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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Trimethylaminuria

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Trimethylaminuria (fish-odour syndrome, fish malodour syndrome, stale fish syndrome).

1.2 OMIM# of the disease

602079.

1.3 Name of the analysed genes or DNA/chromosome segments

FMO3.

1.4 OMIM# of the gene(s)

136132.

1.5 Mutational spectrum

More than 30 mutations have been reported to cause trimethylaminuria. 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[1] and p.Glu305X.[2] In one case, the haplotype in which a mutation occurs is important: p.Val187Ala has no effect on *FMO3* activity, but when it occurs in *cis* with the common polymorphism p.Glu158Lys it severely affects enzyme activity.[3] A human *FMO3* database has been established,[4] and causative mutations identified to date have been reported.[5,6] In addition to rare causative mutations, 15 non-synonymous single-nucleotide polymorphic (SNP) variants of *FMO3* have been identified.[7] Of these, only one, p.Asn61Lys, which occurs at low frequency, results in a severe reduction of enzyme activity.[8] However, some polymorphic variants (eg, p.Glu158Lys and p.Glu308Gly) when present in *cis* can cause a moderate decrease in enzyme activity.[7,9] When present in the homozygous state, they may cause mild or transient trimethylaminuria, particularly in infants and young children,[10,11] who have low expression of *FMO3*.[12] Two *FMO3* haplotypes that contain promoter-region SNPs have been reported to severely reduce expression *in vitro*.[13] Although the impact of these haplotypes *in vivo* has not been validated, it is possible that they contribute to the disorder in the absence of coding-region mutations.

1.6 Analytical methods

The most common method is amplification of the eight coding exons by PCR with exon-specific primers, followed by DNA sequencing of the amplicons. Large deletions are rare, being identified in only one individual,[14] and can be identified by multiplex ligation-dependent probe amplification.

1.7 Analytical validation

Both the strands of DNA should be sequenced. Identified variants should be compared with databases and the literature to establish whether they correspond to known causative mutations. If a novel mutation is found, it is important to establish that it abolishes or substantially reduces the ability of FMO3 to catalyze the *N*-oxygenation of trimethylamine (TMA), as assessed by assay of heterologously expressed mutant protein.[1,15,16] If an individual is heterozygous for two different causative mutations, analysis of the parents' DNA will establish whether the mutations are in *trans*. If an individual is homozygous or compound heterozygous[17] for loss-of-function mutations of *FMO3*, diagnosis is confirmed.

1.8 Estimated frequency of the disease in Germany (incidence at birth ('birth prevalence') or population prevalence)

For severe, inherited trimethylaminuria, the incidence of heterozygous carriers in the white British population is 0.5–1.0%.[18] The frequency of the severe type of the disorder in this population could thus be as high as 1 in 40 000. The true prevalence of the disorder is unknown; however, of patients referred to a malodour clinic in Philadelphia, 35% had trimethylaminuria.[19]

1.9 If applicable, prevalence in the ethnic group of investigated person

The incidence of heterozygous carriers is higher in other ethnic groups studied: 1.7% in Jordanian, 3.8% in Ecuadorian and 11.0% in New Guinean populations,[20] suggesting the frequency of the disorder may be as high as 1 in 3000 and 1 in 400 in the latter two groups, respectively.

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☐	☒
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment:

Trimethylaminuria usually presents with a body odour resembling that of rotten or decaying fish, the result of excess excretion of TMA in the breath, sweat, urine and reproductive fluids.[21–24] Individuals complaining of or exhibiting a fishy odour should be tested for

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urinary excretion of TMA, ideally on two separate occasions. Genetic testing should be offered to individuals who, under normal dietary conditions, excrete more than 10% of total TMA as the free amine. Molecular diagnosis can identify affected individuals and heterozygous carriers. It can also distinguish primary genetic trimethylaminuria (including severe presentations, caused by loss-of-function mutations in *FMO3*, and milder presentations, commonly resulting from compound heterozygosity for milder missense mutations and polymorphisms that affect *FMO3* activity) from other, less common forms of trimethylaminuria such as

(1) An intermittent form, associated with menstruation,[25,26] probably related to decreased expression of *FMO3* in response to steroid hormones. The effect is more pronounced in women homozygous for combinations of polymorphisms that affect FMO3 activity.[26]
(2) A rare transient childhood presentation, as a consequence of immature *FMO3* expression, which is switched on after birth and increases with age;[12] young children who are heterozygous for a loss-of-function mutation or have certain combinations of polymorphisms of *FMO3* may exhibit mild symptoms of the disorder, which disappear with age.[10,11,27]
(3) Unusually, as a consequence of viral hepatitis, liver disease, or major transient overload of dietary precursors of TMA with the coexistence of function-altering polymorphisms of *FMO3*.
Prenatal diagnosis is possible if the disease-causing mutations in the family have been identified.

2. TEST CHARACTERISTICS

	Genotype or disease		A: true positives B: false positives	C: false negative D: true negative
	Present	Absent		
Test				
Pos.	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Neg.	C	D	Positive predictive value:	A/(A+B)
			Negative predictive value:	D/(C+D)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
Insufficient data to comment.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Insufficient data to comment.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Unknown. However, molecular genetic tests should distinguish between mutations that abolish or severely affect FMO3 activity and, thus, cause severe primary trimethylaminuria, from those that have a relatively moderate effect, resulting in mild or transient forms of the disorder. But acquired and secondary forms of trimethylaminuria, which are not caused by mutations, would not give a positive genetic test.

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Only individuals who have tested positive for trimethylaminuria by urinary analysis, or their relatives, will be genetically tested.

2.5 Positive clinical predictive value
(life-time risk to develop the disease if the test is positive)
Unknown. Only those with a biochemical diagnosis of trimethylaminuria are tested.

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
Close to 100%, if known causative mutations have been identified in the index patient.

Index case in that family had not been tested:
Unknown. Only patients that present with symptoms are analysed.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☒
	Electrophysiology	☐
	Other (please describe)	Clinically trimethylaminuria is characterized by a body odour resembling that of rotten or decaying fish. However, diagnosis based on smell is unreliable: the odour is often episodic, it may be caused by chemicals other than trimethylamine, and not all individuals can detect the smell of trimethylamine.[28] Note: on the basis of smell, trimethylaminuria can be difficult to distinguish from other conditions that give rise to an unpleasant body odour, including poor hygiene, forms of gingivitis and blood-borne halitosis,[29] or the rare inherited metabolic disorder dimethylglycinuria, caused by a deficiency of dimethylglycine dehydrogenase.[30] Biochemistry: diagnosis is based on the percent of total trimethylamine (free trimethylamine plus the non-odorous trimethylamine *N*-oxide) excreted in the urine as the unmetabolized free amine.[6,24,31] • >40%: severe trimethylaminuria. • 10-39%: mild trimethylaminuria. • <10%: unaffected. Note: urinary tract infections, bacterial vaginosis, advanced liver or kidney disease and cervical cancer can

(Continued)

	result in large amounts of trimethylamine in the urine. But, in contrast to the inherited form of trimethylaminuria, in these cases the trimethylamine/trimethylamine *N*-oxide ratio is normal. To distinguish transient or episodic forms of trimethylaminuria from the primary inherited form, biochemical testing should be performed on two separate occasions. Unaffected women may have a short episode of trimethylaminuria at the onset of and during menstruation,[26] so females should not be tested during this time. Because of the importance of intestinal bacteria in the production of trimethylamine from dietary precursors, variations in intestinal microbiota might affect the results of the diagnostic test. Under normal dietary conditions, heterozygotes cannot be distinguished from unaffected individuals.[31] However, heterozygous carriers can be detected after administration of a 'trimethylamine load' of 600 mg, given orally in a gelatine capsule.[21,32]

3.1.2 Describe the burden of alternative diagnostic methods to the patient

Very low. However, one individual developed an adverse reaction, with fever and vomiting, after a choline challenge.[33]

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

The initial diagnosis of trimethylaminuria is usually biochemical. Genetic testing will help to confirm the diagnosis, distinguish the various genetic and non-genetic forms of the disorder and identify asymptomatic heterozygous carriers.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐	
Yes	☒	
	Therapy (please describe)	Strategies for treatment of the disorder[6,31] and best-practice guidelines[23,33] have been published. In general, the greater the effect of a mutation on the activity of FMO3, the more severe the symptoms and the less responsive the individual will be to treatment. The main treatment strategy is dietary restriction of precursors of trimethylamine, including choline, lecithin and trimethylamine *N*-oxide. Choline is present in high amounts in some foods such as eggs, offal (liver, kidney), peas, beans, peanuts and soya products. *Brassica* vegetables (such as Brussel sprouts, broccoli, cabbage, cauliflower) are thought to inhibit FMO activity, hence, their intake should be minimized. Trimethylamine *N*-oxide is present in seafood. Choline is essential in the fetus and in young infants for nerve and brain development, and should not be over-restricted in infants, children and pregnant or lactating women. Nutritionally balanced, choline-restricted diets suitable for treatment of the disorder have been developed.[34] Individuals with mild or moderate forms of the disorder usually respond well. For individuals who respond poorly to diet, a stepwise approach to other therapies should be instituted. Intermittent brief courses of antibiotics such as metronidazole used cautiously (eg, perimenstrually in females or for stressful social occasions) have been found to be effective.[33,35,36] In the case of mutations that do not completely abolish FMO3 activity, supplements of riboflavin, a precursor of the flavin adenine dinucleotide prosthetic group of FMO3, might help maximize residual enzyme activity. At present there is only anecdotal evidence of efficacy, and oral riboflavin supplementation requires careful monitoring because gastrointestinal intolerance can occur, especially in children. Other forms of treatment are aimed at sequestering trimethylamine produced in the gut, by taking dietary supplements of copper chlorophyllin or activated charcoal.[37]
	Prognosis (please describe)	Affected individuals appear normal and healthy. No physical symptoms are associated with trimethylaminuria, but the unpleasant body odour characteristic of the disorder often results in social and psychological problems,[6,21,38] which can have serious effects on personal and working lives. These may include: • In childhood, being shunned, ridiculed or bullied at school, leading to aggressive or disruptive behaviour 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 behaviour, desperation and suicidal tendencies. For individuals with primary genetic trimethylaminuria, symptoms are usually present from birth. The condition may worsen during puberty and, in females, is 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.
	Management (please describe)	Affected individuals should avoid: 1. Foods with a high content of precursors of trimethylamine or inhibitors of FMO3 activity, for instance, eggs, offal (liver and kidney), legumes, *Brassicas*, soya products and seafood (fish, crustaceans and cephalopods), should be avoided or eaten in moderation. Freshwater fish are not a problem. 2. Drugs that are metabolized by FMO3, which will exacerbate the condition by competition for residual FMO3 activity and may cause adverse effects. Examples include the antipsychotic clozapine, the monoamine oxidase inhibitor deprenyl, the anti-histamine ranitidine, the anti-oestrogen tamoxifen and the anti-inflammatories sulindac and benzydamine.[7] 3. Food supplements and 'health' foods that contain high amounts of choline and lecithin. 4. Factors that promote sweating, such as fever, exercise, stress and emotional upsets. Trimethylamine is a strong base (pKa 9.8). Thus, at pH 6.0, $<0.02\%$ 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 to retain secreted trimethylamine in a less volatile salt form that can be removed by washing.[39]

3.2 Predictive setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test result is positive (please describe):
Not applicable.

If the test result is negative (please describe):
Not applicable.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?
Not applicable.

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
A genetic test should distinguish primary inherited and secondary forms trimethylaminuria, mild and severe forms of the inherited disorder, and identify heterozygous carriers.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
The parents and offspring of an individual affected by primary inherited trimethylaminuria will be obligate heterozygotes. Sibs of an affected individual would have to be genetically tested to establish whether they were affected, unaffected or a heterozygous carrier.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Not applicable.

3.4 Prenatal diagnosis
(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?
Yes, but it is not indicated.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

Affected individuals and their families benefit from counselling. Realization that the problem is the result of a recognized medical condition may help.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 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* 1997; **17**: 491–494.
2 Treacy EP, Akerman BR, Chow LML *et al*: Mutations of the flavin-containing monooxygenase gene (FMO3) cause trimethylaminuria, a defect in detoxication. *Hum Mol Genet* 1998; **7**: 839–845.
3 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**: 128–135.
4 Hernandez D, Addou S, Lee D, Orengo C, Shephard EA, Phillips IR: Trimethylaminuria and a human *FMO3* mutation database. *Hum Mutat* 2003; **22**: 209–213.
5 Phillips IR, Shephard EA: Flavin-containing monooxygenases: mutations, disease and drug response. *Trends Pharmacol Sci* 2008; **29**: 294–301.
6 Phillips IR, Shephard EA: *Trimethylaminuria*. GeneReviews at GeneTests: Medical Genetics Information Resource (database online): University of Washington, Seattle, USA, 1997–2011. Available at http://www.ncbi.nlm.nih.gov/books/NBK1103/, updated 2011.
7 Phillips IR, Francois AA, Shephard EA: The flavin-containing monoooxygenases (FMOs): genetic variation and its consequences for the metabolism of therapeutic drugs. *Curr Pharmacogenomics* 2007; **5**: 292–313.
8 Koukouritaki SB, Poch MT, Henderson MC *et al*: Identification and functional analysis of common human flavin-containing monooxygenase 3 genetic variants. *J Pharmacol Exp Ther* 2007; **320**: 266–273.
9 Koukouritaki SB, Hines RN: Flavin-containing monooxygenase genetic polymorphism: impact on chemical metabolism and drug development. *Pharmacogenomics* 2005; **6**: 807–822.
10 Zschocke J, Kohlmueller D, Quak E, Meissner T, Hoffmann GF, Mayatepek E: Mild trimethylaminuria caused by common variants in FMO3 gene. *Lancet* 1999; **354**: 834–835.
11 Zschocke J, Mayatepek E: Biochemical and molecular studies in mild flavin monooxygenase 3 deficiency. *J Inherit Metab Dis* 2000; **23**: 378–382.
12 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**: 236–243.
13 Koukouritaki SB, Poch MT, Cabacungan ET, McCarver DG, Hines RN: Discovery of novel flavin-containing monooxygenase 3 (*FMO3*) single nucleotide polymorphisms and functional analysis of upstream haplotype variants. *Mol Pharmacol* 2005; **68**: 383–392.
14 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**: 169–174.
15 Murphy HC, Dolphin CT, Janmohamed A *et al*: A novel mutation in the flavin-containing monooxygenase 3 gene, FM03, that causes fish-odour syndrome: activity of the mutant enzyme assessed by proton NMR spectroscopy. *Pharmacogenetics* 2000; **10**: 439–451.
16 Allerston CK, Vetti HH, Houge G, Phillips IR, Shephard EA: A novel mutation in the flavin-containing monooxygenase 3 gene (FMO3) of a Norwegian family causes trimethylaminuria. *Mol Genet Metab* 2009; **98**: 198–202.
17 Dolphin CT, Janmohamed A, Smith RL, Shephard EA, Phillips IR: Compound heterozygosity for missense mutations in the flavin-containing monooxygenase 3 (FM03) gene in patients with fish-odour syndrome. *Pharmacogenetics* 2000; **10**: 799–807.
18 Al-Waiz M, Ayesh R, Mitchell SC, Idle JR, Smith RL: A genetic polymorphism of the *N*-oxidation of trimethylamine in humans. *Clin Pharmacol Ther* 1987; **42**: 588–594.
19 Wise PM, Eades J, Tjoa S, Fennessey PV, Preti G: Individuals reporting idiopathic malodor production: demographics and incidence of trimethylaminuria. *Am J Med* 2011; **124**: 1058–1063.
20 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.
21 Mitchell SC, Smith RL: Trimethylaminuria: the fish malodor syndrome. *Drug Metab Dispos* 2001; **29**: 517–521.
22 Mitchell S: Trimethylaminuria (fish-odour syndrome) and oral malodour. *Oral Dis* 2005; **11** (Suppl 1): 10–13.
23 Treacy EP: *Trimethylaminuria and deficiency of flavin-containing monooxygenase Type 3 (FMO3)*. www.ommbid.com. New York: McGraw-Hill, 2007, Chapter 88.1.
24 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.
25 Zhang AQ, Mitchell SC, Smith RL: Exacerbation of symptoms of fish-odour syndrome during menstruation. *Lancet* 1996; **348**: 1740–1741.
26 Shimizu M, Cashman JR, Yamazaki H: Transient trimethylaminuria related to menstruation. *BMC Med Genet* 2007; **8**: 2.
27 Mayatepek E, Kohlmüller D: Transient trimethylaminuria in childhood. *Acta Paediatrica* 1998; **87**: 1205–1207.
28 Heaton P: Ability to detect malodour might be genetic (letter; comment). *BMJ* 1993; **307**: 1009.
29 Tangerman A: Halitosis in medicine: a review. *Int Dent J* 2002; **52** (Suppl 3): 201–206.
30 Binzak BA, Wevers RA, Moolenaar SH *et al*: Cloning of dimethylglycine dehydrogenase and a new human inborn error of metabolism, dimethylglycine dehydrogenase deficiency. *Am J Hum Genet* 2001; **68**: 839–847.
31 Cashman JR, Camp K, Fakharzadeh SS *et al*: Biochemical and clinical aspects of the human flavin-containing monooxygenase form 3 (FMO3) related to trimethylaminuria. *Curr Drug Metab* 2003; **4**: 151–170.
32 Al-Waiz M, Ayesh R, Mitchell SC, Idle JR, Smith RL: Trimethylaminuria: the detection of carriers using a trimethylamine load test. *J Inherit Metab Dis* 1989; **12**: 80–85.

33 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**: 162–172.
34 Busby MG, Fischer L, da Costa KA, Thompson D, Mar MH, Zeisel SH: Choline- and betaine-defined diets for use in clinical research and for the management of trimethylaminuria. *J Am Diet Assoc* 2004; **104**: 1836–1845.
35 Treacy E, Johnson D, Pitt JJ, Danks DM: Trimethylaminuria, fish odour syndrome: a new method of detection and response to treatment with metronidazole. *J Inherit Metab Dis* 1995; **18**: 306–312.
36 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**: 203–205.
37 Yamazaki H, Fujieda M, Togashi M *et al*: Effects of the dietary supplements, activated charcoal and copper chlorophyllin, on urinary excretion of trimethylamine in Japanese trimethylaminuria patients. *Life Sci* 2004; **74**: 2739–2747.
38 Todd WA: Psychosocial problems as the major complication of an adolescent with trimethylaminuria. *J Pediatr* 1979; **94**: 936–937.
39 Wilcken B: Acid soaps in the fish odour syndrome. *Br J Med* 1993; **307**: 1497.