GENEReviews

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Trimethylaminuria

[*Fish Odor Syndrome, TMAuria, TMAU*]

Ian R Phillips , PhD
Professor of Molecular Biology
School of Biological and Chemical Sciences
Queen Mary, University of London
London, United Kingdom
i.r.phillips@qmul.ac.uk

Elizabeth A Shephard , PhD
Professor of Molecular Biology
Department of Biochemistry and Molecular Biology
University College London
London, United Kingdom
e.shephard@ucl.ac.uk

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Summary

Disease characteristics. 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. Diagnosis of trimethylaminuria is based on either the percent of total trimethylamine (free trimethylamine [TMA] plus the non-odorous metabolite TMA *N*-oxide) excreted in the urine as unmetabolized free TMA or the concentration of unmetabolized TMA in the urine. *FMO3* is the only gene known to be associated with trimethylaminuria. Sequence analysis is available clinically.

Management. *Treatment of manifestations:* dietary restriction of: (1) 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, (2) trimethylamine *N*-oxide (present in seafood [fish, cephalopods, and crustaceans]), (3) inhibitors of FMO3 enzyme activity such as indoles (found in brassicas); use of acid soaps and body lotions to remove secreted trimethylamine by washing; use of 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; laxatives (e.g., lactulose) to decrease intestinal transit time; riboflavin supplements to enhance residual FMO3 enzyme activity. *Prevention of primary manifestations:* See *Treatment of manifestations.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). *Testing 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. Trimethylaminuria is inherited in an autosomal recessive manner. The parents of an affected individual are obligate heterozygotes and therefore carry one mutant 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. No laboratories offering molecular genetic testing for prenatal diagnosis of trimethylaminuria are listed in the GeneTests Laboratory Directory; however, prenatal testing may be available through laboratories offering custom prenatal testing for families in which the disease-causing mutations have been identified.

Diagnosis

Clinical Diagnosis

Trimethylaminuria may present with a body odor resembling that of rotten or decaying fish.

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

Diagnosis based on the sense of smell of the examiner is complicated by 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 10^9; 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.

Testing

Metabolism of trimethylamine is primarily via *N*-oxygenation, catalyzed by the enzyme flavin-containing monooxygenase 3 (FMO3).

Biochemical testing. Trimethylaminuria is characterized by excretion of excessive amounts of unoxidized trimethylamine in the urine, breath, sweat, and reproductive fluids. Trimethylamine is extremely volatile and has a pungent ammoniacal odor reminiscent of rotting fish. For laboratories offering biochemical testing see Testing.

Diagnosis of trimethylaminuria is based on **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
  - Severe trimethylaminuria: less than 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 10µg/mL (18-20 µmol/mmol creatinine) or higher, correlating with a urinary output of TMA of about 15 to 20 mg/day, appears to represent a threshold for the presence of the fishy body odor associated with the disorder [Mitchell & Smith 2001].

Note: (1) Some forms of trimethylaminuria are transient or episodic; to distinguish them from the primary inherited form, biochemical testing should be performed on two separate occasions. (2) Choline challenge. It may also help to carry out the biochemical testing after an oral challenge of choline bitartrate (2.5 to 15g, depending on age) [Chalmers et al 2006]. Although this level of choline challenge is generally well tolerated, one individual developed an adverse reaction, with fever and vomiting [Chalmers et al 2006]. (3) Because unaffected women may have a short episode of trimethylaminuria at the onset of and during menstruation, females should not be tested during this time frame.

The methods of detecting TMA and TMA *N*-oxide in urine currently available involve sophisticated equipment and require skilled and experienced personnel:

- **Head-space gas chromatography (GC) or GC-mass spectrometry** [Mills et al 1999]. Disadvantages: GC techniques are time consuming, TMA *N*-oxide must be chemically reduced to TMA before analysis, and both TMA and TMA produced by reduction of TMA *N*-oxide must be extracted from urine.
- **Mass spectroscopy (MS)*** including fast atom bombardment MS (FAB-MS) [Mamer et al 1999], direct infusion electrospray MS [Cashman et al 2001], or matrix-assisted laser desorption/ionization time-of-flight MS (MALDI-TOFMS) [Hsu et al 2007]
- **Proton nuclear magnetic resonance (NMR) spectroscopy*** [Maschke et al 1997, Murphy et al 2000, Podadera et al 2005, Lee et al 2006]

* MS and proton NMR have the advantage of being able to detect TMA and TMA *N*-oxide simultaneously with great sensitivity. NMR has the further advantage of requiring no prior extraction or separation of metabolites and thus measurement can be done directly on urine samples.

Heterozygotes

- Under normal dietary conditions heterozygotes (carriers) and unaffected individuals excrete less than 10% of total TMA as the unmetabolized free amine and thus cannot be distinguished.
- **TMA challenge.** Carriers can be detected using a "TMA load" test in which 600 mg of TMA is given orally in a gelatin capsule. After the TMA load test, carriers excrete 20%-30% of total TMA as the free unmetabolized amine, whereas unaffected individuals excrete less than 13% of total TMA as the free unmetabolized amine [Mitchell & Smith 2001].

Molecular Genetic Testing—*GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the* GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.* —ED.

Gene. *FMO3* is the only gene known to be associated with trimethylaminuria.

Clinical testing

- **Sequence analysis.** It is estimated that 99% of *FMO3* mutations may be detected by sequence analysis. Insufficient studies have been published to establish the mutation detection frequency.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Trimethylaminuria

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*FMO3* sequence variants	~99% [1]	Clinical Testing

1. Insufficient studies have been published to establish the actual mutation detection frequency.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Establishing the diagnosis in a proband. Individuals complaining of or exhibiting a fishy odor should be tested for urinary excretion of TMA, ideally on two separate occasions. Testing can be done under normal dietary conditions or following a choline challenge.

Note: The choline challenge described in Testing can help confirm TMA in affected individuals. The choline challenge does not distinguish between carriers and unaffected individuals.

If an individual excretes more than 10% of total TMA as the free amine under normal dietary conditions, sequence analysis should be offered.

- If an individual is found to be homozygous or compound heterozygous for known loss-of-function mutations of *FMO3*, the diagnosis is confirmed.
- If novel mutations are found, it is important to establish that:
  1. The mutations are not relatively common in the general population, i.e., polymorphic variants;
  2. They cosegregate with the disorder in the family;
  3. They abolish (or substantially reduce) the ability of FMO3 to catalyze *N*-oxygenation of TMA, as assessed by assaying heterologously expressed mutant protein.

Carrier testing for at-risk relatives. Carriers can be distinguished from unaffected individuals with the TMA challenge described in Testing: Heterozygotes.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in the *FMO3* gene.

Clinical Description

Natural History

Trimethylaminuria is characterized by fishy odor resulting from excess excretion of trimethylamine in the urine, breath, sweat, and reproductive fluids.

The trimethylamine is derived from dietary precursors, such as choline and trimethylamine *N*-oxide, via the action of bacteria in the gut. It is normally metabolized in the liver by the

enzyme FMO3 to produce trimethylamine *N*-oxide, which is non-volatile and non-odorous. 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 either genetic factors (mutations in the *FMO3* gene), 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 fauna, 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.

No physical symptoms are associated with 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. Affected individuals 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 genetic 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 the *FMO3* gene 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*.

Genotype-Phenotype Correlations

On a normal diet, individuals who are homozygous or compound heterozygous for loss-of-function *FMO3* mutations secrete more than 40% of total TMA as the free unmetabolized amine and consequently have a fishy odor.

Several nonsense or missense mutations that essentially abolish the ability of the FMO3 enzyme to catalyze *N*-oxygenation of TMA have been identified. In general, the greater the effect of the mutation on the FMO3 enzyme activity the more severe the symptoms and the less responsive to treatment.

More common normal variants have little or no effect on enzyme activity; however, combinations of variants (e.g., p.Glu158Lys and p.Glu308Gly) in cis configuration (i.e., on the same chromosome), may cause "mild" trimethylaminuria, resulting in the excretion of 10%-39% of total TMA as the free unmetabolized amine.

Nomenclature

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

Prevalence

The incidence of heterozygous carriers in the white British population is 0.5% to 1.0%. It is higher in other ethnic groups studied: 1.7% in Jordanian, 3.8% in Ecuadorian, and 11.0% in New Guinea [Mitchell et al 1997].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

A classification scheme for trimethylaminuria has been proposed [Mitchell & Smith 2001, Mitchell 2005].

- **Primary genetic trimethylaminuria.** Caused by *FMO3* mutations that result in loss of function of FMO3 enzyme activity, this subtype accounts for the majority of reported cases. Combinations of certain *FMO3* polymorphisms may cause a less severe form of the condition.
- **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 mutation of *FMO3* or have certain combinations of *FMO3* polymorphisms may exhibit mild symptoms of the disorder [Mayatepek & Kohlmuller 1998, Zschocke et al 1999]. Transient childhood forms are a consequence of the immaturity of *FMO3* expression, which is switched on after birth and continues to increase throughout childhood.

- **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 polymorphic variants that result in a limited 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 (up to 20g per day).
- **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. 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, the primary genetic form of trimethylaminuria, caused by FMO3 deficiency, is characterized by a high ratio of TMA/TMA *N*-oxide in the urine.

Management

Evaluations Following Initial Diagnosis

Urinary ratio of TMA *N*-oxide to total TMA on a normal diet indicates the severity of disease in an individual diagnosed with trimethylaminuria:

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

The general rule is that the lower the ratio the more severe the disorder.

Treatment of Manifestations

Strategies for the treatment of trimethylaminuria have been discussed in detail [Cashman et al 2003] and "best-practice" guidelines have been summarized [Chalmers et al 2006].

Restriction of dietary trimethylamine and its precursors. In some cases the disorder can be successfully managed by dietary restriction of precursors of trimethylamine. This is particularly true of "mild" or moderate forms of the disorder. 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), including 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 twice daily for ten days) and copper chlorophyllin (60 mg three times a day after meals for three 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].

Laxatives, such as lactulose, to decrease intestinal transit time may also reduce the amount of trimethylamine produced in the gut.

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. Recommended intake is 30-40 mg, three to five times per 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. 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

Testing of Relatives at Risk

Biochemical testing of sibs is appropriate to identify those who are affected and will benefit from early treatment of manifestations. If the causative mutation(s) in the family has been identified, at-risk relatives can be offered molecular genetic testing.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory. —ED.

Mode of Inheritance

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 and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with trimethylaminuria are obligate heterozygotes (carriers) for a disease-causing mutation.

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

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk family members is available once the mutations have been identified in the family.

Biochemical genetic testing. Carrier status can be clarified using biochemical testing by analyzing the concentration and ratio of trimethylamine and trimethylamine *N*-oxide in urine after an oral challenge of trimethylamine (600 mg).

Related Genetic Counseling Issues

See Management: Treatment of Manifestations for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning. The optimal time for determination of genetic risk and clarification of carrier status 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.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently availahble testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of trimethylaminuria are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as trimethylaminuria that do not affect intellect or life span and have treatment available are not common. 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.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —ED.

Table A. Molecular Genetics of Trimethylaminuria

Gene Symbol	Chromosomal Locus	Protein Name
FMO3	1q24.3	Flavin-containing monooxygenase 3

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Trimethylaminuria

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

Table C. Genomic Databases for Trimethylaminuria

Gene Symbol	Locus Specific	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
FMO3	FMO3	2328 (MIM No. 136132)	FMO3	*FMO3*	135136	FMO3

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *FMO3* gene spans 27 kb and contains nine exons, of which exon 1 is non-coding [Dolphin, Riley et al 1997]. The gene encodes a mature mRNA of 2.1 kb.

Fifteen different nonsynonymous single-nucleotide variants in the gene have been identified [Phillips et al, in press]. 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.

Pathologic allelic variants: At least 30 distinct mutations have been reported [Hernandez et al 2003] (see Table 3) (pdf). Most are missense mutations, but nonsense mutations, small (1- or 2-bp) deletions and one large (12.2 kb) deletion have been reported. The most common mutations identified to date are p.Pro153Leu [Dolphin, Janmohamed et al 1997] and p.Glu305X [Treacy et al 1998]. Some mutations impair assembly of the holoenzyme (i.e., the ability of the apoprotein to bind FAD) whereas others affect kinetic competency [Yeung et al 2007].

Some nonsynonymous variants, when present in cis configuration (e.g., p.Glu158Lys and p.Glu308Gly) can result in a moderate decrease in enzyme activity [Koukouritaki & Hines 2005; Phillips et al, in press]. When present in the homozygous state, they may cause mild or transient trimethylaminuria, particularly in infants and young children, who have low expression of FMO3. The mutation p.Asn61Lys results in a severe reduction in FMO3 activity [Koukouritaki et al 2007] and thus is likely to cause primary genetic trimethylaminuria; however, no affected individuals with this mutation have been identified. The mutation p.Leu360Pro is the only variant to result in an increase in enzyme activity [Lattard et al 2003]. See Table 2.

Table 2. *FMO3* Pathologic Allelic Variants Discussed in This *GeneReview*

Class of Variant Allele	DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
"Mild" variants that affect enzyme activity [1]	c.472G>A	p.Glu158Lys	NP_008825.4 NM_006894.4
	c.923A>G	p.Glu308Gly	
	c.1079T>C	p.Leu360Pro	
Pathologic	c.458C>T	p.Pro153Leu	
	c.913G>T	p.Glu305X	

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

1. See details in paragraph preceding table.

Normal gene product: The normal product of the *FMO3* gene is the protein flavin-containing monooxygenase 3 (FMO3), which has a molecular mass of 60 kd and contains 532 amino acid residues. 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 mutations that cause severe trimethylaminuria essentially abolish FMO3 activity and are thus "null" mutations. The mutation p.Asn61Ser, however, abolishes *N*-oxygenation of trimethylamine and thus causes trimethylaminuria but has no effect on the *S*-oxygenation of methimazole [Dolphin et al 2000].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -ED.

National Human Genome Research Institute
Learning About Trimethylaminuria

National Library of Medicine Genetics Home Reference
Trimethylaminuria

Trimethylaminuria Foundation
PO Box 3361
Grand Central Station
New York NY 10163-3361
Phone: 212-300-4168
Email: thetfnetwk@aol.com

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: 0800 652 3181 (toll free)
Email: info.svcs@climb.org.uk
www.climb.org.uk

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Revision History

- 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