Metabolic disorders of biological oxidation enzymes

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

14/12/2022
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 83

This document contains 32 pathways (see Table of Contents)

https://reactome.org
The ability to process xenobiotica and many endogenous compounds is called biotransformation and is catalysed by enzymes mainly in the liver of higher organisms but also a number of other organs such as kidneys, gut and lungs. Metabolism occurs in two stages; phase 1 functionalisation and phase 2 conjugation. Defects in enzymes in these two phases can lead to disease (Nebert et al. 2013, Pikuleva & Waterman 2013, Zanger & Schwab 2013, Mudd 2013, Messenger et al. 2013, Aoyama & Nakaki 2013, Shih 2004, Millington 2013, Azimi et al. 2014, Sticova & Jirsa 2013).

Literature references


Editions

2014-06-06 Authored, Edited Jassal, B.
2014-11-03 Reviewed Nakaki, T.
Defective ACY1 causes encephalopathy

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579007

**Diseases:** toxic encephalopathy

Aminoacylase 1 (ACY1) is a cytosolic, homodimeric zinc-binding metalloenzyme with a wide range of tissue expression. It hydrolyses acylated L-amino acids (except L-aspartate) into L-amino acids and an acyl group. It can also hydrolyse N-acetylcysteine-S-conjugates. Defects in ACY1 can cause aminoacylase-1 deficiency (ACY1D; MIM:609924) resulting in encephalopathy, delay in psychomotor development, seizures and increased urinary excretion of several N-acetylated amino acids (Sass et al. 2006, Sass et al. 2007).

**Literature references**


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Defective AHCY causes HMAHCHD

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5578997

Diseases: hypermethioninemia

Adenosylhomocysteinase (AHCY) is a tetrameric, NAD+‐bound, cytosolic protein that regulates all adenosylmethionine (AdoMet) dependent transmethylations by hydrolysing the feedback inhibitor adenosylhomocysteine (AdoHcy) to homocysteine (HCYS) and adenosine (Ade-Rib). Defects in AHCY cause Hypermethioninemia with S-adenosylhomocysteine hydrolase deficiency (HMAHCHD; MIM:613752), a metabolic disorder characterised by hypermethioninemia associated with failure to thrive, psychomotor retardation, facial dysmorphism with abnormal hair and teeth and myocardiopathy (Baric et al. 2004).

Literature references


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https://reactome.org
Defective CYP11A1 causes AICSR

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579026

**Diseases:** congenital adrenal insufficiency

Cholesterol side-chain cleavage enzyme, mitochondrial (CYP11A1) normally catalyses the side-chain cleavage of cholesterol to form pregnenolone. Defects in CYP11A1 can cause Adrenal insufficiency, congenital, with 46,XY sex reversal (AICSR; MIM:613743). This is a rare disorder that can present as acute adrenal insufficiency in infancy with elevated ACTH and plasma renin activity and low or absent adrenal steroids. The severest phenotype is loss-of-function mutations associated with prematurity, complete under-androgenisation and severe, early-onset adrenal failure (Kim et al. 2008).

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https://reactome.org
Defective CYP11B1 causes AH4

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579017

Diseases: adrenal gland disease

Cytochrome P450 11B1, mitochondrial (CYP11B1) possesses steroid 11-beta-hydroxylase activity which can convert 11-deoxycortisol to cortisol. 11-beta-hydroxylase deficiency is one of the main causes of congenital adrenal hyperplasia (CAH) (5-8%), second only to 21-hydroxylase deficiency which accounts for more than 90% of CAH (Zhao et al. 2008). Defects in CYP11B1 can cause Adrenal hyperplasia 4 (AH4; MIM:202010), a form of congenital adrenal hyperplasia which is a common recessive disease due to failure to convert 11-deoxycortisol to cortisol. This impaired corticosteroid biosynthesis results in androgen excess, virilization and hypertension (White et al. 1991).

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**Defective CYP11B2 causes CMO-1 deficiency**

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579009

**Diseases:** steroid inherited metabolic disorder

Cytochrome P450 11B2, mitochondrial (CYP11B2 aka aldosterone hydroxylase) is an enzyme necessary for aldosterone biosynthesis via corticosterone (CORST) and 18-hydroxycorticosterone (18HCORST). Defects in CYP11B2 results in disorders of aldosterone synthesis. Corticosterone methyl oxidase 1 and 2 deficiencies (CMO-1; MIM:203400 and CMO-2 deficiency; MIM:61060) are autosomal recessive disorders of aldosterone biosynthesis (Mitsuuchi et al. 1993, Bureik et al. 2002). In CMO-1 deficiency, aldosterone is undetectable in plasma, while its immediate precursor, 18HCORST, is low or normal. In CMO-2 deficiency, aldosterone can be low or normal, but at the expense of increased secretion of 18HCORST. Patients with CMO-2 deficiency have elevated plasma 18-hydroxycorticosterone/aldosterone ratios.

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Defective CYP17A1 causes AH5

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579028

Diseases: adrenal gland disease

Steroid 17-alpha-hydroxylase/17,20-lyase (CYP17A1) mediates both 17-alpha-hydroxylase and 17,20-lyase activity, allowing the adrenal glands and gonads to synthesise both 17-alpha-hydroxylated glucocorticoids and sex steroids respectively (Kagimoto et al. 1998). Defects in CYP17A1 can cause Adrenal hyperplasia 5 (AH5), a form of congenital adrenal hyperplasia (CAH), a common recessive disease due to defective synthesis of cortisol and sex steroids. Common symptoms include mild hypocortisolism, ambiguous genitalia in genetic males or failure of the ovaries to function at puberty in genetic females, metabolic alkalosis due to hypokalemia and low-renin hypertension. CYP17A1 can have defects in either or both of 17-alpha-hydroxylase and 17,20-lyase activities thus patients can show combined partial 17-alpha-hydroxylase/17,20-lyase deficiency or isolated 17,20-lyase deficiency traits (Yanase et al. 1992, Kater & Biglieri 1994, Fluck & Miller 2006, Miller 2012).

Literature references


Defective CYP19A1 causes AEXS

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579030

Diseases: pseudohermaphroditism

Aromatase (CYP19A1) catalyses the conversion of androstenedione (ANDST) to estrone (E1). Defects in CYP19A1 can cause aromatase excess syndrome (AEXS; MIM:139300) and aromatase deficiency (AROD; MIM:613546). Affected individuals cannot synthesise endogenous estrogens. In females the lack of estrogen leads to pseudohermaphroditism and progressive virilization at puberty, whereas in males pubertal development is normal (Bulun 2014).

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Defective CYP1B1 causes Glaucoma

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579000

Diseases: glaucoma, primary congenital glaucoma, primary open angle glaucoma, open-angle glaucoma

Cytochrome P450 1B1 (CYP1B1) can oxidise a variety of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics as well as activating a range of procarcinogens. A specific substrate is the female sex hormone estradiol-17beta (EST17b) which is 4-hydroxylated to 4-hydroxyestradiol-17beta 4OH-EST17b). Defects in CYP1B1 can cause glaucoma disorders such as Glaucoma 3, primary congenital, A (GLC3A; MIM:231300), Glaucoma, primary open angle (POAG; MIM:137760), Glaucoma 1, open angle, A (GLC1A; MIM:137750) and Peters anomaly (PAN; MIM:604229). These disorders cause a progressive optic neuropathy characterised by visual field defects that ultimately lead to irreversible blindness (Li et al. 2011, Sarfarazi et al. 2003, Vincent et al. 2001).

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Defective CYP21A2 causes AH3

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579021

Diseases: adrenal gland disease

Steroid 21-hydroxylase (CYP21A2) specifically catalyses the 21-hydroxylation of steroids which is required for the adrenal synthesis of mineralocorticoids and glucocorticoids. Defects in CYP21A2 can cause adrenal hyperplasia 3 (AH3; MIM:201910), a form of congenital adrenal hyperplasia (CAH) where cortisol synthesis is defective. This results in increased ACTH levels, causing overproduction and accumulation of cortisol precursors, particularly 17-hydroxyprogesterone (17HPROG). The resultant excessive production of androgens causes virilization. 21-hydroxylase deficiency accounts for more than 90% of CAH cases and ranges from mild to complete loss of activity (White et al. 2000, White & Bachega 2012).

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Defective CYP24A1 causes HCAI

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579010

**Diseases:** hypercalcemia

Catabolic inactivation of the active, hormonal form of vitamin D3 (calcitriol, CALTOL, 1,25-dihydroxyvitamin D3) is initially carried out by 24-hydroxylation, mediated by 1,25-dihydroxyvitamin D3 24-hydroxylase (CYP24A1). The product formed is eventually transformed to calcitroic acid, the major water-soluble metabolite that can be excreted in bile. Defects in CYP24A1 can cause hypercalcemia infantile (HCAI; MIM:143880), a disorder characterised by abnormally high level of calcium in the blood, failure to thrive, vomiting, dehydration, and nephrocalcinosis (Schlingmann et al. 2011).

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Defective CYP26B1 causes RHFCRA

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579015

Diseases: craniosynostosis

Retinoic acid (RA) is a biologically active analogue of vitamin A (retinol). RA plays an important role in regulating cell growth and differentiation. CYP26A1 and B1 are involved in the metabolic breakdown of RA by 4-hydroxylation. High expression levels of CYP26B1 in the cerebellum and pons of human brain suggests a protective role of specific tissues against retinoid damage (White et al. 2000). Defects in CYP26B1 can cause radiohumeral fusions with other skeletal and craniofacial anomalies (RHFCRA; MIM:614416), a disease characterised by craniofacial malformations and multiple skeletal anomalies (Laue et al. 2011).

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Defective CYP26C1 causes FFDD4

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579004

Diseases: skin benign neoplasm

Retinoic acid (RA) is a biologically active analogue of vitamin A (retinol). RA plays an important role in regulating cell growth and differentiation. CYP26C1 is involved in the metabolic breakdown of RA by 4-hydroxylation. While CYP26C1 can hydroxylate the trans form, it is unique in hydroxylating the 9-cis isomer of RA (9cRA) (Taimi et al. 2004). Defects in CYP26C1 can cause focal facial dermal dysplasia 4 (FFDD4; MIM:614974), a rare syndrome characterised by facial lesions.

Literature references


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Defective CYP27A1 causes CTX

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5578996

Diseases: cerebrotendinous xanthomatosis

CYP27A1, a mitochondrial matrix sterol hydroxylase, catalyses the 27-hydroxylation of side-chains of sterol intermediates (Cali et al. 1991). In the bile acid synthesis pathway, CYP27A1 catalyses the first step in the oxidation of the side chain of sterol intermediates such as cholestane-triols (Pikuleva et al. 1998). Defects in CYP27A1 can cause Cerebrotendinous xanthomatosis (CTX; MIM:213700), a rare sterol storage disorder. Decreased bile acid production results in the accumulation of sterol intermediates in many tissues, including brain. The disorder is characterised by progressive neurologic dysfunction, premature atherosclerosis and cataracts (Gallus et al. 2006).

Literature references


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Defective CYP27B1 causes VDDR1A↗

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579014

Diseases: rickets

Vitamin D3 (cholecalciferol), synthesised in human skin by ultraviolet radiation action on 7-dehydrocholesterol, does not possess any biological activity. Vitamin D hormonal activity requires hydroxylation at the 25 and 1-alpha positions by cytochrome P450 enzymes CYP2R1 and CYP27B1 respectively. Vitamin D 25-hydroxylase (CYP2R1) catalyses the hydroxylation of vitamin D3 to calcidiol (CDL). Subsequent 1-alpha-hydroxylation of CDL by CYP27B1 produces calcitriol (CTL). CTL binds and activates the nuclear vitamin D receptor, with subsequent regulation of physiologic events such as calcium homeostasis, cellular differentiation and proliferation.

Defects in CYP27B1 can cause rickets, vitamin D-dependent 1A (VDDR1A; MIM:264700), a disorder caused by deficiency of the active form of vitamin D (CTL) resulting in defective bone mineralization and clinical features of rickets. To date, 47 mutations have been identified, the majority of them (28) being missense mutations (Kim 2011, Cui et al. 2012).

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Defective CYP27B1 causes VDDR1B

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579027

**Diseases:** rickets

Vitamin D3 (cholecalciferol), synthesised in human skin by ultraviolet radiation action on 7-dehydrocholesterol, does not possess any biological activity. Vitamin D hormonal activity requires hydroxylation at the 25 and 1-alpha positions by cytochrome P450 enzymes CYP2R1 and CYP27B1 respectively.

Vitamin D 25-hydroxylase (CYP2R1) catalyses the hydroxylation of vitamin D3 to calcidiol (CDL). Subsequent 1-alpha-hydroxylation of CDL produces calcitriol (CTL). CTL binds and activates the nuclear vitamin D receptor, with subsequent regulation of physiologic events such as calcium homeostasis, cellular differentiation and proliferation.

Defects in CYP2R1 can cause rickets, vitamin D-dependent 1B (VDDR1B; MIM:600081), a disorder caused by a selective deficiency of the active form of vitamin D (CTL) resulting in defective bone mineralization and clinical features of rickets (Pikuleva et al. 2013).

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Defective CYP2U1 causes SPG56

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579011

Diseases: hereditary spastic paraplegia

Cytochrome P450 2U1 (CYP2U1) catalyses the hydroxylation of arachidonic acid, docosahexaenoic acid and other long chain fatty acids, generating bioactive eicosanoid derivatives which may play an important physiological role in fatty acid signaling processes. Defects in CYP2U1 can cause Spastic paraplegia 56, autosomal recessive (SPG56; MIM:615030), a neurodegenerative disorder characterised by a slow, gradual, progressive weakness and spasticity of the lower limbs (Tesson et al. 2012, Fink 2013).

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Defective CYP4F22 causes ARCI5

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579005

**Diseases:** congenital ichthyosiform erythroderma

Cytochrome P450 4F22 (CYP4F22) is thought to 20-hydroxylate trioxilin A3 (TrXA3), an intermediary metabolite from the 12(R)-lipoxygenase pathway. This pathway is implicated in proliferative skin diseases. The major products of arachidonic acid in keratinocytes are 12- and 15-HETE which undergo bio-transformation to products involved in skin hydration. CYP4F22 mutations can lead to autosomal recessive congenital ichthyosis 5 (ARCI5) (Lefevre et al. 2006, Lugassy et al. 2008).

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Defective TBXAS1 causes GHDD

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579032

**Diseases:** bone disease, anemia

Thromboxane-A synthase (TBXAS1), an enzyme of the arachidonic acid cascade, produces thromboxane A2 (TXA2) from prostaglandin H2 (PGH2). Together with prostacyclin (PGI2), TXA2 plays a key role in the maintenance of haemostasis. It is also a constrictor of vascular and respiratory smooth muscle and implicated in the induction of osteoclast differentiation and activation. Defects in TBXAS1 can cause Ghalosal hematodiaphyseal dysplasia (GHDD; MIM:231095), a rare autosomal recessive disorder characterised by increased bone density with predominant diaphyseal involvement and aregenerative anemia, a bone marrow failure where functional marrow cells are regenerated slowly or not at all (Genevieve et al. 2008).

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Defective CYP7B1 causes SPG5A and CBAS3

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579013

Diseases: hereditary spastic paraplegia

Bile acids are synthesised from cholesterol via two pathways - a classic neutral pathway involving cholesterol 7-alpha-hydroxylase (CYP7A1), and an acidic pathway involving 25-hydroxycholesterol 7-alpha-hydroxylase (CYP7B1). Defects in CYP7B1 can cause spastic paraplegia 5A (SPG5A), a neurodegenerative disorder characterised by a slow, gradual, progressive weakness and spasticity of the lower limbs (Tsaousidou et al. 2008). Defects in CYP7B1 can also cause Congenital bile acid synthesis defect 3 (CBAS3; MIM:613812), a disorder resulting in severe cholestasis, cirrhosis and liver synthetic failure. Hepatic CYP7B1 activity is undetectable (Setchell et al. 1998).

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Defective FMO3 causes TMAU

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579019

Diseases: inherited metabolic disorder

Trimethylamine (TMA) is present in the diet (in fish) but primarily formed in vivo from the breakdown of choline. It is N-oxidised by FMO3 in the liver, the major isoform active towards TMA. Trimethylaminuria (TMAU; MIM:602079, fish-odour syndrome) is a human genetic disorder characterised by an impaired ability to convert the malodourous TMA to its odourless N-oxide. Patients emit a foul odour, which resembles that of rotting fish and can be a psychologically disabling condition (Messenger et al. 2013).

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Defective GCLC causes HAGGSD

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5578999

Diseases: hemolytic anemia

In mammalian cells, many antioxidant defence systems exist which protect cells from subsequent exposure to oxidant stresses. One antioxidant is glutathione (GSH), a tripeptide present in virtually all cells that regulates the intracellular redox state and protects cells from oxidative injury. It is metabolised via the gamma-glutamyl cycle, which is catalysed by six enzymes. In man, hereditary deficiencies have been found in five of the six enzymes. Gamma-glutamylcysteine ligase (GCL) catalyses the first and rate-limiting step in GSH biosynthesis. GCL is a heterodimer of a catalytic heavy chain (GCLC) and a regulatory light chain (GCLM). Defects in the catalytic GCLC can cause hemolytic anemia due to gamma-glutamylcysteine synthetase deficiency (HAGGSD; MIM:230450), a disease characterised by hemolytic anemia, glutathione deficiency, myopathy, late-onset spinocerebellar degeneration, and peripheral neuropathy (Ristoff & Larsson 2007, Aoyama & Nakaki 2013).

Literature references


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Defective GGT1 causes GLUTH

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579022

Diseases: inherited metabolic disorder

To be excreted in urine, glutathione conjugates undergo several hydrolysis steps to form mercapturic acids which are readily excreted. The first step is the hydrolysis of a gamma-glutamyl residue from the conjugate catalysed by gamma-glutamyltransferases (GGTs). These are membrane-bound, heterodimeric enzymes composed of light and heavy peptide chains. Extracellular glutathione (GSH) or its conjugates can be hydrolysed to give cysteinylglycine (CG, or CG conjugates) and free glutamate (L-Glu). Hydrolysis of GSH provides cells with a local cysteine supply and contributes to intracellular GSH levels (Heisterkamp et al. 2008). Defects in GGT1 can cause glutathionuria (GLUTH; MIM:231950), an autosomal recessive disorder characterised by increased GSH concentration in the plasma and urine. Mutations that cause GLUTH can occur in both chains of the GGT1 dimer (Heisterkamp et al. 2008, Aoyama & Nakaki 2013).

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Defective GGT1 in aflatoxin detoxification causes GLUTH

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-9035968

Diseases: inherited metabolic disorder

To be excreted in urine, glutathione conjugates undergo several hydrolysis steps to form mercapturic acids which are readily excreted. The first step is the hydrolysis of a gamma-glutamyl residue from the conjugate catalysed by gamma-glutamyltransferases (GGTs). These are membrane-bound, heterodimeric enzymes composed of light and heavy peptide chains. Extracellular glutathione (GSH) or its conjugates can be hydrolysed to give cysteinylglycine (CG, or CG conjugates) and free glutamate (L-Glu). Hydrolysis of GSH provides cells with a local cysteine supply and contributes to intracellular GSH levels (Heisterkamp et al. 2008). Defects in GGT1 can cause glutathionuria (GLUTH; MIM:231950), an autosomal recessive disorder characterised by increased GSH concentration in the plasma and urine. Mutations that cause GLUTH can occur in both chains of the GGT1 dimer (Heisterkamp et al. 2008, Aoyama & Nakaki 2013).

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In mammalian cells, many antioxidant defence systems exist which protect cells from subsequent exposure to oxidant stresses. One antioxidant is glutathione (GSH), a tripeptide present in virtually all cells that regulates the intracellular redox state and protects cells from oxidative injury. It is metabolised via the gamma-glutamyl cycle, which is catalysed by six enzymes. In man, hereditary deficiencies have been found in five of the six enzymes. Glutathione synthetase deficiency is the most frequently recognised disorder. Defects in GSS can cause glutathione synthetase deficiency (GSSD aka 5-oxoprolinase deficiency, MIM:266130), a severe autosomal recessive disorder characterised by an increased rate of haemolysis, 5-oxoprolinuria, CNS damage and recurrent bacterial infections. In this condition, decreased levels of cellular glutathione result in overstimulation of gamma-glutamylcysteine synthesis and its subsequent conversion to 5-oxoproline. Glutathione synthetase deficiency can be classed as mild, moderate or severe (Ristoff & Larsson 2007, Aoyama & Nakaki 2013).

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The gamma-glutamyl cycle is a six-enzyme cycle that represents the primary pathway for glutathione synthesis and degradation. One step is the cleavage of 5-oxo-L-proline (OPRO) to form L-glutamate, coupled to the hydrolysis of ATP. This is catalysed by 5-oxoprolinase (OPLAH) is a homodimeric, cytosolic protein. Defects in OPLAH can cause 5-oxoprolinase deficiency (OPLAHD; MIM:260005), an extremely rare disorder of the gamma-glutamyl cycle about which debate continues as to whether it is a disorder or just a biochemical condition with no adverse clinical effects apart from 5-oxoprolinuria (Calpena et al. 2013, Almaghlouth et al. 2012, Aoyama & Nakaki 2013).

**Literature references**


Defective MAOA causes BRUNS

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579012

Diseases: disease of mental health

Amine oxidase (flavin-containing) A (MAOA) catalyses the oxidative deamination of biogenic and dietary amines, the regulation of which is critical for mental state homeostasis. MAOA, located on the mitochondrial outer membrane and requiring FAD as cofactor (Weyler 1989), preferentially oxidises biogenic amines such as 5-hydroxytryptamine (5HT), dopamine, noradrenaline and adrenaline. Defects in MAOA can cause Brunner syndrome (BRUNS; MIM:300615), a form of X-linked non-dysmorphic mild mental retardation. Male patients are affected by mild mental retardation and exhibit abnormal behaviour, including impulsive aggression (Brunner et al. 1993, Shih et al. 1999, Shih 2004).

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Defective MAT1A causes MATD

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579024

Diseases: hypermethioninemia

S-adenosylmethionine (AdoMet, SAM) is an important methyl donor in most transmethylation reactions. S-adenosylmethionine synthase isoform type-1 (MAT1A) catalyses the formation of AdoMet from methionine and ATP. Defects in MAT1A can cause methionine adenosyltransferase deficiency (MATD; MIM:250850), an inborn error of metabolism resulting in hypermethioninemia. In this condition, methionine accumulates because its conversion to AdoMet is impaired (Furujo et al. 2012, Mudd 2011).

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https://reactome.org
Defective SLC35D1 causes SCHBCKD

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5579020

Diseases: schneckenbecken dysplasia

The UDP-glucuronic acid/UDP-N-acetylgalactosamine transporter (SLC35D1) is an ER membrane-spanning protein that transports nucleotide-sugars from the cytosol into the ER lumen. SLC35D1 transports UDP-GlcUA and UDP-GalNAc, which are substrates for the synthesis of chondroitin sulfate disaccharide repeats, suggesting a role in chondroitin sulfate biosynthesis. Mutations in SLC35D1 can cause Schneckenbecken dysplasia (SCHBCKD; MIM:269250), a rare, autosomal recessive, lethal short-limbed skeletal dysplasia affecting cartilage and skeletal development (Liu et al. 2010, Liu & Hirschberg 2013).

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Defective TPMT causes TPMT deficiency

Location: Metabolic disorders of biological oxidation enzymes

Stable identifier: R-HSA-5578995

Diseases: inherited metabolic disorder

Methylation is a major biotransformation route of thiopurine drugs such as 6-mercaptopurine (6MP), used in the treatment of inflammatory diseases such as rheumatoid arthritis and childhood acute lymphoblastic leukemia. 6MP and its thioguanine nucleotide metabolites are principally inactivated by thiopurine methyltransferase (TPMT)-catalysed S-methylation.

Defects in TPMT can cause thiopurine S-methyltransferase deficiency (TPMT deficiency; MIM:610460). Patients with intermediate or no TPMT activity are at risk of toxicity such as myelosuppression after receiving standard doses of thiopurine drugs. Inter individual differences in response to these drugs are largely determined by genetic variation at the TPMT locus. TPMT exhibits an autosomal co dominant phenotype: About one in 300 people in Caucasian, African, African-American, and Asian populations are TPMT deficient. Approximately 6-10% of people in these populations inherit intermediate TPMT activity and are heterozygous at the TPMT locus. The rest are homozygous for the wild type allele and have high levels of TPMT activity. (Remy 1963, Weinshilboum et al. 1999, Coulthard & Hogarth 2005, Al Hadithy et al. 2005, Azimi et al. 2014).

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Defective UGT1A1 causes hyperbilirubinemia

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579002

**Diseases:** Gilbert syndrome, Crigler-Najjar syndrome, bilirubin metabolic disorder

UDP-glucuronosyltransferases (UGTs) play a major role in the conjugation and therefore elimination of potentially toxic xenobiotics and endogenous compounds. The 1-1 isoform UGT1A1 is able to act upon lipophilic bilirubin, the end product of heme breakdown. Defects in UGT1A1 can cause hyperbilirubinemia syndromes ranging from mild forms such as Gilbert syndrome (GILBS; MIM:143500) and transient familial neonatal hyperbilirubinemia (HBLRTFN; MIM:237900) to the more severe Crigler-Najjar syndromes 1 and 2 (CN1, CN2; MIM:218800 and MIM:606785) (Sticova & Jirsa 2013, Strassburg 2010, Udomuksorn et al. 2007, Costa 2006, Maruo et al. 2000).

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[https://reactome.org](https://reactome.org)
Defective UGT1A4 causes hyperbilirubinemia

**Location:** Metabolic disorders of biological oxidation enzymes

**Stable identifier:** R-HSA-5579016

**Diseases:** Gilbert syndrome, Crigler-Najjar syndrome, bilirubin metabolic disorder

UDP-glucuronosyltransferases (UGTs) play a major role in the conjugation and therefore elimination of potentially toxic xenobiotics and endogenous compounds. The 1-4 isoform UGT1A4 is able to act upon lipophilic bilirubin, the end product of heme breakdown. Defects in UGT1A4 can cause hyperbilirubinemia syndromes ranging from mild forms such as Gilbert syndrome (GILBS; MIM:143500) to the more severe Crigler-Najjar syndromes 1 and 2 (CN1, CN2; MIM:218800 and MIM:606785) (Sticova & Jirsa 2013, Strassburg 2010, Udomuksorn et al. 2007, Costa 2006, Maruo et al. 2000).

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