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**New genomic study further explains thyroid treatment problems.**

I am very grateful to the patient who alerted me to the paper by Panicker et al (*J Clin Endocrinol Metab* 94: 1623–1629, 2009) that shows one reason why some people do better on T4 plus T3 than they do on T4 alone. Their introduction says; *...a significant number of patients report persistent symptoms despite titration of T4 replacement to adequate serum levels of thyroid hormone and normalization of TSH levels.*

They identified a gene, DIO2, which is one of three very similar genes; DIO1and DIO2 code for the enzyme deiodinase that converts T4 (thyroxine) into the much more active hormone T3 (triiodothyronine). But DIO1 is not present inside the brain, and DIO3 produces a deactivating enzyme, so inside the central nervous system only DIO2 activates the hormone.

A tiny alteration in the DIO2 gene, known as a polymorphism (in fact a Single Nucleotide Polymorphism, or SNiP), can mean that while the rest of the body gets plenty of T3, and the blood tests look accordingly normal and healthy, inside the brain there is less T3. This is a good illustration of what we are finding genomics can do. Remember that we all have two copies of every gene, every chromosome; one from your mother, one from your father. So you can have both copies normal, both copies abnormal (with the SNiP) or one of each.

What these researchers found is firstly that, when on treatment with T4 alone, those with one of each gene felt worse than those with two normal genes, and those with two SNiP'd genes felt even worse. The difference wasn't very big though - about 10-15% in the scores.

When it came to treatment, those with two normal copies did the same on both regimes; those with one of each type did somewhat better on T4 and T3, and those with two SNiP'd copies did even better, which brought them up to the level of wellness that the ones with "normal" genes achieved on T4 alone.

Interestingly, although the chemical difference seems to be inside the brain, the difference in scores showed on items like the General Health Questionnaire (GHQ), and not on the scales for anxiety and depression (HAD).

Although only about 2 in 12 of us has two SNiP'd genes, 5 out of 12 have one, so only 5 out of 12 have two normal genes. In other words, more than half of us are "abnormal" in this way - no, correct that, more than half of the study population, who all had a diagnosis of underactive thyroid, and were on thyroxine treatment already. So if you have a thyroid problem and are on T4, there is at least an even chance that you would be better off on T3 as well.

And we can tell which genes you have. I emailed my colleagues at the laboratory in Luxembourg where we send much of our genomics, and they have been at work setting up the test. We've started sending samples already. The cost for testing this one gene will be no more than £50.

If I know one thing about laboratory testing, it's that you can't always get what you want. Some people will be disappointed to find that they have the good version of the gene, for instance. But it seems to me to be an open and shut case for others; if you are on T4 but disapponted with progress, and you have the SNiP'd gene, you deserve at least a trial of T4 plus T3. And the ordinary thyroid function tests won't help you sort this out.