**Introduction**

Betaine (trimethylglycine) is essential for re-methylation therapy in Homocystinuria. Reports of a fishy body odour as a side effect of betaine ingestion in some patients suggest dimethylglycine or trimethylamine as possible causes of odour. Associated body odour might cause patients to withdraw from betaine therapy with adverse clinical consequences reflected by increased levels of total homocysteine. TMAU can be caused by both increased enterobacterial production of trimethylamine (TMA) and deficiency of the hepatic cytochrome enzyme flavin containing mono-oxygenase type 3 (FMO3) [EC1.14.1.38] [OMIM 136132]. The latter is referred to as Primary TMAU (TMAU1) and the former as Secondary TMAU (TMAU2). Riboflavin acts as a co-factor for FMO3 and its use has been associated with reduced TMA excretion in some cases of TMAU.

**Case**

The patient who presented at 7 years with dislocated lenses was diagnosed with Homocystinuria (partially pyridoxine responsive) with plasma total homocysteine (HcYS) of 145 µmol/L (121 after B6). Betaine therapy was started at a dose of 3x2 grams/day (HcYS = 59) and was increased to 2x8 grams/day by 15 years of age. At 17 years of age and friends started to notice a strong FISHY ODOUR. This odour caused unfortunate social problems for this patient at a particularly sensitive time of life. Current DAILY medication: BETAINA 8g x 2 / PYRIDOXINE 600mg / VITAMIN C 5mg / FOLIC ACID 10mg / RIBOFLAVIN 100mg x 2

Protein restriction 50g per day. Vitamin B12 injection 1mg every 3 months.

Following RIBOFLAVIN therapy the fishy body odour diminished and was less of a problem (family members could barely detect it), although the fishy breath odour is still evident to the patient, who remains on riboflavin, high-dose betaine and a normal diet.

**Methods**

**TMA**

Urinary measurement (with TMA-oxide by titanium chloride reduction) alkalinised samples heated in headspace autosampler. GCMS of gaseous TMA. Stable isotope ratio TMA:d9-TMA for quantitation.

**DMG**

Urine with d2-DMG internal standard by ionophosphilisation and GCMS of tert-butyldimethylsilyl ester.

**DNA**

Patient genomic DNA was extracted from peripheral blood samples using the Magnetic Separation Module I (Chemagen). Genomic DNA was amplified by PCR using Red Hot Taq polymerase (ABGene) at 37°C. Primers were designed to amplify the exon region and at least 25bp of the intron/exon boundaries of exons 2-9 of the FMO3 gene (Accession number NM_006894; primer sequences available on request). Cycle sequencing was performed using standard M13 primers attached to the gene specific primers, and samples electrophoresed on ABI3730 DNA analysers.

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Pre-riboflavin</th>
<th>After 32 weeks on riboflavin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary TMA</td>
<td>392</td>
<td>22</td>
</tr>
<tr>
<td>Free TMA / Total TMA</td>
<td>93%</td>
<td>17%</td>
</tr>
<tr>
<td>Urinary DMG</td>
<td>1,076</td>
<td>2,100</td>
</tr>
<tr>
<td>[Plasma HcYS (µmol/L)]</td>
<td>[133]</td>
<td>[111]</td>
</tr>
</tbody>
</table>

**FMO3 gene:** HOMOZYGOUS for variant allele [Glu158Lys;Glu308Gly] consistent with a diagnosis of mild or intermittent primary trimethylaminuria

**Discussion 1.** This homocystinuria patient with TMAU may demonstrate a significant conversion of betaine to TMA when high doses are used. Previous reports of a body odour with betaine suggest that at high doses the odour may be due to TMA. DMG has also been associated with fish odour, however when our patient’s odour reduced, DMG was maintained at high values (high DMG without odour also reported for glutaric aciduria type2).

**Discussion 2.** Fish odour during betaine therapy has led to a diagnosis of a mild FMO3 deficiency genotype first described in 2000 (ref.2) with a possible incidence of > 1%. This common variant allele may affect other Homocystinuria patients on betaine therapy causing what may be a minor conversion of betaine to TMA to become a significant challenge resulting in betaine-related TMA body odour, although potentially treatable to some degree by RIBOFLAVIN.