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Primary Trimethylaminuria

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

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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 more than 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]);

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- Inhibitors of FMO3 enzyme activity such as indoles (found in brassicas).

Note: 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.

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.

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 enzyme FMO3; circumstances that promote sweating (e.g., exercise, stress, 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 (i.e., presumed to be carriers of one *FMO3* pathogenic variant based on family history). If both parents are known to be heterozygous for an *FMO3* pathogenic variant, each sib of an affected individual has at conception 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 the *FMO3* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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].

Suggestive Findings

Primary trimethylaminuria **should be suspected** in individuals with the following clinical findings and family history.

Body odor resembling that of rotten or decaying fish. Unoxidized trimethylamine (TMA) excreted in the urine, breath, sweat, and reproductive fluids is highly volatile and has a pungent ammoniac odor reminiscent of rotting fish [Mitchell & Smith 2001, 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 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.

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., 2 eggs + 400 g "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], women 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].

  Note: Currently available specific methods of detecting TMA and TMA *N*-oxide in urine involve sophisticated equipment and require skilled, experienced personnel. The methods used in mass spectrometry [Li et al 2017] and proton NMR [Murphy et al 2000] can detect TMA and TMA *N*-oxide simultaneously with great sensitivity. NMR has the additional advantage of requiring no prior extraction or separation of metabolites, making measurement possible directly on urine samples.

Family history consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

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

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

  Note: Identification of biallelic *FMO3* variants of uncertain significance (or identification of one known *FMO3* pathogenic variant and one *FMO3* variant of uncertain significance) does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing and genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of primary trimethylaminuria has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of primary trimethylaminuria, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FMO3* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *FMO3* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of primary trimethylaminuria has not been considered, **comprehensive genomic testing,** which does not require the clinician to determine which gene is likely involved, is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Primary Trimethylaminuria

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
FMO3	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 6.

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. 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may 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.
6. 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.

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 & Smith 2001, 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]. Although affected individuals would be expected to exhibit altered metabolism of drugs that are acted upon by FMO3 [Phillips & Shephard 2017], there are no published reports of such effects.

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

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.

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 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 [Phillips et al 2007, Yamazaki & Shimizu 2013]. In general, the more severe the reduction in FMO3 enzyme activity, the more severe the manifestations and the less the response to treatment.

Some nonsynonymous variants, when present in *cis* configuration (e.g., p.Glu158Lys and p.Glu308Gly) result in moderately decreased enzyme activity [Phillips & Shephard 2020]. 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 & Mayatepek 2000], who have low expression of *FMO3* [Koukouritaki et al 2002].

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 germline pathogenic variants in *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 [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].
- **Olfactory reference syndrome (ORS).** In some individuals who perceive that they have a body odor, clinical investigation reveals that they do not have trimethylaminuria or other body-odor disorders, but rather the psychiatric disorder ORS [McNiven et al 2019]. A distinguishing feature of ORS is its late onset.
- **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 the case of congenital portosystemic shunt, manifestations of trimethylaminuria can be resolved by endovascular closure [Ponce-Dorrego & Garzón-Moll 2019].
    - 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, Mogilnicka et al 2020] resulting from malodorous compounds other than trimethylamine. Another condition in this category is the rare metabolic disorder dimethylglycine dehydrogenase deficiency caused by biallelic pathogenic variants in *DMGDH* (OMIM 605850). 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

No clinical practice guidelines for primary trimethylaminuria have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary trimethylaminuria, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Determine the urinary ratio of trimethylamine (TMA) *N*-oxide to total TMA on a normal diet. 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.
- Assess social issues associated with body odor. These may include harassment, bullying, discrimination, negative self-image, social isolation, and relationship problems [Lateef & Marshall-Lucette 2017, Roddy et al 2020]. An assessment tool for evaluation of social and mental health effects of the disorder has been proposed [Rutkowski et al 2019].
- Consult with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of primary trimethylaminuria in order to facilitate medical and personal decision making.

Treatment of Manifestations

Strategies for the treatment of primary trimethylaminuria summarized in this section are reviewed by Schmidt & Leroux [2020].

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.

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 [National Academies Collection 1998]. For adults, adequate daily intake of choline is 550 mg for males and 425 mg for females.

- **Choline** is one of the most important dietary sources of trimethylamine. 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].

  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.

- **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.

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

  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 [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.

Assessment of efficacy of treatment. A tool for patient self-assessment of the effect of treatment on social and mental health aspects of the disorder has been proposed [Rutkowski et al 2019].

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 & Shephard 2017]. 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 (e.g., exercise, stress, emotional upsets)

Evaluation of Relatives at Risk

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 with primary trimethylaminuria.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise 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., presumed to be carriers of one *FMO3* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for an *FMO3* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *FMO3* pathogenic variant, each sib of an affected individual has at conception 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. Each sib of the proband's parents is at a 50% risk of being a carrier of an *FMO3* pathogenic variant.

Carrier 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]; carriers are best identified by molecular genetic testing.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic 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 Testing

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Genetic and Rare Diseases Information Center (GARD)**
  Phone: 888-205-2311
  Trimethylaminuria
- **National Human Genome Research Institute (NHGRI)**
  About Trimethylaminuria
- **National Library of Medicine Genetics Home Reference**
  Trimethylaminuria
- **National Organization for Rare Disorders (NORD)**
  Trimethylaminuria
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org

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 Databases	HGMD	ClinVar
FMO3	1q24.3	Flavin-containing monooxygenase 3	FMO3 database	FMO3	FMO3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Trimethylaminuria (View All in OMIM)

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

Molecular Pathogenesis

Metabolism of trimethylamine is primarily via *N*-oxygenation, catalyzed by the enzyme flavin-containing monooxygenase 3 (FMO3) [Dolphin et al 1997, Lang et al 1998].

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, Fennema et al 2016]. It is normally metabolized in the liver by the enzyme FMO3 to produce trimethylamine *N*-oxide, which is non-volatile and non-odorous [Fennema et al 2016]. 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.

Mechanism of disease causation. Loss of function

Table 2. Notable *FMO3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_006894.5 NP_008825.4	c.[472G>A;923A>G]	p.[Glu158Lys;Glu308Gly] [1]	Homozygotes may experience mild symptoms [Zschocke & Mayatepek 2000] (see Genotype-Phenotype Correlations).
	c.182A>G	p.Asn61Ser	Abolishes *N*-oxygenation of trimethylamine causing trimethylaminuria, but has no effect on the *S*-oxygenation of methimazole [Dolphin et al 2000]
	c.458C>T	p.Pro153Leu	First pathogenic variant identified; one of the most common [Dolphin et al 1997]
	c.[472G>A;560T>C]	p.[Glu158Lys;Val187Ala] [1]	p.Val187Ala alone does not affect enzyme activity, but when in *cis* configuration w/p.Glu158Lys it has a severe effect on enzyme activity [Motika et al 2009] (see Genotype-Phenotype Correlations).

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Denotes two *FMO3* variants in *cis* configuration (present on 1 allele)

Chapter Notes

Revision History

- 5 November 2020 (bp) Comprehensive update posted live
- 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 live
- 30 July 2007 (eas) Original submission

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