme activity and the risk of schizophrenia in Koreans. *Hum Genet* 116:319–328.
- Lenders JW, Eisenhofer G, Abeling NG, Berger W, Murphy DL, Konings CH, Wagemakers LM, Kopin IJ, Karoum F, van Gennip AH, Brunner HG. 1996. Specific genetic deficiencies of the A and B isoenzymes of monoamine oxidase are characterized by distinct neurochemical and clinical phenotypes. *J Clin Invest* 97:1010–1019.
- Lovenberg W, Weissbach H, Udenfriend S. 1962. Aromatic L-amino acid decarboxylase. *J Biol Chem* 237:89–93.
- Lucki I. 1998. The spectrum of behaviors influenced by serotonin. *Biol Psychiatry* 44:151–162.
- Ludecke B, Bartholome K. 1995. Frequent sequence variant in the human tyrosine hydroxylase gene. *Hum Genet* 95:716.
- Ludecke B, Dworniczak B, Bartholome K. 1995. A point mutation in the tyrosine hydroxylase gene associated with Segawa's syndrome. *Hum Genet* 95:123–125.
- Ludecke B, Knappskog PM, Clayton PT, Surtees RA, Clelland JD, Heales SJ, Brand MP, Bartholome K, Flatmark T. 1996. Recessively inherited L-DOPA-responsive parkinsonism in infancy caused by a point mutation (L205P) in the tyrosine hydroxylase gene. *Hum Mol Genet* 5: 1023–1028.
- Lundström K, Tenhunen J, Tilgmann C, Karhunen T, Panula P, Ulmanen I. 1995. Cloning, expression and structure of catechol-O-methyltransferase. *Biochim Biophys Acta* 1251:1–10.
- Mallet J. 1999. Tyrosine hydroxylase from cloning to neuropsychiatric disorders. *Brain Res Bull* 50:381–382.
- Man in 't Veld AJ, Boomsma F, Moleman P, Schalekamp MA. 1987. Congenital dopamine-beta-hydroxylase deficiency. A novel orthostatic syndrome. *Lancet* 1:183–188.
- Mann MB, Wu S, Rostamkhani M, Tourtellotte W, MacMurray J, Comings DE. 2001. Phenylethanolamine N-methyltransferase (PNMT) gene and early-onset Alzheimer disease. *Am J Med Genet* 105:312–316.
- Mannisto PT, Kaakkola S. 1999. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. *Pharmacol Rev* 51:593–628.
- McKinney J, Knappskog PM, Haavik J. 2005. Different properties of the central and peripheral forms of human tryptophan hydroxylase. *J Neurochem* 92:311–320.
- Mezey E, Eisenhofer G, Hansson S, Harta G, Hoffman BJ, Gallatz K, Palkovits M, Hunyady B. 1999. Non-neuronal dopamine in the gastrointestinal system. *Clin Exp Pharmacol Physiol Suppl* 26:S14–S22.
- Moller LB, Romstad A, Paulsen M, Hougaard P, Ormazabal A, Pineda M, Blau N, Guttler F, Artuch R. 2005. Pre- and postnatal diagnosis of tyrosine hydroxylase deficiency. *Prenat Diagn* 25:671–675.
- Nackley AG, Shabalina SA, Tchivileva IE, Satterfield K, Korchynski O, Makarov SS, Maixner W, Diatchenko L. 2006. Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science* 314:1930–1933.
- Nagatsu T, Levitt M, Udenfriend S. 1964. Tyrosine hydroxylase. The initial step in norepinephrine biosynthesis. *J Biol Chem* 239:2910–2917.
- Nutt DJ. 2006. The role of dopamine and norepinephrine in depression and antidepressant treatment. *J Clin Psychiatry* 67(Suppl 6):3–8.
- Ozbay F, Wigg KG, Turanli ET, Asherson P, Yazgan Y, Sandor P, Barr CL. 2006. Analysis of the dopamine beta hydroxylase gene in Gilles de la Tourette syndrome. *Am J Med Genet B Neuropsychiatr Genet* 141: 673–677.
- Park JK, Kim JW, Lee HJ, Chung JH, Ha EY, Oh DJ, Song JY. 2007. Dopamine beta-hydroxylase gene polymorphisms and psychotic symptoms in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 144:944–945.
- Peters WR, MacMurry JP, Walker J, Giese RJ Jr, Comings DE. 2003. Phenylethanolamine N-methyltransferase G-148A genetic variant and weight loss in obese women. *Obes Res* 11:415–419.
- Pons R, Ford B, Chiriboga CA, Clayton PT, Hinton V, Hyland K, Sharma R, De Vivo DC. 2004. Aromatic L-amino acid decarboxylase deficiency: clinical features, treatment, and prognosis. *Neurology* 62:1058–1065.
- Quaife CJ, Hoyle GW, Froelick GJ, Findley SD, Baetge EE, Behringer RR, Hammang JP, Brinster RL, Palmiter RD. 1994. Visualization and ablation of phenylethanolamine N-methyltransferase producing cells in transgenic mice. *Transgenic Res* 3:388–400.

- Raftogianis RB, Wood TC, Otterness DM, Van Loon JA, Weinshilbom RM. 1997. Phenol sulfotransferase pharmacogenetics in humans: association of common SUL1A1 alleles with TS PST phenotype. *Biochem Biophys Res Commun* 239:298–304.
- Ramaekers VT, Senderek J, Hausler M, Haring M, Abeling N, Zerres K, Bergmann C, Heimann G, Blau N. 2001. A novel neurodevelopmental syndrome responsive to 5-hydroxytryptophan and carbidopa. *Mol Genet Metab* 73:179–187.
- Ribasas M, Serrano M, Fernandez-Alvarez E, Pahisa S, Ormazabal A, Garcia-Cazorla A, Perez-Duenas B, Campistol J, Artuch R, Cormand B. 2007. A homozygous tyrosine hydroxylase gene promoter mutation in a patient with dopa-responsive encephalopathy: clinical, biochemical and genetic analysis. *Mol Genet Metab* 92:274–277.
- Ribasas M, Ramos-Quiroga JA, Hervás A, Bosch R, Bielsa A, Gastaminza X, Artigas J, Rodriguez-Ben S, Estivill X, Casas M, Cormand B, Bayés M. Exploration of 19 serotonergic candidate genes in adults and children with attention-deficit/hyperactivity disorder identifies association for 5HT2A, DDC and MAOB. *Mol Psychiatry* (in press). [Epub ahead of print].
- Rosenberg S, Templeton AR, Feigin PD, Lancet D, Beckmann JS, Selig S, Hamer DH, Skorecki K. 2006. The association of DNA sequence variation at the MAOA genetic locus with quantitative behavioural traits in normal males. *Hum Genet* 120:447–459.
- Royo M, Daubner SC, Fitzpatrick PF. 2005. Effects of mutations in tyrosine hydroxylase associated with progressive dystonia on the activity and stability of the protein. *Proteins* 58:14–21.
- Savitz J, Solms M, Ramesar R. 2006. The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behav* 5:311–328.
- Scheuch K, Lautenschlager M, Grohmann M, Stahlberg S, Kirchheiner J, Zill P, Heinz A, Walther DJ, Priller J. 2007. Characterization of a functional promoter polymorphism of the human tryptophan hydroxylase 2 gene in serotonergic raphe neurons. *Biol Psychiatry* 62:1288–1294.
- Schiller A, Wevers RA, Steenbergen GC, Blau N, Jung HH. 2004. Long-term course of l-dopa-responsive dystonia caused by tyrosine hydroxylase deficiency. *Neurology* 63:1524–1526.
- Senard JM, Rouet P. 2006. Dopamine beta-hydroxylase deficiency. *Orphanet J Rare Dis* 1:7.
- Shih JC, Thompson RF. 1999. Monoamine oxidase in neuropsychiatry and behavior. *Am J Hum Genet* 65:593–598.
- Shih JC, Chen K, Ridd MJ. 1999. Monoamine oxidase: from genes to behavior. *Annu Rev Neurosci* 22:197–217.
- Shih JC. 2004. Cloning, after cloning, knock-out mice, and physiological functions of MAO A and B. *Neurotoxicology* 25:21–30.
- Sumi-Ichinose C, Ichinose H, Takahashi E, Hori T, Nagatsu T. 1992. Molecular cloning of genomic DNA and chromosomal assignment of the gene for human aromatic l-amino acid decarboxylase, the enzyme for catecholamine and serotonin biosynthesis. *Biochemistry* 31:2229–2238.
- Swaans RJ, Rondot P, Renier WO, Van Den Heuvel LP, Steenbergen-Spanjers GC, Wevers RA. 2000. Four novel mutations in the tyrosine hydroxylase gene in patients with infantile parkinsonism. *Ann Hum Genet* 64(Pt 1):25–31.
- Swoboda KJ, Saul JP, McKenna CE, Speller NB, Hyland K. 2003. Aromatic l-amino acid decarboxylase deficiency: overview of clinical features and outcomes. *Ann Neurol* 54(Suppl 6):S49–S55.
- Tay SK, Poh KS, Hyland K, Pang YW, Ong HT, Low PS, Goh DL. 2007. Unusually mild phenotype of AADC deficiency in 2 siblings. *Mol Genet Metab* 91:374–378.
- Thomae BA, Rifki OF, Theobald MA, Eckloff BW, Wieben ED, Weinshilbom RM. 2003. Human catecholamine sulfotransferase (SULT1A3) pharmacogenetics: functional genetic polymorphism. *J Neurochem* 87:809–819.
- Thony B, Blau N. 2006. Mutations in the BH4-metabolizing genes GTP cyclohydrolase I, 6-pyruvoyl-tetrahydropterin synthase, sepiapterin reductase, carbinolamine-4a-dehydratase, and dihydropteridine reductase. *Hum Mutat* 27:870–878.
- Thöny B, Gibson KM. 2006. Murine models of inherited monoaminergic and GABAergic neurotransmitter disorders. *Future Neurol* 1:665–676.
- Van Den Bogaert A, Slegers K, De Zutter S, Heyrman L, Norrback KF, Adolfsson R, Van Broeckhoven C, Del-Favero J. 2006. Association of brain-specific tryptophan hydroxylase, TPH2, with unipolar and bipolar disorder in a Northern Swedish, isolated population. *Arch Gen Psychiatry* 63:1103–1110.
- van den Heuvel LP, Luiten B, Smeitink JA, de Rijk-van Aniel JF, Hyland K, Steenbergen-Spanjers GC, Janssen RJ, Wevers RA. 1998. A common point mutation in the tyrosine hydroxylase gene in autosomal recessive l-DOPA-responsive dystonia in the Dutch population. *Hum Genet* 102:644–646.
- Verbeek MM, Geurtz PB, Willemsen MA, Wevers RA. 2007a. Aromatic l-amino acid decarboxylase enzyme activity in deficient patients and heterozygotes. *Mol Genet Metab* 90:363–369.
- Verbeek MM, Steenbergen-Spanjers GC, Willemsen MA, Hol FA, Smeitink J, Seeger J, Grattan-Smith P, Ryan MM, Hoffmann GF, Donati MA, Blau N, Wevers RA. 2007b. Mutations in the cyclic adenosine monophosphate response element of the tyrosine hydroxylase gene. *Ann Neurol* 62:422–426.
- Walther DJ, Bader M. 2003. A unique central tryptophan hydroxylase isoform. *Biochem Pharmacol* 66:1673–1680.
- Walther DJ, Peter JU, Bashammakh S, Hortnagl H, Voits M, Fink H, Bader M. 2003. Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science* 299:76.
- Waters PJ. 2003. How PAH gene mutations cause hyper-phenylalaninemia and why mechanism matters: insights from in vitro expression. *Hum Mutat* 21:357–369.
- Wevers RA, de Rijk-van Aniel JF, Brautigam C, Geurtz B, van den Heuvel LP, Steenbergen-Spanjers GC, Smeitink JA, Hoffmann GF, Gabreels FJ. 1999. A review of biochemical and molecular genetic aspects of tyrosine hydroxylase deficiency including a novel mutation (291delC). *J Inher Metab Dis* 22:364–373.
- Wildeman M, van Ophuizen E, den Dunnen JT, Taschner PEM. 2008. Improving sequence variant descriptions in mutation databases and literature using the Mutalyzer sequence variation. *Hum Mutat* 29:6–13.
- Winge I, McKinney JA, Knappskog PM, Haavik J. 2007. Characterization of wild-type and mutant forms of human tryptophan hydroxylase 2. *J Neurochem* 100:1648–1657.
- Wong DL, Tai TC, Wong-Faull DC, Claycomb R, Kvetnansky R. 2004. Genetic mechanisms for adrenergic control during stress. *Ann NY Acad Sci* 1018:387–397.
- Wu YH, Fischer DF, Swaab DF. 2007. A promoter polymorphism in the monoamine oxidase A gene is associated with the pineal MAOA activity in Alzheimer's disease patients. *Brain Res* 1167:13–19.
- Zhang X, Gainetdinov RR, Beaulieu JM, Sotnikova TD, Burch LH, Williams RB, Schwartz DA, Krishnan KR, Caron MG. 2005. Loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. *Neuron* 45:11–16.
- Zhang H, Ye Y, Wang X, Gelernter J, Ma JZ, Li MD. 2006a. DOPA decarboxylase gene is associated with nicotine dependence. *Pharmacogenomics* 7:1159–1166.
- Zhang X, Beaulieu JM, Gainetdinov RR, Caron MG. 2006b. Functional polymorphisms of the brain serotonin synthesizing enzyme tryptophan hydroxylase-2. *Cell Mol Life Sci* 63:6–11.
- Zhou Z, Peters EJ, Hamilton SP, McMahon F, Thomas C, McGrath PJ, Rush J, Trivedi MH, Charney DS, Roy A, Wisniewski S, Lipsky R, Goldman D. 2005a. Response to Zhang et al. ([126]2005): loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. *Neuron* 45, 11–16. *Neuron* 48:702–703; author reply 705–706.
- Zhou Z, Roy A, Lipsky R, Kuchipudi K, Zhu G, Taubman J, Enoch MA, Virkkunen M, Goldman D. 2005b. Haplotype-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations. *Arch Gen Psychiatry* 62:1109–1118.
- Ziegler MG, Bao X, Kennedy BR, Joyner A, Enns R. 2002. Location, development, control, and function of extraadrenal phenylethanolamine N-methyltransferase. *Ann NY Acad Sci* 971:76–82.

SUPPLEMENTARY TABLE S1. Mutations in the *TH* Gene

Mutant designation ^a	Mutant type	Nucleotide aberration in cDNA or gDNA ^{a,b}	Location in gene ^a	Predicted protein ^a	Comment (% activity of wild-type)	References ^c
-69T>A	substitution	c.-69T>A	promoter	5' untranslated		(Verbeek, et al., 2007b)
-70G>A	substitution	c.-70G>A	promoter	5' untranslated		(Verbeek, et al., 2007b)
-71C>T	substitution	c.-71C>T	promoter	5' untranslated		(Ribases, et al., 2007b) (Verbeek, et al., 2007b)
P45	substitution, SNP	c.135G>A	exon 2	p.P45, synonymous coding		rs1799833
S93 (S62)	substitution, SNP	c.280G>A (c.186G>A)	exon 3 (exon 2)	p.S93, synonymous coding (p.S62)		rs34510659
L99Wfs (L68Wfs)	deletion	c.295delC (c.202delC)	exon 3 (exon 2)	p.L99WfsX15 (p.L68WfsX15)	frame shift and protein truncation corrected from 'c.291delC'	(Wevers, et al., 1999) (de Rijk-Van Andel, et al., 2000)
L99Rfs (L68Rfs)	deletion	c.296delT (c.203delT)	exon 3 (exon 2)	p.L99RfsX15 (p.L68RfsX15)	frame shift and protein truncation	(Furukawa, et al., 2001)
A101 (A70)	substitution, SNP	c.303T>C (c.210T>C)	exon 3 (exon 2)	p.A101, synonymous coding (p.A70)		rs7950050
V112M (V81M)	substitution, SNP	c.334G>A (c.241G>A)	exon 3 (exon 2)	p.V112M, non-synonymous coding (p.V81M)		rs6356 (de Rijk-Van Andel, et al., 2000) (Ludecke and Bartholome, 1995) (Hoffmann, et al., 2003) (Ishiguro, et al., 1998)
L204P (L173P)	substitution, SNP	c.611T>C (c.518T>C)	exon 5 (exon 4)	p.L204P, non-synonymous coding (p.L173P)		rs28934579

CONT. SUPPLEMENTARY TABLE S1. **Mutations in the TH Gene**

Mutant designation ^a	Mutant type	Nucleotide aberration in cDNA or gDNA ^{a,b}	Location in gene ^a	Predicted protein ^a	Comment (% activity of wild-type)	References ^c
R233H (R202H)	substitution	c.698G>A (c.605G>A)	exon 6 (exon 5)	p.R233H (p.R202H)	error in abstract of ref. van den Heuvel et al, 1998: 'a698g' instead of 'g698a'	(Wevers, et al., 1999) (de Rijk-Van Andel, et al., 2000) (Hoffmann, et al., 2003) (van den Heuvel, et al., 1998) (Grattan-Smith, et al., 2002)
L236P (L205P)	substitution	c.707T>C (c.614T>C)	exon 6 (exon 5)	p.L236P (p.L205P)	< 1% in A293 cells	(Hoffmann, et al., 2003) (Ludecke, et al., 1996)
H246Y (H215Y)	substitution	c.736C>T (c.643C>T)	exon 7 (exon 6)	p.H246Y (p.H215Y)		(Diepold, et al., 2005)
E259 (E228)	substitution, SNP	c.777G>A (c.684G>A)	exon 7 (exon 6)	p.E259, synonymous coding (p.E228)		rs11564716
K271 (K240)	substitution, SNP	c.813G>A (c.720G>A)	exon 8 (exon 7)	p.K271, synonymous coding (p.K240)		rs6357
T276P (T245P)	substitution, SNP	c.826A>C (c.733A>C)	exon 8 (exon 7)	p.T276P, non-synonymous coding (p.T245P)	reduced stability	rs28934581 (Swaans, et al., 2000) (Royo, et al., 2005)
F309S (F278S)	substitution	c.926T>C (c.833T>C)	exon 8 (exon 7)	p.F309S (p.F278S)		(De Lonlay, et al., 2000)
T314M (T283M)	substitution	c.941C>T (c.848C>T)	exon 9 (exon 8)	p.T314M (p.T283M)	reduced stability	(Swaans, et al., 2000) (Royo, et al., 2005)
R328W (R297W)	substitution	c.982C>T (c.889C>T)	exon 9 (exon 8)	p.R328W (p.R297W)		(Moller, et al., 2005)

CONT. SUPPLEMENTARY TABLE S1. **Mutations in the *TH* Gene**

Mutant designation ^a	Mutant type	Nucleotide aberration in cDNA or gDNA ^{a,b}	Location in gene ^a	Predicted protein ^a	Comment (% activity of wild-type)	References ^c
R337H (R306H)	substitution, SNP	c.1010G>A (c.917G>A)	exon 9 (exon 8)	p.R337H, non-synonymous coding (p.R306H)	reduced stability	rs28934580 (Swaans, et al., 2000) (Royo, et al., 2005)
C359F (C328F)	substitution	c.1076G>T (c.983G>T)	exon 10 (exon 9)	p.C359F (p.C328F)		(Hoffmann, et al., 2003) (Brautigam, et al., 1999)
A376V (A345V)	substitution	c.1127C>T (c.1034C>T)	exon 10 (exon 9)	p.A376V (p.A345V)		(Schiller, et al., 2004)
A376 (A345)	substitution, SNP	c.1128G>T (c.1035G>T)	exon 10 (exon 9)	p.A376, synonymous coding (p.A345)		rs11826260
L387M (L356M)	substitution	c.1159C>A (c.1066C>A)	exon 11 (exon 10)	p.L387M (p.L356M)		(Verbeek, et al., 2007b)
T399M (T368M)	substitution	c.1196C>T (c.1103C>T)	exon 11 (exon 10)	p.T399M (p.T368M)		(Moller, et al., 2005)
IVS11-24T>A (IVS10-24T>A)	substitution	c.1198-24T>A (c.1105-24T>A)	intron 11 (intron 10)	p. L400del32 (exon 12) (p. L369del32 (exon 11)) and p.T399insLSLGRCCPASPQ (p.T368insLSLGRCCPASPQ)	2 alternative splicing variants: <i>in frame</i> deletion of exon 12 (exon 11) with 32 aa and insertion of 12 aa between exon 11 and 12 (exons 10 and 11)	(Hoffmann, et al., 2003) (Janssen, et al., 2000)
Q412K (Q381K)	substitution	c.1234C>A (c.1141C>A)	exon 12 (exon 11)	p.Q412K (p.Q381K)	15% when expressed in bacteria	(Hoffmann, et al., 2003) (Ludecke, et al., 1995) (Knappskog, et al. 1995),
T457 (T426)	substitution, SNP	c.1371G>A (c.1278G>A)	exon 13 (exon 12)	p.T457, synonymous coding (p.T426)		rs36097848

CONT. SUPPLEMENTARY TABLE S1. **Mutations in the *TH* Gene**

Mutant designation ^a	Mutant type	Nucleotide aberration in cDNA or gDNA ^{a,b}	Location in gene ^a	Predicted protein ^a	Comment (% activity of wild-type)	References ^c
P492L (P461L)	substitution	c.1475C>T (c.1382C>T)	exon 14 (exon 13)	p.P492L (p. P461L)		(Verbeek, et al., 2007b)
T494M (T463M)	substitution	c.1481C>T (c.1388C>T)	exon 14 (exon 13)	p.T494M (p.T463M)	reduced stability	(Swaans, et al., 2000) (Royo, et al., 2005)
D498G (D467G)	substitution	c.1493A>G (c.1400A>G)	exon 14 (exon 13)	p.D498G (p.D467G)		(Furukawa, et al., 2001) (Hoffmann, et al., 2003) (Diepold, et al., 2005) (Schiller, et al., 2004)
D498 (D467)	substitution, SNP	c.1494C>T (c.1401C>T)	exon 14 (exon 13)	p.D498, synonymous coding (p.D467)		rs3842724
V499M (V468M)	substitution, SNP	c.1495G>A (c.1402G>A)	exon 14 (exon 13)	p.V499M, non-synonymous coding (p.V468M)	precise nucleotide change not clear in ref. Ishiguro et al, 1998	rs1800033 (Ishiguro, et al., 1998)

^a Mutation designation are based on transcript *TH-4* with 14 exons and 528 aa, i.e. extended exon 1 with 34 aa plus exon 2 with 27 aa resulting a total of 93 nucleotides and 31 aa difference to transcript *TH-1*; see also Table 1; for ref. see (Kaneda, et al., 1987); the nomenclature in parenthesis is for transcript *TH-1*.

^b Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000324155 (or NM_199292.2 for variant TH-4/528 aa and NM_000360.3 for variant TH-1/497 aa) for human cDNA; the numbering starts with 1 at A at the ATG-start codon. This sequence is based on 14 exons with a total of 528 aa according to transcript *TH-4* (human gene ENSG00000180176).

^c for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info.'; SNPs only in the coding region are shown.

SUPPLEMENTARY TABLE S2. **Mutations in the *TPH1* Gene**

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
V177I	substitution, SNP	c.529G>A	exon 5	p.V177I, non-synonymous coding	normal activity erroneously exon 6 in ref. Ramaekers et al, 2001	(Ramaekers, et al., 2001)
F241	substitution, SNP	c.723C>T	exon 6	p.F241, synonymous coding		rs503964
F263	substitution, SNP	c.789C>T	exon 6	p.F263, synonymous coding		rs490895

^a Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000250018 (NM_004179.1) for human cDNA; the numbering starts with 1 at A at the ATG-start codon. This sequence is based on 10 coding exons plus the non-coding exon 11 with a total of 444 aa according to transcript *TPH1* (human gene ENSG00000129167).

^b for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info.'; SNPs only in the coding region are shown.

SUPPLEMENTARY TABLE S3. Mutations in the *TPH2* Gene

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
L36V	substitution, SNP	c.106C>G	exon 2	p.L36V, non-synonymous coding	splice site	rs34115267
S41Y	substitution, SNP	c.122C>A	exon 2	p.S41Y, non-synonymous coding		(Zhou, et al., 2005a)
R55C	substitution, SNP	c.163C>T	exon 2	p.R55C, non-synonymous coding		(Zhou, et al., 2005a)
P206S	substitution, SNP	c.616C>T	exon 6	p.P206S, non-synonymous coding		rs17110563 (Zhou, et al., 2005a) (Zhou, et al., 2005b)
P312	substitution, SNP	c.936A>G	exon 7	p.P312, synonymous coding		rs7305115 (Harvey, et al., 2004)
L327	substitution, SNP	c.981T>A	exon 8	p.L327, synonymous coding		rs2887148
A328V	substitution, SNP	c.983C>T	exon 8	p.A328V, non-synonymous coding		rs2887147
A375	substitution, SNP	c.1125A>T	exon 9	p.A375, synonymous coding		rs4290270 (Harvey, et al., 2004)
R441H	substitution, SNP	c.1322G>A	exon 11	p.R441H, non-synonymous coding	80% loss of function	(Zhang, et al., 2005)
D479E	substitution, SNP	c.1437T>G	exon 11	p.D411E, non-synonymous coding		rs7488262

^a Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000333850 (or NM_173353.2) for human cDNA; the numbering starts with 1 at A at the ATG-start codon. This sequence is based on 11 exons with a total of 490 aa according to transcript *TPH2* (Walther and Bader, 2003; Walther, et al., 2003) (human gene ENSG00000139287).

^b for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info.'; SNPs only in the coding region are shown.

SUPPLEMENTARY TABLE S4. Mutations in the *DDC* Gene

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
delGAGA	deletion	c.-65_-68delGAGA	exon 1	5' untranslated	'neuronal' 5' exon (see under ^a)	(Chang, et al., 1998) (Borglum, et al., 1999)
R7X	substitution	c.19C>T	exon 2	p.R7X, truncation	non-sense mutation causing premature stop codon	(Pons, et al., 2004)
V17M	substitution, SNP	c.49G>A	exon 2	p.V17M, non-synonymous coding		rs6264
E25K	substitution	c.73G>A	exon 2	p.E25K		(Verbeek, et al., 2007a)
D32	substitution, SNP	c.96C>T	exon 2	p.D32, synonymous coding		rs11575290
P43fs	deletion	c.128delC	exon 2	p.P43LfsX21	frameshift; 1 bp deletion in a sequence of 3 C corrected from 'p.43fsX20'	(Pons, et al., 2004)
A45	substitution, SNP	c.135T>C	exon 2	p.A45, synonymous coding		rs11575291
P47H	substitution	c.140C>A	exon 2	p.P47H		(Pons, et al., 2004)
E61D	substitution, SNP	c.183G>T	exon 2	p.E61D, non-synonymous coding		rs11575292
A78	substitution, SNP	c.234C>T	exon 3	p.A78, synonymous coding		rs11575302
A91V	substitution	c.272C>T	exon 3	p.A91V		(Chang, et al., 1998)
G102S	substitution	c.304G>A	exon 3	p.G102S	16% of wild-type activity; decrease in binding affinity for the substrate	(Chang, et al., 1998) (Chang, et al., 2004)
S147R	substitution	c. 439A>C	exon 5	p.S147R		(Chang, et al., 1998)

CONT. SUPPLEMENTARY TABLE S4. **Mutations in the *DDC* Gene**

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
P210L	substitution, SNP	c.629C>T	exon 6	p.P210L, non-synonymous coding		rs6262
M217V	substitution, SNP	c.649A>G	exon 6	p.M217V, non-synonymous coding		rs6263
IVS6+4A>T	substitution	c.714+4A>T	intron 6	p.F238fsX?	donor 5'-splice site mutation with unknown effect	(Tay, et al., 2007)
M239L	substitution, SNP	c.715A>T	exon 7	p.M239L, non-synonymous coding		rs11575376
M239I	substitution, SNP	c.717G>T	exon 7	p.M239I, non-synonymous coding	splice-site	rs11575377
S250F	substitution	c.749C>T	exon 7	p.S250F		(Chang, et al., 1998) (Pons, et al., 2004) (Fiumara, et al., 2002)
A275T	substitution	c.823G>A	exon 8	p.A275T		(Chang, et al., 1998)
R285W	substitution	c.853C>T	exon 8	p.R285W		(Tay, et al., 2007)
F309L	substitution	c.925T>C	exon 9	p.F309L		(Chang, et al., 1998)
R347Q	substitution	c.1040G>A	exon 11	p.R347Q		(Pons, et al., 2004)
R358H	substitution	c.1073G>A	exon 12	p.R358H		(Verbeek, et al., 2007a)
L408I	substitution	c.1222C>A	exon 13	p.L408I	published erroneously as mutation in exon 11	(Pons, et al., 2004)
R447H	substitution	c.1340G>A	exon 14	p.R447H		(Verbeek, et al., 2007a)
V460G	substitution	c.1379T>G	exon 14	p.V460G		(Verbeek, et al., 2007a)

CONT. SUPPLEMENTARY TABLE S4. **Mutations in the *DDC* Gene**

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
R462Q	substitution, SNP	c.1385G>A	exon 14	p.R462Q, non-synonymous coding		rs11575542
R462P	substitution	c.1385G>C	exon 14	p.R462P		(Verbeek, et al., 2007a)

^a Reference sequence for cDNA is published by Ichinose et al, 1989 ((Ichinose, et al., 1989); RefSeq accession number NM_000790.3 for transcript variant 2) and the corresponding genomic DNA by Sumi-Ichinose et al, 1992 ((Sumi-Ichinose, et al., 1992), accession numbers for 5' exons are M77828 for exon 1 and M84600 for exon 2). Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000340197 (or NM_000790.3) for human cDNA; the numbering starts with 1 at A at the ATG-start codon. The sequence is based on 15 exons with a total of 480 aa according to transcript *DDC* (human gene ENSG00000132437). Note that the ENST and ENSG sequences 5' to the ATG start codon differ from the cDNA and gDNA published by (Ichinose, et al., 1989; Sumi-Ichinose, et al., 1992).

^b for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info.'; SNPs only in the coding region are shown.

SUPPLEMENTARY TABLE S5. Mutations in the *DBH* Gene

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
R2W	substitution, SNP	c.4C>T	exon 1	p.R2W, non-synonymous coding		rs13306306
G74A	substitution, SNP	c.221G>C	exon 1	p.G74A, non-synonymous coding		rs3025380
V87M	substitution	c.259G>A	exon 1	p.V87M		(Kim, et al., 2002)
D92A	substitution, SNP	c.275A>C	exon 1	p.D92A, non-synonymous coding		rs2797848
IVS1+2T>C	substitution	c.297+2T>C	intron 1	p.A99fsX38		(Kim, et al., 2002) (Deinum, et al., 2004)
D100E	substitution	c.300C>A	exon 2	p.D100E		(Kim, et al., 2002)
E148	substitution, SNP	c.444A>G	exon 2	p.E148, synonymous coding	splice site	rs1108580
E167Q	substitution, SNP	c.499G>C	exon 3	p.E167Q, non-synonymous coding		rs5319
E192fs	deletion	c.575delA	exon 3	p.E192GfsX82		(Deinum, et al., 2004)
A197T	substitution, SNP	c.589G>A	exon 3	p.A197T, non-synonymous coding		rs5320
K225N	substitution, SNP	c.675G>C	exon 3	p.K225N, non-synonymous coding		rs5321
H231	substitution, SNP	c.693C>T	exon 3	p.H231, synonymous coding		rs5322
Y235	substitution, SNP	c.705C>T	exon 4	p.Y235, synonymous coding	splice site	rs35465867
E236Q	substitution, SNP	c.706G>C	exon 4	p.E236Q, non-synonymous coding		rs5323
C255F	substitution	c.764G>T	exon 4	p.C255F		(Deinum, et al., 2004)

CONT. SUPPLEMENTARY TABLE S5. **Mutations in the *DBH* Gene**

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
D270N	substitution, SNP	c.808G>A	exon 4	p.D270N, non-synonymous coding		rs1330630
D276N	substitution, SNP	c.826G>A	exon 4	p.D276N, non-synonymous coding		rs5324
Y297	substitution, SNP	c.891C>T	exon 5	p.Y297, synonymous coding		rs3025400
L303P	substitution, SNP	c.908T>C	exon 5	p.L303P, non-synonymous coding		rs5325
A304S	substitution, SNP	c.910G>T	exon 5	p.A304S, non-synonymous coding		rs4531
D331N	substitution	c.991G>A	exon 6	p.D331N		(Kim, et al., 2002)
T453M	substitution, SNP	c.1358C>T	exon 9	p.T453M, non-synonymous coding		rs13306303
T456	substitution, SNP	c.1368A>G	exon 9	p.T456, synonymous coding		rs77905
W530S	substitution, SNP	c.1589G>C	exon 11	p.W530S, non-synonymous coding		rs3025421
R535C	substitution, SNP	c.1603C>T	exon 11	p.R535C, non-synonymous coding		rs6271
Y542C	substitution	c.1625A>G	exon 11	p.Y542C		(Deinum, et al., 2004)

^a Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000263611 for human cDNA encoding a protein of 703 aa (or NM_000787.2; note that version NM_000787.3 translates the open reading with a 5' extension of 14 codons resulting in a protein of 617 aa); the numbering starts with 1 at A at the ATG-start codon. This sequence is based on 12 exons with a total of 603 aa according to transcript *DBH* (human gene ENSG00000123454).

^b for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info'; SNPs only in the coding region are shown.

SUPPLEMENTARY TABLE S6. Mutations in the *PNMT* Gene

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
N9S	substitution, SNP	c.26A>G	exon 1	p.N9S, non-synonymous coding	slight increase of activity in COS-1	(Ji, et al., 2005)
N51	substitution, SNP	c.153C>T	exon 1	p.N51, synonymous coding		rs9903907 (Ji, et al., 2005)
P82	substitution, SNP	c.246C>G	exon 2	p.P82, synonymous coding		rs11554306
T98A	substitution, SNP	c.292A>G	exon 2	p.T98A, non-synonymous coding	decreased activity in COS-1 (7%)	(Ji, et al., 2005)
R112C	substitution, SNP	c.334C>T	exon 2	p.R112C, non-synonymous coding	no change in activity in COS-1	(Ji, et al., 2005)
K152	substitution, SNP	c.456A>G	exon 3	p.K152, synonymous coding		rs5638 (Ji, et al., 2005) (Kepp, et al., 2007)
A175T	substitution, SNP	c.523G>A	exon 3	p.A175T, non-synonymous coding	no change in activity in COS-1	rs34341496 (Ji, et al., 2005) (Kepp, et al., 2007)
S188C	substitution, SNP	c.562A>T	exon 3	p.S188C, non-synonymous coding		rs5639
L211H	substitution, SNP	c.632T>A	exon 3	p.L211H, non-synonymous coding		rs5640
L217Q	substitution, SNP	c.650T>A	exon 3	p.L217Q, non-synonymous coding		rs5641
R254H	substitution, SNP	c.761G>A	exon 3	p.R254H, non-synonymous coding		rs5642
W276R	substitution, SNP	c.826T>A	exon 3	p.W276R, non-synonymous coding		rs5643

^a Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000269582 (or NM_002686.3) for human cDNA; the numbering starts with 1 at A at the ATG-start codon. This sequence is based on 3 exons with a total of 282 aa according to transcript *PNMT* (human gene ENSG00000141744).

^b for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info.'; SNPs only in the coding region are shown.

SUPPLEMENTARY TABLE S7. Mutations in the *MAOA* Gene

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
R129	substitution, SNP	c.385A>C	exon 4	p.R129, synonymous coding		rs1800464
Q296X	substitution	c.886C>T	exon 8	p.Q296X	protein truncation	(Brunner, et al., 1993)
R297	substitution, SNP	c.891G>T	exon 8	p.R297, synonymous coding	<i>Fnu</i> 4HI polymorphism	(Hotamisligil and Breakefield, 1991) rs6323
F314V	substitution, SNP	c.940T>G	exon 8	p.F314V, non-synonymous coding		rs1799835
P342	substitution, SNP	c.1026A>T	exon 9	p.P342, synonymous coding		rs1800465
L381	substitution, SNP	c.1143G>T	exon 11	p.L381, synonymous coding		rs1803987
L387	substitution, SNP	c.1161A>G	exon 11	p.L387, synonymous coding		rs7065428
M445I	substitution, SNP	c.1335G>T	exon 13	p.M445I, non-synonymous coding		rs1803986
D470	substitution, SNP	c.1410T>C	exon 14	p.D470, synonymous coding	<i>Eco</i> RV polymorphism	(Hotamisligil and Breakefield, 1991) (Huang, et al., 2007) rs1137070,
K520R	substitution, SNP	c.1559A>G	exon 15	p.K520R, non-synonymous coding		rs1800466

^a Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000338702 (release 43; or OTTHUMT00000056300 or NM_000240.2) for human cDNA; the numbering starts with 1 at A at the ATG-start codon. This sequence is based on 15 exons with a total of 527 aa according to transcript *MAOA* (human gene ENSG00000189221).

^b for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info. '; SNPs only in the coding region are shown.

SUPPLEMENTARY TABLE S8. Mutations in the *COMT* Gene

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
L9F	substitution, SNP	c.27G>T	exon 3	p.L9F, non-synonymous coding		rs11544670
C34S	substitution, SNP	c.101G>C	exon 3	p.C34S, non-synonymous coding		rs6270
H62	substitution, SNP	c.186C>T	exon 3	p.H62, synonymous coding		rs4633 (Nackley, et al., 2006)
A72S	substitution, SNP	c.214G>T	exon 3	p.A72S, non-synonymous coding	reduced enzyme activity	(Lee, et al., 2005) rs6267
Q73	substitution, SNP	c.219G>A	exon 3	p.Q73, synonymous coding		rs740602
V92M	substitution, SNP	c.274G>A	exon 3	p.V92M, non-synonymous coding		rs13306281
A102T	substitution, SNP	c.304G>A	exon 4	p.A102T, non-synonymous coding		rs5031015
L112	substitution, SNP	c.336G>C	exon 4	p.L112, synonymous coding		rs11544669
A134	substitution, SNP	c.402G>A	exon 4	p.A134, synonymous coding		rs769223
L136	substitution, SNP	c.408C>T	exon 4	p.L136, synonymous coding		rs4818 (Nackley, et al., 2006)
A146V	substitution, SNP	c.437C>T	exon 4	p.A146V, non-synonymous coding		rs4986871
A146	substitution, SNP	c.438C>T	exon 4	p.A146, synonymous coding		rs8192488
V158M	substitution, SNP	c.472G>A	exon 4	p.V158M, non-synonymous coding		rs4680 (Nackley, et al., 2006)
P199L	substitution, SNP	c.596C>T	exon 5	p.P199L, non-synonymous coding		rs13306279

CONT. SUPPLEMENTARY TABLE S8. **Mutations in the *COMT* Gene**

Mutant designation	Mutant type	Nucleotide aberration in cDNA or gDNA ^a	Location in gene	Predicted protein (or RNA change)	Comment (% activity of wild-type)	References ^b
P199	substitution, SNP	c.597G>A	exon 5	p.P199, synonymous coding		rs769224
L203	substitution, SNP	c.609C>T	exon 5	p.L203, synonymous coding		rs165631

^a Accession numbers in Genome Sequence Data Base or Ensembl database: ENST00000207636 (NM_000754.2 for MB-COMT mRNA; NM_007310.1 for S-COMT mRNA) for human cDNA; the numbering starts with 1 at A at the ATG-start codon. This sequence is based on 6 exons with a total of 271 aa according to transcript NM_000754.2 for MB-COPT with 271 aa (human gene ENSG00000093010).

^b for SNPs (or ID of 'rs') see in the Ensembl v43 Database under 'Gene variation info.'; SNPs only in the coding region are shown.