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Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.

Primary Trimethylaminuria

Synonyms: Fish Odor Syndrome, TMAuria, TMAU, FMO3 Deficiency

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Initial Posting: October 8, 2007; Last Update: October 1, 2015.

Summary

Clinical characteristics. Primary trimethylaminuria is characterized by a fishy odor resembling that of rotten or decaying fish that results from excess excretion of trimethylamine in the urine, breath, sweat, and reproductive fluids. No physical symptoms are associated with trimethylaminuria. Affected individuals appear normal and healthy; however, the unpleasant odor often results in social and psychological problems. Symptoms are usually present from birth and may worsen during puberty. In females, symptoms are more severe just before and during menstruation, after taking oral contraceptives, and around the time of menopause.

Diagnosis/testing. The diagnosis of primary trimethylaminuria is established in a proband who:

- Excretes (under normal dietary conditions) in the urine >10% of total trimethylamine (TMA) as the free amine; and
- Has biallelic (homozygous or compound heterozygous), known loss-of-function pathogenic variants in *FMO3* on molecular genetic testing.

Management. *Treatment of manifestations:*

Dietary restriction of:

- Trimethylamine (present in milk obtained from wheat-fed cows) and its precursors including choline (present in eggs, liver, kidney, peas, beans, peanuts, soya products, and brassicas [Brussels sprouts, broccoli, cabbage, cauliflower]), lecithin and lecithin-containing fish oil supplements;
- Trimethylamine *N*-oxide (present in seafood [fish, cephalopods, and crustaceans]);
- Inhibitors of FMO3 enzyme activity such as indoles (found in brassicas).

Use of:

- Acid soaps and body lotions to remove secreted trimethylamine by washing;
- Activated charcoal and copper chlorophyllin to sequester trimethylamine produced in the gut;
- Antibiotics (metronidazole, amoxicillin, and neomycin) to suppress production of trimethylamine by reducing bacteria in the gut;
- Riboflavin supplements to enhance residual FMO3 enzyme activity.

Prevention of secondary complications: Planning and monitoring of diet to ensure that the daily intake of choline and folate meets recommendations for age and sex; no restriction of dietary choline during pregnancy and lactation.

Agents/circumstances to avoid: Foods with a high content of precursors of trimethylamine or inhibitors of FMO3 enzyme activity (seafoods: fish, cephalopods, and crustaceans), eggs, offal, legumes, brassicas, and soya products; food supplements and "health" foods that contain high doses of choline and lecithin; drugs metabolized by the FMO3 enzyme; circumstances that promote sweating (exercise, stress, and emotional upsets).

Evaluation of relatives at risk: Biochemical testing of sibs to identify those who are affected and will benefit from management to reduce production of trimethylamine.

Genetic counseling. Primary trimethylaminuria is inherited in an autosomal recessive manner. The parents of an affected individual are obligate heterozygotes and therefore carry one mutated allele. Heterozygotes (carriers) are asymptomatic. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible once the *FMO3* pathogenic variants have been identified in the family.

Diagnosis

Diagnosis of primary trimethylaminuria has been discussed in detail [Cashman et al 2003] and "best-practice" diagnostic guidelines have been summarized [Chalmers et al 2006] (full text).

Suggestive Findings

Primary trimethylaminuria **should be suspected** in individuals with a body odor resembling that of rotten or decaying fish [Mitchell & Smith 2001, Mitchell 2005, Mackay et al 2011] and excessive urinary excretion of trimethylamine (TMA).

Body odor. Unoxidized trimethylamine excreted in the urine, breath, sweat, and reproductive fluids is highly volatile and has a pungent ammoniac odor reminiscent of rotting fish [Mitchell 2005, Mackay et al 2011].

Note: Diagnosis of primary trimethylaminuria cannot be based on the examiner's sense of smell due to the following:

- The presence of the odor is often episodic and thus may not be noticeable when the person is examined.
- The human nose is normally very sensitive to trimethylamine, with some individuals being able to detect concentrations as low as 1 part in 10⁹; however, olfactory testing is subjective and some people are unable to detect the smell of trimethylamine.
- The odor may be caused by compounds other than trimethylamine.

Urinary excretion of trimethylamine (TMA). Individuals complaining of or exhibiting a fishy odor should be tested for urinary excretion of TMA, ideally on two separate occasions [Mitchell & Smith 2001, Mitchell 2005]. Although testing can be done under normal dietary conditions, it may help to consume a meal rich in choline (e.g., two eggs plus 400 g of 'baked' [haricot] or soya beans) prior to testing.

Note: Because unaffected women may have transient trimethylaminuria at the onset of and during menstruation [Shimizu et al 2007], females should not be tested during this time frame.

Urinary excretion of TMA is measured as **one** of the following:

- **Percent of total trimethylamine (TMA)** (i.e., free TMA plus the non-odorous metabolite TMA *N*-oxide) excreted in the urine as unmetabolized free TMA [Cashman et al 2003, Mackay et al 2011]
 - Severe trimethylaminuria: >40% of total TMA excreted as unmetabolized free TMA
 - Mild trimethylaminuria: 10%-39% of total TMA excreted as unmetabolized free TMA
 - Unaffected: 0%-9% of total TMA excreted as unmetabolized free TMA
- **Concentration of unmetabolized TMA in the urine.** A urinary concentration of free TMA of 10 µg/mL (18-20 µmol/mmol creatinine) or higher, correlating with a urinary output of TMA of ~15-20 mg/day, appears to

represent a threshold for the presence of the fishy body odor associated with the disorder [Mitchell & Smith 2001].

Click [here](#) for more detailed information on specific methods of detecting TMA and TMA *N*-oxide in urine.

Establishing the Diagnosis

The diagnosis of primary trimethylaminuria **is established** in a proband who:

- Excretes (under normal dietary conditions) in the urine >10% of total trimethylamine (TMA) as the free amine; and
- Has biallelic (homozygous or compound heterozygous), known loss-of-function pathogenic variants in *FMO3* on molecular genetic testing (see [Table 1](#)).

Molecular testing includes **single-gene testing**. Sequence analysis of *FMO3* is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

Table 1.

Molecular Genetic Testing Used in Primary Trimethylaminuria

Gene ¹	Test Method	Proportion of Probands with Pathogenic Variants ² Detectable by This Method
<i>FMO3</i>	Sequence analysis ³	~99%
	Gene-targeted deletion/duplication analysis ⁴	Unknown ⁵

1. See [Table A. Genes and Databases](#) for chromosome locus and protein.
2. See [Molecular Genetics](#) for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used can include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. One individual with primary trimethylaminuria homozygous for a deletion of exons 1 and 2 has been reported [Forrest et al 2001]. To date, this is the only *FMO3* pathogenic variant reported to be a large deletion.

Test characteristics. See [Clinical Utility Gene Card](#) [Shephard et al 2015] for information on test characteristics including sensitivity and specificity.

Clinical Characteristics

Clinical Description

Primary trimethylaminuria is characterized by fishy odor resulting from excess excretion of trimethylamine in the urine, breath, sweat, and reproductive fluids [Mitchell 2005, Mackay et al 2011].

No physical symptoms are associated with primary trimethylaminuria; affected individuals appear normal and healthy. However, the unpleasant odor characteristic of the disorder often results in social and psychological problems [Mitchell & Smith 2001] and can have serious effects on personal and working lives. These may include the following:

- In childhood, being shunned, ridiculed, or bullied at school, leading to aggressive or disruptive behavior and poor educational performance

- A sense of shame or embarrassment, leading to low self-esteem and reluctance to seek medical help
- Avoidance of contact with people, leading to social isolation, loneliness, frustration, and depression
- Difficulties in initiating or maintaining relationships
- In extreme cases: paranoid behavior, desperation, and suicidal tendencies

The enzyme FMO3 is also involved in the metabolism of various therapeutic drugs. Individuals with primary trimethylaminuria exhibit abnormal metabolism of the nonsteroidal anti-inflammatory benzydamine [Mayatepek et al 2004]. Anecdotal evidence suggests that the metabolism of other drugs that are substrates of the enzyme FMO3 may also be affected.

Dysfunctional metabolism of endogenous amines such as tyramine that are substrates of the enzyme FMO3 may contribute to the depression seen in some persons.

For individuals with primary trimethylaminuria, symptoms are usually present from birth. The condition may worsen during puberty. In females, symptoms are more severe just before and during menstruation, after taking oral contraceptives, and around menopause, probably because of a decrease in expression of *FMO3* in response to steroid hormones.

Treatment and dietary management may alleviate symptoms in some, but not all individuals.

Other. Historical references to individuals who appear to have had trimethylaminuria include the description of Satyavati, a young woman who smelled of rotting fish, in the *Mahabharata*, the Indian epic of the Bharata Dynasty compiled in about AD 400, and Trinculo's description of Caliban ("he smells like a fish") in Shakespeare's *The Tempest*.

Pathophysiology

Metabolism of trimethylamine is primarily via *N*-oxygenation, catalyzed by the enzyme flavin-containing monooxygenase 3 (FMO3) [Lang et al 1998, Cashman et al 2003, Phillips et al 2007].

Trimethylamine is derived from dietary precursors, such as choline and trimethylamine *N*-oxide, via the action of bacteria in the gut [Mitchell 2005, Mackay et al 2011]. It is normally metabolized in the liver by the enzyme FMO3 to produce trimethylamine *N*-oxide, which is non-volatile and non-odorous [Cashman et al 2003, Phillips et al 2007]. Excess trimethylamine results from a mismatch between the ability of the enzyme FMO3 to catalyze the *N*-oxygenation of trimethylamine and the amount of substrate.

Two types of trimethylaminuria exist, resulting from one of the following:

- **Decrease in the amount or activity of the enzyme FMO3**, resulting from genetic factors (mutation of *FMO3*), physiologic factors (hormone levels), or environmental factors (presence of inhibitory chemicals). This type of trimethylaminuria is characterized by a high urinary TMA/TMA *N*-oxide ratio.
- **Substrate overload of FMO3 enzyme activity** resulting from either an excess of dietary precursors of TMA or variations in gut flora, causing increased release of TMA. This type of trimethylaminuria is characterized by a high concentration of TMA in the urine, but a normal urinary TMA/TMA *N*-oxide ratio.

The two types of trimethylaminuria are intimately interrelated: a combination of genetic, physiologic, and environmental factors may interact to give rise to the disorder. For instance, a substrate load that is handled by one individual may represent a substrate overload for a person whose FMO3 enzyme activity is decreased.

Genotype-Phenotype Correlations

On a normal diet, individuals with biallelic loss-of-function *FMO3* pathogenic variants secrete more than 40% of total TMA as the free unmetabolized amine and consequently have a fishy odor.

Several pathogenic nonsense or missense variants that abolish or severely impair the ability of the FMO3 enzyme to catalyze *N*-oxygenation of TMA have been identified [Hernandez et al 2003, Phillips et al 2007, Yamazaki & Shimizu 2013]. In general, the more severe the reduction in FMO3 enzyme activity, the more severe the symptoms and the less the response to treatment.

While most common variants have little or no effect on enzyme activity, p.Glu158Lys and p.Glu308Gly in *cis* configuration (i.e., on the same chromosome) have been associated with "mild" trimethylaminuria, resulting in the excretion of 10%-39% of total TMA as the free unmetabolized amine [Zschocke et al 1999].

Although the rare variant p.Val187Ala alone does not affect enzyme activity, a combination of this variant in *cis* configuration with p.Glu158Lys severely affects enzyme activity and contributes to severe trimethylaminuria [Motika et al 2009].

Nomenclature

Primary trimethylaminuria has been described as fish-odor syndrome, fish malodor syndrome, and stale fish syndrome.

Prevalence

The incidence of heterozygotes (carriers) in the white British population is 0.5% to 1.0%. It is higher in other populations studied: 1.7% in Jordan, 3.8% in Ecuador, and 11.0% in New Guinea [Mitchell et al 1997].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *FMO3*.

Differential Diagnosis

Molecular diagnosis can distinguish primary trimethylaminuria from trimethylaminuria not caused by genetic *FMO3* deficiency [Shimizu et al 2014]. A classification scheme for the latter has been proposed [Mitchell & Smith 2001, Mitchell 2005].

- **Acquired trimethylaminuria** emerges during adult life as a consequence of hepatitis in individuals with no previous personal history or familial history of the disorder. The metabolic changes persist after the liver problems have resolved, suggesting a permanent change in the expression or activity of the *FMO3* enzyme.
- **Transient childhood trimethylaminuria** has been reported in preterm infants fed a choline-containing infant formula. Symptoms disappear as the children mature or when the choline source is discontinued [Pardini & Sapien 2003]. Young children who are heterozygous for a loss-of-function *FMO3* pathogenic variant or have certain combinations of *FMO3* variants (see *Genotype-Phenotype Correlations*) may exhibit mild symptoms of the disorder [Mayatepek & Kohlmuller 1998, Zschocke et al 1999, Zschocke & Mayatepek 2000]. Transient childhood forms are a consequence of the immaturity of *FMO3* expression, which is switched on after birth and continues to increase throughout childhood [Koukouritaki et al 2002].
- **Transient trimethylaminuria associated with menstruation.** A short episode of trimethylaminuria can occur in women during menstruation [Mitchell & Smith 2001, Shimizu et al 2007]. The effect is more pronounced in women homozygous for variants that result in a mild decrease in *FMO3* enzyme activity [Shimizu et al 2007].
- **Precursor overload** can cause a transient form of trimethylaminuria that results from saturation of the enzyme *FMO3*. It can occur in individuals with *Huntington disease* or *Alzheimer disease* who have been given large oral therapeutic doses of choline (≤ 20 g/day) [Mitchell & Smith 2001, Mitchell 2005].
- **Disease states**
 - Liver cirrhosis, impaired hepatocellular function, or the existence of portosystemic shunts may affect clearance of TMA absorbed from the gut. The resulting trimethylaminuria may contribute to the development of hepatic encephalopathy and coma and associated foetor hepaticus [Mitchell et al 1999].
 - In uremia, increased release of TMA from dietary precursors as a consequence of bacterial overgrowth in the small intestine, coupled with reduced renal clearance of TMA, can result in trimethylaminuria [Mitchell 2005]. The elevated blood concentration of TMA may contribute to nephritic neurologic conditions.

Other causes of unpleasant body odor fall into two categories:

- **Those not involving an increase of trimethylamine in the urine**, including poor hygiene, gingivitis, and cases of blood-borne halitosis [Tangerman 2002] resulting from malodorous compounds other than trimethylamine.

Another condition in this category is the rare metabolic disorder dimethylglycinuria, caused by dimethylglycine dehydrogenase deficiency [Binzak et al 2001]. Such conditions are distinguished by low urinary TMA and a normal urinary TMA/TMA *N*-oxide ratio.

- **Those resulting in an increase of trimethylamine in the urine**, including urinary tract infections, bacterial vaginosis, advanced liver or kidney disease, and cervical cancer. In these cases, the TMA/TMA *N*-oxide ratio is normal, but affected individuals have large amounts of TMA in the urine. In contrast, primary trimethylaminuria, caused by FMO3 deficiency, is characterized by a high ratio of TMA/TMA *N*-oxide in the urine.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary trimethylaminuria, it is recommended that the urinary ratio of trimethylamine (TMA) *N*-oxide to total TMA on a normal diet be determined. The general rule is that the lower the ratio the more severe the disorder:

- Ratios of 70%-89% are classified as mild.
- Ratios lower than 70% are classified as severe.

Consultation with a clinical geneticist and/or genetic counselor is also recommended.

Treatment of Manifestations

Strategies for the treatment of primary trimethylaminuria summarized below are covered in detail in [Cashman et al \[2003\]](#) and in "best-practice" guidelines [[Chalmers et al 2006](#)] (full text).

Restriction of dietary trimethylamine and its precursors. In some instances the disorder can be successfully managed by dietary restriction of precursors of trimethylamine. This is particularly true of "mild" or moderate forms of primary trimethylaminuria. Affected individuals respond differently to different forms of dietary restriction; thus, urinary excretion of trimethylamine and trimethylamine *N*-oxide should be monitored to identify the most effective dietary regimen for an individual.

- **Choline.** One of the most important dietary sources of trimethylamine is choline. Dietary choline is absorbed through the small intestine; however, when the absorptive capacity of the small intestine is overloaded, gut bacteria metabolize choline into trimethylamine, which is readily absorbed into the blood stream.

Foods rich in choline include eggs, liver, kidney, peas, beans, peanuts, soya products, and brassicas (Brussels sprouts, broccoli, cabbage, cauliflower) as well as rapeseed products such as oil and flour. Nutritionally balanced, choline-restricted diets suitable for the treatment of trimethylaminuria have been developed [[Busby et al 2004](#)].

Affected individuals should avoid lecithin (an important dietary source of choline) and lecithin-containing fish oil supplements.

- **Trimethylamine *N*-oxide.** Affected individuals should avoid eating seafood (fish, cephalopods, and crustaceans) because of its high content of trimethylamine *N*-oxide, which is reduced to trimethylamine in the human gut. Babies with trimethylaminuria who are breastfed after their mothers have eaten seafood may develop a fishy odor. Note: Freshwater fish have a lower content of trimethylamine *N*-oxide and thus are not a problem.
- **Other.** Milk obtained from wheat-fed cows may have significant amounts of trimethylamine and thus should be avoided.

In addition to being a source of trimethylamine precursors, brassicas (Brussels sprouts, broccoli, cabbage, and cauliflower) contain indoles, which may inhibit FMO3 enzyme activity and thus increase urinary excretion of trimethylamine [[Cashman et al 1999](#)]. Intake of such vegetables should be restricted.

Use of acid soaps and body lotions. Trimethylamine is a strong base (pKa 9.8). Thus, at pH 6.0, less than 0.02% of trimethylamine exists as the volatile free base. The use of soaps and body lotions with a pH close to that of normal skin (pH 5.5-6.5) helps retain secreted trimethylamine in a less volatile salt form that can be removed by washing.

Sequestering of trimethylamine produced in the gut. When taken as dietary supplements, activated charcoal (750 mg 2x/day for 10 days) and copper chlorophyllin (60 mg 3x/day after meals for 3 weeks) decrease the concentration of free trimethylamine in the urine [Yamazaki et al 2004].

Suppression of intestinal production of trimethylamine. A short course of antibiotics to modulate or reduce the activity of gut microflora, and thus suppress the production of trimethylamine, is effective in some cases [Fraser-Andrews et al 2003, Chalmers et al 2006]. Such treatment may be useful when dietary restriction needs to be relaxed (e.g., for important social occasions), or when trimethylamine production appears to increase (e.g., during menstruation, infection, emotional upset, stress, or exercise). Three antibiotics with different target organisms have been used: metronidazole, amoxicillin, and neomycin. Neomycin appears to be the most effective in preventing formation of trimethylamine from choline [Chalmers et al 2006].

Enhancement of residual FMO3 enzyme activity. Supplements of riboflavin, a precursor of the FAD prosthetic group of FMOs, may help maximize residual FMO3 enzyme activity [Manning et al 2012]. Recommended intake is 30-40 mg 3-5x/day with food. Children given riboflavin should be monitored closely because excessive amounts may cause gastrointestinal distress.

Counseling. Affected individuals and their families benefit from counseling. Realization that the problem is the result of a recognized medical condition may help. As well as receiving dietary advice, affected individuals should be advised that the condition may be exacerbated during menstruation and by factors that promote sweating, such as fever, exercise, stress, and emotional upsets.

Prevention of Primary Manifestations

See [Treatment of Manifestations](#).

Prevention of Secondary Complications

Because choline is essential in the fetus and in young infants for nerve and brain development, it should not be over-restricted in infants, children, and pregnant or lactating women. Large amounts of choline are transferred to the fetus via the placenta and to the newborn infant via the mother's milk, thus potentially depleting maternal choline reserves. Dietary restriction of choline increases the requirement for folate, a methyl donor.

Dietary regimens should be planned and monitored to ensure that the daily intake of choline and folate meet recommendations for the age and sex of the individual [Institute of Medicine National Academy of Sciences USA 1998, Cashman et al 2003]. For adults, adequate daily intake of choline is 550 mg for males and 425 mg for females.

Agents/Circumstances to Avoid

The following should be avoided:

- Foods with a high content of precursors of trimethylamine or inhibitors of FMO3 enzyme activity, including seafood (fish, cephalopods, and crustaceans), eggs, offal, legumes, brassicas, and soya products; avoid or eat in moderation.
- Food supplements and "health" foods that contain high doses of the trimethylamine precursors choline and lecithin
- Drugs that are metabolized by the FMO3 enzyme; for example, the antipsychotic clozapine; the monoamine oxidase B inhibitor deprenyl; the anti-histamine ranitidine; the anti-estrogen tamoxifen; and the nonsteroidal anti-inflammatories benzydamine and sulindac [Phillips et al 2007]. These compete for residual FMO3 activity. As well as exacerbating the condition, reduced metabolism of the drug may cause adverse effects.
- Factors that promote sweating, such as exercise, stress, and emotional upsets

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of an affected individual in order to identify as early as possible those who would benefit from early [treatment of manifestations](#). Evaluations can include:

- Molecular genetic testing if the *FMO3* pathogenic variants in the family are known;

- If the familial *FMO3* pathogenic variants are not known, molecular genetic testing may detect pathogenic variants.
- Biochemical testing if the *FMO3* pathogenic variants in the family are not known and/or molecular genetic testing fails to reveal a well-known pathogenic variant.

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Choline, which is essential for nerve and brain development in the fetus, should not be over-restricted in pregnant women.

Therapies Under Investigation

Search [ClinicalTrials.gov](#) for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary trimethylaminuria is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *FMO3* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with primary trimethylaminuria are obligate heterozygotes (carriers) for a pathogenic variant in *FMO3*.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of a *FMO3* pathogenic variant.

Carrier (Heterozygote) Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *FMO3* pathogenic variants in the family.

Biochemical genetic testing. Under normal dietary conditions heterozygotes (carriers) and unaffected individuals excrete less than 10% of total trimethylamine (TMA) as the unmetabolized free amine and thus cannot be distinguished [Cashman et al 2003]; thus, carriers are best identified by molecular genetic testing.

Related Genetic Counseling Issues

See [Management, Evaluation of Relatives at Risk](#) for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *FMO3* pathogenic variants have been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk for primary trimethylaminuria are possible options.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **National Human Genome Research Institute (NHGRI)**
[Learning About Trimethylaminuria](#)
- **National Library of Medicine Genetics Home Reference**
[Trimethylaminuria](#)
- **Trimethylaminuria Foundation**
Grand Central Station
PO Box 3361
New York NY 10163-3361
Phone: 212-300-4168
Email: thetfnetwk@aol.com
- **Children Living with Inherited Metabolic Diseases (CLIMB)**
United Kingdom
Phone: 0800-652-3181
Email: info.svcs@climb.org.uk
www.climb.org.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Primary Trimethylaminuria: Genes and Databases

Gene	Chromosome Locus	Protein	Locus Specific	HGMD

[FMO3](#) [1q24.3](#) [Dimethylaniline monooxygenase \[N-oxide-forming\] 3](#) [FMO3 database](#) [FMO3](#)

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click [here](#).

Table B.

OMIM Entries for Primary Trimethylaminuria ([View All in OMIM](#))

136132	FLAVIN-CONTAINING MONOOXYGENASE 3; FMO3
602079	TRIMETHYLAMINURIA; TMAU

Gene structure. *FMO3* spans 27 kb and contains nine exons; exon 1 is non-coding [Dolphin et al 1997b]. The gene encodes a mature mRNA of 2.1 kb. For a detailed summary of gene and protein information, see [Table A](#), **Gene**.

Benign allelic variants. Fifteen different nonsynonymous single-nucleotide variants have been identified [Phillips et al 2007] (see *FMO3* Database). Individually, with the exception of p.Asn61Lys and p.Leu360Pro, these have little or no effect on protein function. However, some nonsynonymous variants when present in *cis* configuration in the homozygous state can cause a "mild" phenotype.

Pathogenic allelic variants. More than 30 distinct pathogenic variants have been reported [Hernandez et al 2003, Yamazaki & Shimizu 2013] (see *FMO3* Database and [Table 3](#) [pdf]). Most are missense variants, but nonsense variants, small (1- or 2-bp) deletions, and one large (12.2-kb) deletion have been reported.

The most common pathogenic variants identified to date are p.Pro153Leu [Dolphin et al 1997a] and p.Glu305Ter [Treacy et al 1998].

Some nonsynonymous variants, when present in *cis* configuration (e.g., p.Glu158Lys and p.Glu308Gly) result in moderately decreased enzyme activity [Koukouritaki & Hines 2005, Phillips et al 2007]. In the homozygous state (i.e., p.Glu158Lys and p.Glu308Gly present in *cis* configuration on both chromosomes), they may cause mild or transient primary trimethylaminuria, particularly in infants and young children [Zschocke et al 1999, Zschocke & Mayatepek 2000], who have low expression of *FMO3* [Koukouritaki et al 2002].

The variant p.Val187Ala alone does not affect enzyme activity, but p.Val187Ala in *cis* configuration with p.Glu158Lys has a severe effect on enzyme activity [Motika et al 2009].

The pathogenic variant p.Asn61Ser abolishes *N*-oxygenation of trimethylamine and thus causes trimethylaminuria but has no effect on the *S*-oxygenation of methimazole [Dolphin et al 2000].

The p.Leu360Pro variant is the only variant known to result in an increase in enzyme activity [Lattard et al 2003].

When novel variants are identified, it is important to establish that they (1) cosegregate with the disorder in the family and (2) abolish or substantially reduce the ability to catalyze *N*-oxygenation of TMA as assessed by assaying heterologously expressed variant protein.

Table 2.

Selected *FMO3* Allelic Variants

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
"Mild" variants that affect enzyme activity ¹	c.[472G>A;923A>G]	p. [Glu158Lys;Glu308Gly]	NM_006894.4 NP_008825.4
Increased enzyme activity	c.1079T>C	p.Leu360Pro	
Pathogenic	c.182A>G	p.Asn61Ser	
	c.458C>T	p.Pro153Leu	

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
	c.[472G>A;560T>C] ²	p.[Glu158Lys;Val187Ala] ²	
	c.913G>T	p.Glu305Ter	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. See details in discussion preceding table.
2. Denotes two changes in one allele

Normal gene product. The normal product of *FMO3* is the protein flavin-containing monooxygenase 3 (FMO3), which has a molecular mass of 60 kd and contains 532 amino acid residues [Phillips et al 2007]. FMO3 is located in the membranes of the endoplasmic reticulum. The enzyme catalyzes the oxygenation of a wide range of foreign chemicals. At the site of oxygenation preferred substrates contain a soft nucleophile – typically a nitrogen, sulfur, phosphorous, or selenium atom [Krueger & Williams 2005]. One of the reactions catalyzed by FMO3 is the oxygenation of the odorous tertiary amine trimethylamine to its non-odorous *N*-oxide.

Abnormal gene product. The pathogenic variants that cause severe trimethylaminuria essentially abolish FMO3 activity and are thus "null" variants [Phillips et al 2007].

Some pathogenic variants impair assembly of the holoenzyme (i.e., the ability of the apoprotein to bind FAD) whereas others affect kinetic competency [Yeung et al 2007].

References

Published Guidelines/Consensus Statements

1. Chalmers RA, Bain MD, Michelakakis H, Zschocke J, Iles RA. Diagnosis and management of trimethylaminuria (FMO3 deficiency) in children. 2006. Available online. Accessed 6-14-16. [PubMed: 16601883]

Literature Cited

1. Binzak BA, Wevers RA, Moolenaar SH, Lee YM, Hwu WL, Poggi-Bach J, Engelke UF, Hoard HM, Vockley JG, Vockley J. Cloning of dimethylglycine dehydrogenase and a new human inborn error of metabolism, dimethylglycine dehydrogenase deficiency. *Am J Hum Genet.* 2001;68:839–47. [PMC free article: PMC1275637] [PubMed: 11231903]
2. Busby MG, Fischer L, da Costa KA, Thompson D, Mar MH, Zeisel SH. Cho. *J Am Diet Assoc.* 2004;104:1836–45. [PubMed: 15565078]
3. Cashman JR, Camp K, Fakharzadeh SS, Fennessey PV, Hines RN, Mamer OA, Mitchell SC, Nguyen GP, Schlenk D, Smith RL, Tjoa SS, Williams DE, Yannicelli S. Biochemical and clinical aspects of the human flavin-containing monooxygenase form 3 (FMO3) related to trimethylaminuria. *Curr Drug Metab.* 2003;4:151–70. [PubMed: 12678693]
4. Cashman JR, Xiong Y, Lin J, Verhagen H, van Poppel G, van Bladeren PJ, Larsen-Su S, Williams DE. In vitro and in vivo inhibition of human flavin-containing monooxygenase form 3 (FMO3) in the presence of dietary indoles. *Biochem Pharmacol.* 1999;58:1047–55. [PubMed: 10509757]
5. Chalmers RA, Bain MD, Michelakakis H, Zschocke J, Iles RA. Diagnosis and management of trimethylaminuria (FMO3 deficiency) in children. *J Inherit Metab Dis.* 2006;29:162–72. [PubMed: 16601883]
6. Dolphin CT, Janmohamed A, Smith RL, Shephard EA, Phillips IR. Missense mutation in flavin-containing mono-oxygenase 3 gene, FMO3, underlies fish-odour syndrome. *Nat Genet.* 1997a;17:491–4. [PubMed: 9398858]
7. Dolphin CT, Janmohamed A, Smith RL, Shephard EA, Phillips IR. Compound heterozygosity for missense mutations in the flavin-containing monooxygenase 3 (FMO3) gene in patients with fish-odour syndrome.

- Pharmacogenetics. 2000;10:799–807. [PubMed: 11191884]
8. Dolphin CT, Riley JH, Smith RL, Shephard EA, Phillips IR. Structural organization of the human flavin-containing monooxygenase 3 gene (FMO3), the favored candidate for fish-odor syndrome, determined directly from genomic DNA. *Genomics*. 1997b;46:260–7. [PubMed: 9417913]
 9. Forrest SM, Knight M, Akerman BR, Cashman JR, Treacy EP. A novel deletion in the flavin-containing monooxygenase gene (FMO3) in a Greek patient with trimethylaminuria. *Pharmacogenetics*. 2001;11:169–74. [PubMed: 11266081]
 10. Fraser-Andrews EA, Manning NJ, Ashton GH, Eldridge P, McGrath J, Menage Hdu P. Fish odour syndrome with features of both primary and secondary trimethylaminuria. *Clin Exp Dermatol*. 2003;28:203–5. [PubMed: 12653714]
 11. Hernandez D, Addou S, Lee D, Orengo C, Shephard EA, Phillips IR. Trimethylaminuria and a human FMO3 mutation database. *Hum Mutat*. 2003;22:209–13. [PubMed: 12938085]
 12. Institute of Medicine National Academy of Sciences USA. *Dietary Reference Intakes for Folate, Thiamin, Riboflavin, Niacin, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academy Press; 1998.
 13. Koukouritaki SB, Hines RN. Flavin-containing monooxygenase genetic polymorphism: impact on chemical metabolism and drug development. *Pharmacogenomics*. 2005;6:807–22. [PubMed: 16296944]
 14. Koukouritaki SB, Simpson P, Yeung CK, Rettie AE, Hines RN. Human hepatic flavin-containing monooxygenases 1 (FMO1) and 3 (FMO3) developmental expression. *Pediatr Res*. 2002;51:236–43. [PubMed: 11809920]
 15. Krueger SK, Williams DE. Mammalian flavin-containing monooxygenases: structure/function, genetic polymorphisms and role in drug metabolism. *Pharmacol Ther*. 2005;106:357–87. [PMC free article: PMC1828602] [PubMed: 15922018]
 16. Lang DH, Yeung CK, Peter RM, Ibarra C, Gasser R, Itagaki K, Philpot RM, Rettie AE. Isoform specificity of trimethylamine *N*-oxygenation by human flavin-containing monooxygenase (FMO) and P450 enzymes: selective catalysis by FMO3. *Biochem Pharmacol*. 1998;56:1005–12. [PubMed: 9776311]
 17. Lattard V, Zhang J, Tran Q, Furnes B, Schlenk D, Cashman JR. Two new polymorphisms of the FMO3 gene in Caucasian and African-American populations: comparative genetic and functional studies. *Drug Metab Dispos*. 2003;31:854–60. [PubMed: 12814961]
 18. Mackay RJ, McEntyre CJ, Henderson C, Lever M, George PM. Trimethylaminuria: causes and diagnosis of a socially distressing condition. *Clin Biochem Rev*. 2011;32:33–43. [PMC free article: PMC3052392] [PubMed: 21451776]
 19. Manning NJ, Allen EK, Kirk RJ, Sharrard MJ, Smith EJ. Riboflavin-responsive trimethylaminuria in a patient with homocystinuria on betaine therapy. *JIMD Rep*. 2012;5:71–5. [PMC free article: PMC3509925] [PubMed: 23430919]
 20. Mayatepek E, Flock B, Zschocke J. Benzydamine metabolism in vivo is impaired in patients with deficiency of flavin-containing monooxygenase 3. *Pharmacogenetics*. 2004;14:775–7. [PubMed: 15564885]
 21. Mayatepek E, Kohlmuller D. Transient trimethylaminuria in childhood. *Acta Paediatr*. 1998;87:1205–7. [PubMed: 9846928]
 22. Mitchell SC. Trimethylaminuria (fish-odour syndrome) and oral malodour. *Oral Dis*. 2005;11 Suppl 1:10–3. [PubMed: 15752091]
 23. Mitchell S, Ayesh R, Barrett T, Smith R. Trimethylamine and foetor hepaticus. *Scand J Gastroenterol*. 1999;34:524–8. [PubMed: 10423071]
 24. Mitchell SC, Smith RL. Trimethylaminuria: the fish malodour syndrome. *Drug Metab Dispos*. 2001;29:517–21. [PubMed: 11259343]
 25. Mitchell SC, Zhang AQ, Barrett T, Ayesh R, Smith RL. Studies on the discontinuous *N*-oxidation of trimethylamine among Jordanian, Ecuadorian and New Guinean populations. *Pharmacogenetics*. 1997;7:45–50. [PubMed: 9110361]
 26. Motika MS, Zhang J, Zheng X, Riedler K, Cashman JR. Novel variants of the human flavin-containing monooxygenase 3 (FMO3) gene associated with trimethylaminuria. *Mol Genet Metab*. 2009;97:128–35. [PMC free article: PMC2739593] [PubMed: 19321370]
 27. Pardini RS, Sapien RE. Trimethylaminuria (fish odor syndrome) related to the choline concentration of infant formula. *Pediatr Emerg Care*. 2003;19:101–3. [PubMed: 12698036]
 28. Phillips IR, Francois AA, Shephard EA. The flavin-containing monooxygenases (FMOs): genetic variation and its consequences for the metabolism of therapeutic drugs. *Curr Pharmacogenet Pharmacogenom*. 2007;5:292–

313.

29. Shephard EA, Treacy EP, Phillips IR. Clinical utility gene card for: Trimethylaminuria – update 2014. *Eur J Hum Genet.* 2015;23(9) [PMC free article: PMC4538216] [PubMed: 25335494]
30. Shimizu M, Allerston CK, Shephard EA, Yamazaki H, Phillips IR. *Br J Clin Pharmacol.* 2014;77:839–51. [PMC free article: PMC4004404] [PubMed: 24028545]
31. Shimizu M, Cashman JR, Yamazaki H. Transient trimethylaminuria related to menstruation. *BMC Med Genet.* 2007;8:2. [PMC free article: PMC1790885] [PubMed: 17257434]
32. Tangerman A. Halitosis in medicine: a review. *Int Dent J.* 2002;52 Suppl 3:201–6. [PubMed: 12090453]
33. Treacy EP, Akerman BR, Chow LM, Youil R, Bibeau C, Lin J, Bruce AG, Knight M, Danks DM, Cashman JR, Forrest SM. Mutations of the flavin-containing monooxygenase gene (FMO3) cause trimethylaminuria, a defect in detoxication. *Hum Mol Genet.* 1998;7:839–45. [PubMed: 9536088]
34. Yamazaki H, Fujieda M, Togashi M, Saito T, Preti G, Cashman JR, Kamataki T. Effects of the dietary supplements, activated charcoal and copper chlorophyllin, on urinary excretion of trimethylamine in Japanese trimethylaminuria patients. *Life Sci.* 2004;74:2739–47. [PubMed: 15043988]
35. Yamazaki H, Shimizu M. Survey of variants of human flavin-containing monooxygenase 3 (FMO3) and their drug oxidation activities. *Biochem Pharmacol.* 2013;85:1588–93. [PubMed: 23567996]
36. Yeung CK, Adman ET, Rettie AE. Functional characterization of genetic variants of human FMO3 associated with trimethylaminuria. *Arch Biochem Biophys.* 2007;464:251–9. [PMC free article: PMC2039921] [PubMed: 17531949]
37. Zschocke J, Kohlmüller D, Quak E, Meissner T, Hoffmann GF, Mayatepek E. Mild trimethylaminuria caused by common variants in FMO3 gene. *Lancet.* 1999;354:834–5. [PubMed: 10485731]
38. Zschocke J, Mayatepek E. Biochemical and molecular studies in mild flavin monooxygenase 3 deficiency. *J Inher Metab Dis.* 2000;23:378–82. [PubMed: 10896299]

Suggested Reading

1. Phillips IR, Shephard EA. Flavin-containing monooxygenases: mutations, disease and drug response. *Trends Pharmacol Sci.* 2008;29:294–301. [PubMed: 18423897]
2. Treacy EP. Trimethylaminuria and deficiency of flavin-containing monooxygenase type 3 (FMO3). In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson K, Mitchell G, eds. *The Online Metabolic and Molecular Bases of Inherited Disease (OMMBID)*. Chap 88.1. McGraw-Hill. Available online. Accessed 6-14-16.

Chapter Notes

Revision History

- 1 October 2015 (me) Comprehensive update posted live
- 19 April 2011 (me) Comprehensive update posted live
- 18 March 2008 (cd) Revision: sequence analysis available clinically
- 8 October 2007 (me) Review posted to live Web site
- 30 July 2007 (eas) Original submission

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