

35.1 Nomenclature

No.	Disorder	Enzyme defect	Chromosome localisation	MIM
35.1	Trimethylaminuria	Flavine-containing monooxygenase 3 (FMO3)	1q23-q25	602079; 136132
35.2	Dimethylglycinuria	Dimethylglycine dehydrogenase	5q12.2-q12.3	605849; 605850
35.3	Hypophosphatasia	Tissue non-specific alkaline phosphatase (TNSALP)	1p36.1-p34	146300; 171760; 241500; 241510
35.4	Defect in transport of long-chain fatty acids	?	?	603376

35.2 Trimethylaminuria (TMAuria)

This recessively inherited condition causes accumulation of trimethylamine (TMA) in body fluids. Its incidence is not known; while marked cases appear to be quite rare, milder cases may be more frequent. TMA is formed in the gut by bacterial metabolism from dietary precursors such as lecithin and choline.

■ Signs

Though no metabolic harm has been associated with TMA accumulation, the compound is highly volatile and affected individuals are troubled by body odour similar to rotting fish – the “fish odour syndrome” (MIM 602079). The condition is often the cause of social stigmatization and quite severe psychologic distress to affected individuals.

■ Biochemistry and Diagnosis

In TMAuria, the oxidation of TMA to TMA-oxide, catalyzed by flavine-containing monooxygenase 3 (FMO3; E.C. 1.14.13.8) is impaired. TMA can be detected in urine using several methods which are not widely available such as dedicated gaschromatography-mass spectrometry with stable isotope dilution and, more elegantly, NMR (see chapter F). The ratio between TMA and TMA-oxide (which is increased in TMAuria) has been proposed to discriminate between affected homozygotes and heterozygotes [1, 2] but this concept has not yet been validated by comparison with mutation data (see below).

■ DNA Analysis

The genetic basis of TMAuria are recessive mutations in the gene for FMO3 (chromosome 1q23-q25; MIM 136132) [3–5]. Genotypes leading to mild variants of trimethylaminuria have been described [6].

■ Treatment

Treatment with restriction of dietary protein, in particular dairy food and eggs, and with metronidazole have been reported as beneficial in reducing the offending body odour [9].

■ Remarks

Heterozygote detection using a TMA loading test has been proposed but may be replaced in the future by mutation detection. It is unclear, at present, how frequently FMO3 deficiency may cause other clinical manifestations such as adverse reactions to tyramine-containing food (wine and cheese) and to epinephrine and sulfur-containing drugs [7]. The existence of “transitory” TMAuria with normal TMA oxidation has been suggested, possibly associated with high protein intake [8].

35.3 Dimethylglycinuria

Dimethylglycine is formed by endogenous demethylation of betaine, a choline metabolite, with concomitant methylation of homocysteine to methionine. DMG is then converted to sarcosine by oxidative demethylation catalyzed by DMG-dehydrogenase, a flavin-containing enzyme requiring folate as a cofactor. Increased excretion of DMG has been observed in individuals with folate deficiency or receiving large doses of betaine as a

therapeutic agent [10]. “Primary” DMGuria has been observed in a single individual [11, 12] (see below).

■ Signs

Dimethylglycinuria was recently described in one adult individual with the “fish odour syndrome”, muscle fatigability and increased serum creatine kinase [12].

■ Biochemistry and Diagnosis

In one patient, accumulation of dimethylglycine in plasma and urine was confirmed by ^1H - and ^{13}C -NMR spectroscopy (see chapter F) and by GC-MS.

■ DNA Analysis

Using genomic DNA, homozygosity for a missense mutation in the dimethylglycine dehydrogenase gene (DMGDH; 5q12) was found [11, 12].

■ Remarks

The relationship between DMGDH deficiency and the muscle symptoms in the index case are unclear. DMG has been used as a performance enhancer in athletes as well as to treat autistic children, with little evidence of efficacy. Prior to the use of NMR spectroscopy, DMG was detected by dedicated GC-MS methods and by HPLC with appropriate derivatization [13]. Increased levels of DMG in plasma and urine have been observed during betaine therapy and in some individuals with folate deficiency, because of impaired methyl transfer reactions [10].

35.4 Hypophosphatasia

Hypophosphatasia mainly affects bone and teeth; involvement of muscle tissue has been suggested but is probably subclinical in most cases. The clinical spectrum of hypophosphatasia is broad (MIM 241500, 241510, 146300) and includes a perinatally lethal, generalized skeletal mineralization defect (“*the boneless fetus*”), infantile and juvenile forms with rickets-like skeletal disease, and an exclusively dental form (“*odontohypophosphatasia*”). The incidence of the condition in its various forms is not known precisely.

■ Signs [14]

The neonatal form presents as a skeletal disorder with bent bones, soft, undermineralized skull, and respiratory distress because of soft and dysplastic ribs. The infantile form can present unspecifically as poor feeding, failure to thrive, signs of rickets, flail chest and – most importantly – signs of elevated intracranial pressure. Apparently, the mineralization defect results in growth arrest of the cranial sutures (“functional” craniosynostosis). In adults, mild hypophosphatasia may present as recurrent stress fractures and so-called pseudofractures (looser zones). In both children and adults, premature loss of teeth may be a sign of hypophosphatasia.

■ Biochemistry and Diagnosis [14]

The alkaline phosphatase activity in plasma is usually reduced to values below the age-related normal range. Overall, there is a tendency to observe the lowest values in the more severely affected individuals, but individual cases may display activity just below the normal range. Heterozygotes may have reduced values. For that reason, the diagnosis should be confirmed by the demonstration of substrate accumulation *ex vivo*. As a consequence of reduced phosphatase activity, three compounds are present at increased concentrations: pyridoxal-phosphate (PLP; vitamin B6) in plasma, inorganic pyrophosphate (PPi) in plasma and urine, and phosphoethanolamine (PET) in urine. Increased PLP is a sensitive marker for hypophosphatasia (provided no oral supplement has been ingested) and is probably quite specific. Its elevation in plasma does not appear to have clinical consequences, as intracellular levels are not increased. PPi is equally sensitive but not routinely determined. Urinary PET is moderately sensitive (it may be normal in mild cases) but potentially nonspecific.

■ DNA Analysis

Hypophosphatasia is caused by recessive mutations in the gene coding for tissue nonspecific alkaline phosphatase (TNSALP; formerly liver/bone/kidney type alkaline phosphatase) on chromosome 1p [14, 15]. The sensitivity and speed of mutation analysis has turned it into a valuable diagnostic tool. Over 50 different mutations have been identified. There are reasonably good genotype-phenotype correlations [16], probably explained by the type and site of the individual mutations and their structural consequences. Rarely, mild forms of the disease appear to be transmitted as dominant traits. In one such family, a TNSALP mutation was identified which upon coexpression in cultured cells reduced the activity of wild-type TNSALP [17].

35.5 The Putative LCFA Transporter

Al Odaib and colleagues have described two children who had recurrent episodes of liver disease culminating in liver failure and who underwent liver transplantation [18]. The laboratory data, as well as the hepatic acylcarnitine profile in one of those patients, were interpreted as suggestive of a fatty acid oxidation disorder. Cultured fibroblasts derived from both patients showed a moderate reduction in the uptake and oxidation of oleic and palmitic acid. It was concluded that an impairment in the uptake of long-chain fatty acids, probably caused by a defective transporter, was the cause of liver disease in these patients [18]. The molecular defect remains undetermined; in particular, the relationship between this putative “liver/fibroblast LCFA transporter” and the widely expressed CD36/LCFA transporter molecule, a genetic deficiency of which is rather common and may be implicated in cardiomyopathy, is unclear [19].

References

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