

a case for discomfort

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There is no life without smells. In the wild, smells – and the capacity to sense them – are the basis for survival for plants and animals. They are used to attract, seduce, repel or protect, and are with us night and day; so much so that life would seem very bland without them. On the whole, for any given species, a pleasant perfume implies that all is well, while a bad one suggests that something is wrong. The smells the human body gives off are a combination of who we are, what we eat, and the general state of certain metabolic cycles. When part of a metabolic cycle is deficient, a change in our bodily odours can occur. This is the unfortunate case of what is known as the ‘fish malodour syndrome’, or trimethylaminuria. People afflicted with trimethylaminuria release a smell of rotting fish. The symptoms were first clinically described in the 1970s and, in the 1990s, scientists discovered the cause: a malfunction of an enzyme known as flavin-containing monooxygenase 3.



"Ish Fish", Sergey Engel (Israel)

Courtesy of the artist

Though the condition was first clearly described in the 1970s, there is little doubt that it had already occurred in a human being. Anecdotal descriptions appear in the ancient literature. The first known depiction goes back almost 3'000 years and recounts the case of an Indian woman who smelt so bad that she had been cast from society. About 750 years ago, it seems that the syndrome was the cause of suicide amongst Thai concubines. Shakespeare himself, obviously came across the condition since he portrays a character who smells of fish in 'The Tempest'; a 'Poor John' he calls him which, in

those days, referred to a salted and dried hake. Various other descriptions followed but the first official clinical report was made in the 1970s, on a six year old girl who also suffered from Noonan syndrome*.

Consequently, for a time, not only was it believed that trimethylaminuria was rare but that it was probably linked to other afflictions, such as Noonan syndrome. Over the years, however, scientists have discovered that trimethylaminuria is hereditary and caused by the presence of too much trimethylamine in bodily excretions, i.e. in breath, sweat, saliva and vaginal secretions.

Trimethylamine – or TMA – is the result of bacterial digestion of foods that are rich in choline and carnitine, such as eggs, liver, peas, soybeans and sea fish for example. When everything is working properly, TMA is modified by our liver so that it becomes water soluble. This procedure not only facilitates TMA excretion but also makes the amine odourless. On the whole, for 50 mg of TMA, a human being usually excretes about 1 mg of non-modified 'smelly' TMA, while the rest has been transformed and is odourless.

What is happening inside someone who is suffering from fish malodour syndrome? There are a number of enzymes in our liver that spend their time modifying chemical compounds for further use or excretion. One of these enzymes is a flavin-containing monooxygenase of which

there are five different kinds: FMO1 to 5. Flavin-containing monooxygenase 3 – or FMO3 – is the major catalytic form found in the liver. In normal conditions, FMO3 oxidises incoming TMA, which is further modified to increase water solubility and hence facilitate excretion. The oxidation of TMA by FMO3 acts like a deodorant and wipes away its fishy smell. If FMO3 is faulty, however, the oxidising step is skipped and TMA leaves our body the way it entered it: with a smell.

So far, 150 different mutations have been found in FMO3, which alter the enzyme in such a way that it can no longer work the way it usually does. Despite this abundance of mutations, researchers are still not clear on how the mutations affect TMA oxidation. What they do know, though, is that the mutations do not affect the flavin binding sites. But they may affect the protein's tertiary structure, or directly affect the site where TMA is supposed to bind for its subsequent oxidation. And, if TMA is unable to bind to FMO3, it will not be oxidised.

An intriguing discovery is that fish malodour syndrome seems to go hand in hand with other conditions. Psychological disorders, such as depression and psychoses are frequently stated. Naturally, the simple fact of not smelling nice in society is something extremely difficult to deal with and hardly surprising that it causes

* *See Spotlight issue 121, 'The Matchmaker'.*

individuals to develop antisocial behaviour. Especially as the syndrome can affect children at a very early age. Despite this, researchers are now positive that fish malodour syndrome is frequently associated with neurochemical disorders. This is probably due to the fact that – besides TMA – FMO3 also oxidises other amines which may have a direct effect on depression and psychoses. Foreign compounds that enter our bodies – such as pollutants or environmental chemicals that predispose us to carcinogenesis and birth defects for instance – may also be affected by a deficiency in FMO3.

In the case of fish malodour syndrome, very little can be done. Diets that diminish the amount of TMA entering the body can be followed. Medication to reduce our floral bacterial activity – and hence the amount of TMA released – can also be taken. In the future, we could imagine engineering microorganisms to produce FMO3 in our digestive tract, or the development of suppressants that are able to mask the rotten fish smell. Of course, gene therapy could be used to replace the deficient FMO3 gene by a healthy one... It is always an astonishing thing to realise how such minute changes in our chemical composition are able to affect a person's whole life. How vulnerable each one of us is with respect to our chemical make-up.

Cross-references to UniProt

Dimethylaniline monooxygenase [N-oxide-forming] 3, *Homo sapiens* (Human) : P31513

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