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

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SUMMARY

Background

Thyroid and lipid pathways interact at many levels. The authors of the current paper observed a patient with obesity and hypothyroidism who, while being overreplaced with L-T_4, continued to have bradycardia despite having a high free T_4, an undetectable TSH, and a 40-lb weight loss, although the body-mass index (BMI) remained above 30. They sequenced her entire thyroid hormone receptor-α (THRα) locus, and found a relatively uncommon single nucleotide polymorphism (SNP). The authors then examined the frequency of this mutation in samples from a cohort of patients at high risk for cardiovascular disease. They also examined the frequency of a more common SNP in THRα in two normal cohorts to determine whether either of these SNPs was associated with obesity or serum lipid disorders.

Methods

The authors had access to blood samples collected between 2003 and 2007 from a cohort of 4734 Spaniards at high risk of cardiovascular disease who had at least three risk factors (history of hypertension or dyslipidemia, BMI <25 , current smoker or family history of premature cardiovascular disease) or two risk factors plus a diagnosis of type 2 diabetes. Blood samples were also available from a cohort of 3417 healthy Spaniards from four regions of Spain taken between 1996 and 1999, as well as additional samples obtained between 2003 and 2005 from 2139 of the same subjects. Finally, 2325 normal French samples taken between 1995 and 1997 were studied. The samples were analyzed for TSH, free T_4 and free T_3 levels. The two SNPs in THRα were a relatively common SNP at residue (rs) 1568400, which is in linkage disequilibrium with the less common allele at rs12939700 found in the index case. Student's t-test and analysis of variance were used to compare crude differences of means between genotypes, while more complicated analyses were used to assess SNP associations with risks for obesity and high triglycerides, and to assess the interaction between the THRα polymorphisms and fat intake.

Results

In the cohort at high risk for cardiovascular disease, analysis for the SNP at rs12939700 (C/A in the index case) showed that 93% had C/C, 6.8% had C/A and 0.2% had A/A. Those with A/A or A/C were likely to be heavier and to have a BMI > 30 (P = 0.03).

Analysis for the SNP at rs15684000 in the normal Spanish cohort showed that 50% had A/A, 42% had A/G, and 8% had G/G. Those with A/G or G/G had a higher total cholesterol, fasting triglyceride levels, BMI, and larger waist circumference. The higher BMI remained significant after adjusting for age, sex, triglycerides and geographic region. In the subgroup of the same normal subjects who gave samples 6 years later, the risk of having developed obesity over the

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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 interaction 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 THRα gene polymorphisms display a moderate association with obesity, high triglycerides, and/or development of obesity.

ANALYSIS AND COMMENTARY

Differences in the function of THRα and THRβ are clearly evident in mice and patients with mutations in the THR genes, and THRα 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 THRα 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 THRα transcripts will be spliced to make THRα1 mRNA (the active isoform) or to make THRα2 mRNA (the antagonistic isoform). Furthermore, this group of researchers previously studied factors that regulate THRα splicing, so it would be interesting to learn whether the ratio of the two THRα 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 THRα, covalent modifiers or cytoplasmic transporters of THRα, 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 THRα SNPs, including some also known to be associated with thyroid hormone action (e.g., TUB, BNDF) or with thyroid hormone metabolism (e.g., TEB4) (2). Nonetheless, either of the SNPs in THRα 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.

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