



## Two single nucleotide polymorphisms (SNPs) in thyroid hormone receptor-alpha may affect the risk of obesity and dyslipidemia

6-year period was significantly increased in GG homozygotes (odds ratio, 2.93; 95% CI, 1.05 to 6.95) after adjusting for age, sex, education, and thyroid function. Analysis of the normal French cohort detected associations either with BMI or with log-transformed triglyceride levels, depending on whether a G allele was considered dominant or recessive. In the high-cardiovascular-risk group (many of whom were obese), there was no significant association between SNPs at rs1568400 and BMI, but there was a significant inter-

action term between BMI and fat intake ( $P < 0.001$ ). In patients whose saturated fat intake was in the highest tertile, those with G/A or G/G had a significantly higher BMI than those with A/A, after controlling for energy intake and physical activity.

### Conclusions

Two  $THR\alpha$  gene polymorphisms display a moderate association with obesity, high triglycerides, and/or development of obesity.

### ANALYSIS AND COMMENTARY ● ● ● ● ●

Differences in the function of  $THR\alpha$  and  $THR\beta$  are clearly evident in mice and patients with mutations in the  $THR$  genes, and  $THR\alpha$  has been implicated in adipocyte growth and adrenergic sensitivity. Studies in vitro and on cells in culture, however, have not shown as much gene specificity, possibly indicating the importance of specific intracellular modifications of the receptors (1). What is more, the cellular responses to  $THR\alpha$  expression depend on how the transcripts are spliced. The authors called attention to the fact that the SNP at rs12939700 is located at the end of a sequence that determines whether  $THR\alpha$  transcripts will be spliced to make  $THR\alpha 1$  mRNA (the active isoform) or to make  $THR\alpha 2$  mRNA (the antagonistic isoform). Furthermore, this group of researchers previously studied factors that regulate  $THR\alpha$  splicing, so it would be interesting to learn whether the ratio of the two  $THR\alpha$  isoforms in the patient's fat differs from normal and/or whether any of the patient's splicing factors have unusual SNPs or mutations. Obviously, the A/C heterozygosity found at rs12939700 in the index patient is not solely responsible for her clinical features, although it is interesting that patients in the high-cardiovascular-risk group who had A/A or A/C were more likely to be heavier and to have a BMI  $> 30$ . Additional clinical details on the patient (e.g., cardiovascular responses to exercise, evidence of Hashimoto's thyroiditis, sex hormone-binding globulin levels, etc.) would be interesting to know. Mutations or unusual SNPs in other

genes known to influence thyroid receptor action, such as heterodimerization partners, coactivators, corepressors of  $THR\alpha$ , covalent modifiers or cytoplasmic transporters of  $THR\alpha$ , as well as thyroid hormone transporters and deiodinases could also be implicated. It is also quite possible that this SNP is not responsible for the associations with obesity but is simply in linkage disequilibrium with another region that is the actual cause of the metabolic changes observed. Plainly, studies on the SNP at rs12939700 need to be repeated in larger samples.

It was not clear whether the index patient was ever genotyped for the SNP at rs15684000, which the authors showed had some associations with increased BMI and triglycerides in two normal cohorts, whereas in the cohort at high risk for cardiovascular disease, the SNP analysis indicated a significant interaction between high saturated fat intake and obesity.


Genomewide association studies have uncovered several dozen gene variants much more highly associated with risk for obesity in the general population than either of the  $THR\alpha$  SNPs, including some also known to be associated with thyroid hormone action (e.g., TUB, BDNF) or with thyroid hormone metabolism (e.g., TEB4) (2). Nonetheless, either of the SNPs in  $THR\alpha$  reported in the current paper could be involved in the development of obesity indirectly, say in individuals who also have variants in other genes involved in thyroid or lipid pathways. *continued on next page*

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### References

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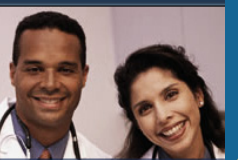
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