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ORIGINAL ARTICLE

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Variants in MCT10 protein do not affect FT3 levels in athyreotic patients

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Abstract

Purpose Several single-nucleotide polymorphisms in genes encoding for transporters have been associated with serum thyroid hormone concentrations with inconsistent results. The aim of this study was to assess the clinical significance of the rs17606253 in *SLC16A10* gene alone and in combination with the *DIO2* Thr92Ala variation in athyreotic patients.

Methods One-hundred patients submitted to total thyroidectomy and treated with levothyroxine were included. Pre- and post surgical serum TSH levels did not differ by more than ± 0.5 mIU/l.

Results Both patients carrying the wild-type allele or heterozygous for rs17606253 in *SLC16A10* gene had a significant reduction in FT3 post surgical levels ($p = 0.01$ and $p < 0.0001$, respectively) while Thr92Ala in *DIO2* gene was associated with reduced FT3 levels for heterozygous and rare homozygous patients ($p < 0.0001$ and $p = 0.01$, respectively). We identified two groups ("FT3 unchanged" and "FT3 reduced") using a cutoff of at least 0.5 pg/ml as a significant variation between pre- and post surgical FT3 values. In this case, the rs17606253 was not statistically associated with reduced FT3 levels at genotype and allele levels. On the contrary, the Thr92Ala in *DIO2* gene was confirmed statistically associated with reduced FT3 levels after surgery with a $p = 0.035$ at genotype level and $p = 0.014$ at allele level.

Conclusions We confirmed the role of *DIO2* Thr92Ala polymorphism on T3 levels. On the contrary, *SLC16A1* rs17606253 polymorphism did not impair hormone levels in athyreotic patients treated with levothyroxine therapy.

Keywords MCT10 · DIO2 · Thyroid hormone levels · Gene polymorphisms

Introduction

Hypothyroidism is very common and affects up to 10% of the female population [1]. Although levothyroxine (LT4) replacement is the standard of care for hypothyroid patients, many subjects treated with LT4 complain of symptoms of hypothyroidism (memory loss, weight gain, fatigue, depression, and reduced quality of life) despite values of thyroid-stimulating hormone (TSH) in the reference range [2–4]. In athyreotic patients, both circulating and intracellular T3 levels strictly depend on deiodinase-mediated T4-to-T3 conversion [5]. However, in ~20% of patients, LT4 did not ensure physiological T3 levels in spite of TSH levels in the reference range, while physiological T3 levels were obtained in the presence of suppressed TSH [6–10]. In healthy subjects, conversion of T4 to T3 is normally mediated by type 1 (D1) and type 2 deiodinases (D2), which are widely expressed in organs and tissues (D1, in liver, kidney and thyroid, and D2 in central nervous system, bone, skin, pituitary gland, brown adipose tissue, and muscles). A polymorphism (SNP) in the *DIO1* gene, rs2235544, was strongly associated with the free T3 to free T4 ratio by applying a genome-wide approach. The rare allele of this SNP was associated with increased D1 function [11, 12]. Comparing D1 and D2 enzymes, D2 has a higher catalytic efficiency than D1, and, in euthyroid humans, D2 accounts for ~70% of circulating T3, whereas only ~15% derives from D1-mediated T4 activation [13]. Human D2 is encoded by the type II iodothyronine deiodinase (*DIO2*) gene. We have recently demonstrated an association between low FT3 values and the *DIO2* gene polymorphism Thr92Ala in athyreotic patients [14]. In details, the mean post surgical FT3 levels were significantly lower in patients carrying the

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mutated allele(s) than in those carrying the wild-type allele. We also found that endogenous wild-type D2 and Thr92Ala differ in protein stability and Thr92Ala reduced D2-mediated T4 to T3 conversion. Another report [15] studied the effects of genetic variants in 68 genes involved with thyroid hormone (TH) pathways on serum TSH and FT4 levels in more than 3000 subjects. Using a large-scale association analysis, they found a relationship between the intronic polymorphism rs17606253 in *SLC16A10* gene and FT4. The Solute Carrier Family 16 Member 10 (*SLC16A10)* gene encodes for Monocarboxylate transporter 10 (MCT10), which allows both uptake and efflux of T3 and T4 [16]. Considering MCT10 wide tissue distribution, including intestine, kidney, liver, heart, skeletal muscle, and placenta [17] and its role in T3/T4 transport, it is quite likely that MCT10 mutations/polymorphisms are associated with significant alterations in tissue and/or serum thyroid hormone concentration. Carlé et al. [18] published a double-blind study in which patients (no subjected to surgery) carrying both the Thr92Ala DIO2 and the rs17606253 MCT10 polymorphisms preferred the combined therapy LT4 + LT3. Nevertheless, no variants in MCT10 protein [19] have been clearly associated with TH levels in athyreotic patients, yet. The aim of this study was to assess the clinical and biochemical significance of the *SLC16A10* SNP alone and in combination with the *DIO2* Thr92Ala in athyreotic patients.

Patients and methods

Patients' selection

Patients submitted to total thyroidectomy were enrolled in this study. Inclusion criteria were: thyroid profile data obtained within 10 months of surgery, and a post surgical thyroid profile obtained at least 6 months after achievement of a stable thyroid hormone status on L-T4 therapy. In addition, pre- and post surgical serum TSH levels should not differ by more than ± 0.5 mIU/l. We excluded patients with an abnormal thyroid profile (hypo- or hyperthyroidism) before surgery, patients receiving drugs that can interfere with thyroid function, and patients affected by malabsorption-related conditions. Based on these criteria, we recruited 100 patients for the study with suspicious/malignant cytology (Thy4/Thy5) or multinodular goiter (73% females with a mean age of 53.1 ± 14.3 years, range 20–78 years; 27% males with a mean age of 54,8 ± 15,4 years, range 24–76 years). Most of patients in the female group (65%) were in a post menopausal stage and patients taking oral contraceptives had been excluded from the study. At final histology, 6/100 (6%) patients had a benign goiter and 94/100 (94%) had differentiated thyroid carcinoma and were submitted to radioiodine ablation (131-I). All patients had been evaluated with neck ultrasound after surgery and none of them had a residual thyroid tissue. Immediately after surgery, patients were treated with LT4 to obtain comparable pre-surgical TSH levels, with a mean dose/kg of 1.54 µg of LT4. Fasting blood samples were collected at 08.00–09.00 h before patients assumed the LT4 tablet, and all determinations were performed with a chemiluminescent immunometric assay (Access Immunoassay Systems 2006, Beckman Coulter, Milan, Italy). Normal ranges in our laboratory were 2.5–4.5 pg/ml for FT3, 5.8–16.4 pg/ml for FT4 and 0.4-4-0 mIU/l for TSH. In our laboratory the inter-assay variation of the FT3 assay was 8%, which corresponds to ± 0.26 pg/ml. Thus, we arbitrarily selected a change of at least 0.5 pg/ml as a significant variation between pre- and post surgical FT3 value.

Genetic analysis

For gene analysis, each patient provided written informed consent to the study. Genomic DNA was extracted with the QIAamp DNA Micro Kit (Qiagen, Milan, Italy) according to kit instructions. DNA concentration was assessed with Nanodrop (Thermo Scientific, Milan, Italy). The rs17606253 SNP was analyzed by Q-PCR (Rotor-gene Q, Qiagen, Milan, Italy) using the pre-designed TaqMan SNP genotyping Assay (Applied Biosystem, Milan, Italy). Allelic discrimination plots clearly distinguish between WT, heterozygous and homozygous alleles [20]. Coding sequences of *SLC16A10* gene were analyzed by end point PCR, DHPLC, and direct sequencing. *DIO2* gene polymorphisms were investigated as described [14]. Primers and PCR conditions are available upon request.

Statistics

Association analyses were carried out by using the software package SPSS v13.0. Statistical significance was analyzed by the Mann-Whitney test in not normally distributed data (Tables 1 and 3). We used contingency tables to evaluate significant differences in data frequency. Interaction with SNP was tested by χ^2 analysis at genotype and allele levels. In addition to basic tests, the association of genotype with FT3 levels was evaluated assuming dominant and recessive models.

To evaluate the association between *DIO2* and *SLC16A10* polymorphisms with post surgical FT3 levels, patients were stratified according with the cut offs defined above (0.5 pg/ml for FT3 and 1.2 pg/ml for FT4). We defined "reduced FT3" when post surgical FT3 levels were at least lower than 0.5 pg/ml respect to pre-surgical FT3 values. Association analyses were carried out by χ^2 or Fischer's exact tests.

Table 1 Pre and post surgical FT3 levels according to DIO2 genotypes

	Pre-surgical FT3 (pg/ml)	Post surgical FT3 (pg/ml)	*p*
AA (no. 50)			
Mean ± SD	3.2 ± 0.35	3.1 ± 0.36	0.097
Range	2.4–3.9	2.6–4.1	
Median	3.2	3.1	
AG (no. 37)			
Mean ± SD	3.4 ± 0.52	3.0 ± 0.29	<0.0001
Range	2.7–5.4	2.5–3.9	
Median	3.3	2.9	
GG (no. 13)			
Mean ± SD	3.4 ± 0.37	2.9 ± 0.34	0.01
Range	2.9–4.2	2.5–3.6	
Median	3.4	2.9	

For the analysis of polymorphism association with FT3 post surgical levels, the simultaneous presence of risk alleles (rare alleles for each analyzed SNP) in patients' groups was considered. Association analyses were carried out by χ^2 test.

Results

Association of *DIO2* rs225014 polymorphism with FT3 post surgical levels

Table 1 shows pre- and post surgical FT3 levels according with *DIO2* genotype. As outlined in the table, patients carrying the wild-type allele (50%) had similar pre- and post surgical FT3 levels (3.2 ± 0.35 vs. 3.1 ± 0.36, $p = 0.097$). On the contrary heterozygous (37%) and rare homozygous (13%) patients displayed a significant reduction in FT3 post surgical levels (3.4 ± 0.52 vs. 3 ± 0.29, $p < 0.0001$ and 3.4 ± 0.37 vs. 2.9 ± 0.34, $p = 0.01$; respectively).

After applying a cutoff of at least 0.5 pg/ml as a significant variation between pre- and post surgical FT3 values, we divided patients into two groups namely "FT3 un-changed" ($n = 67$) and "FT3 reduced" ($n = 33$).

Genotype and allele frequencies for *DIO2* polymorphism in respect with these two groups are shown in Table 2. The Thr92Ala (rs225014) in *DIO2* gene was statistically associated with reduced FT3 levels after surgery with a $p = 0.035$ at genotype level and $p = 0.014$ at allele level resulting in an odd ratio (OR) of 2.116 (1.157–3.870 95% CI) (Table 2).

Data were also analyzed assuming both dominant and recessive models (Table 2). In the case of rs225014 in *DIO2* gene, both models displayed a statistically significant *p*-value ($p = 0.001$ and $p = 0.024$, respectively) indicating that this polymorphism is associated with reduced FT3 post surgical levels regardless of the model used.

Association of *SLC16A10* polymorphisms with FT3 post surgical levels

We then evaluated the association between *SLC16A10* gene polymorphism rs17606253 with pre- and post surgical FT3 levels (Table 3). As shown in the table, both wild-type (29%) and heterozygous (66%) patients had a significant reduction in FT3 post surgical levels (3.3 ± 0.37 vs. 3 ± 0.31, $p = 0.01$ and 3.4 ± 0.48 vs. 3 ± 0.34, $p < 0.0001$; respectively). No difference ($p = 0.4$) was observed in the rare homozygous group (5% of the patients) probably due to the low number of subjects in this category. We applied the cutoff of 0.5 pg/ml as a significant variation between pre- and post surgical FT3 values and analyzed genotype and allele frequencies for *SLC16A10* polymorphisms in respect with post surgical FT3 levels among the two groups (Table 2). No significant difference in *SLC16A10* rs17606253 distributions was observed ($p = 0.223$). Similarly, another variant, the p.K507Q in *SLC16A10* gene was not associated with reduced FT3 levels after surgery (Table 2). This variant is the only established non-synonymous polymorphism in MCT10 protein corresponding to a lysine to glutamine substitution at position 508 with a reported minor allele frequency (MAF) approximately of 2%. The prediction of functional effects of humans evaluated with PolyPhen-2 program resulted in "possibly damaging" with a score of 0.810 (sensitivity: 0.84, specificity: 0.93) (data not shown).

For rs17606253, data were also analyzed assuming both dominant and recessive models (Table 2). No statistically significant results were observed with the dominant model. In the case of recessive model, only for rs17606253 we obtained a *p*-value of 0.01 linked to the total absence of the rare allele in the FT3 reduced group (Table 2).

Analysis of rs225014 in *DIO2* gene in combination with rs17606253 in *SLC16A10* gene

We hypothesized that the significant reduction in FT3 post surgical levels observed in wild-type and heterozygous patients with *SLC16A10* gene polymorphism rs17606253 prior the application of the cut-off, could be related to the simultaneously presence of *DIO2* variation in these patients. To confirm our hypothesis, we performed the analysis of the distributions of rs225014 alleles in *DIO2* in combination with rs17606253 polymorphism in *SLC16A10*.

The analysis showed a statistically significant difference ($p = 0.017$) in allele distribution. However, as detailed in Table 4, this difference was only linked to allele distribution of rs225014 in *DIO2* gene.

Table 2 Genotype and allele frequency for *DIO2* and *SLC16A10* SNPs respect with post surgical FT3 levels

DIO2 Thr92Ala rs225014	FT3 unchanged %	FT3 reduced %	*p*-value	OR	95% CI	
AA	44.8	21.2				
AG	46.3	57.6	0.035			
GG	9.0	21.2				
A	67.9	50	0.014	2.116	1.157–3.870	Additive model
G	32.1	50				
A	44.8	21.2	0.001	3.012	1.524–5.952	Dominant model
G	55.2	78.8				
A	91.0	78.8	0.024	2.737	1.186–6.319	Recessive model
G	9.0	21.2				
SLC16A10 rs17606253						
TT	22.4	27.3				
TC	68.7	72.7	0.233			
CC	9	0				
T	56.7	63.6	0.364	0.749	0.408–1.374	Additive model
C	43.3	36.4				
T	22.4	27.3	0.483	0.769	0.391–1.514	Dominant model
C	77.6	72.7				
T	91.0	100.0	0.01	0.910	0.863–0.960	Recessive model
C	9.0	0.0				
SLC16A10 rs17072442 p.K507Q						
AA	92.5	90.9				
AC	7.5	9.1	1.000			
CC	0	0				
A	96.3	95.5	0.721	1.229	0.285–5.305	Additive model
C	3.7	4.5				
A	92.5	90.9	0.783	1.349	0.285–5.715	Dominant model
C	7.5	9.1				
A	100	100	n.a.			Recessive model
C	0.0	0.0				

Discussion

LT4 monotherapy is the treatment of choice for hypothyroid patients as the peripheral conversion of T4 to T3 is able to guarantee a biologically active amount of thyroid hormone in most patients. However, some subjects in LT4-therapy complain symptoms of hypothyroidism together with a reduction in circulating FT3 and an increase in FT4 levels despite normal levels of TSH. Several single-nucleotide polymorphisms (SNPs) in genes responsible for T4 to T3 conversion (i.e., *DIO2 or DIO1*) or for TH transport (i.e., *SLC16A10*) were reported to be associated with altered serum TH concentrations [14, 15, 18] however, results have been inconsistent [6, 10, 15, 16, 18]. A polymorphism (SNP) in the DIO1 gene, rs2235544, was strongly associated with the free T3 to free T4 ratio by applying a genome-wide approach. The rare allele of this SNP was associated with increased D1 function [11, 12]. Regarding DIO2 polymorphisms, although clinical studies suggest that in the presence of D2-Ala polymorphism the enzymatic activity may be impaired [21–24], a clear association between Thr92Ala and reduced tissue T3 levels has not been established. These conflicting results may be due to the lack of pre and post surgical hormonal values in the same patient and to the low number of patients enrolled in these studies. Recently, Carlé et al. [18] published a double-blind study in which autoimmune hypothyroid patients carrying both the Thr92Ala *DIO2* and the rs17606253 *SLC16A10* polymorphisms preferred the combined therapy LT4 + LT3. Unfortunately, no data about TH levels were available in this study. We have already published [14] a report on the effect of Thr92Ala SNP in *DIO2* gene and post

Table 3 Pre and post surgical FT3 levels according to *SLC16A10* genotypes

	Pre-surgical FT3 (pg/ml)	Post surgical FT3 (pg/ml)	*p*
TT (no. 29)			
Mean ± SD	3.3 ± 0.37	3.0 ± 0.31	0.01
Range	2.8–4.1	2.5–3.7	
Median	3.3	3.0	
TC (no. 66)			
Mean ± SD	3.4 ± 0.48	3.0 ± 0.34	<0.0001
Range	2.4–5.4	2.5–4.1	
Median	3.3	3.0	
CC (no. 5)			
Mean ± SD	3.0 ± 0.37	2.9 ± 0.19	0.4
Range	2.6–3.5	2.7–3.1	
Median	2.9	2.9	

Table 4 Allele distribution of rs225014 SNP in *DIO2* in association with rs17606253 SNP in *SLC16A10*

Haplotype	FT3 un-changed %	FT3 reduced %
A-T	47.0	42.4
A-C	20.9	7.6
G-T	9.7	21.2
G-C	22.4	28.8

rs225014 in *DIO2*: A = more frequent allele, G = rare allele; rs17606253 in *SLC16A10*: T = more frequent allele, C = rare allele

surgical FT3 levels and we have also demonstrated that Thr92Ala reduced enzymatic activity and T4-to-T3 conversion. No data on transporter were available in our previous work. Therefore, in this paper, we analyzed the presence of *SLC16A10* polymorphisms alone or in combination with Thr92Ala to uncover whether *SLC16A10* gene is also linked to post surgical hypothyroidism. To that aim, we genotyped for *SLC16A10* gene, 100 patients on LT4-replacement therapy with similar TSH levels before and after surgery. We found two SNPs: the intronic rs17606253 and the rs17072442 responsible for the p.K507Q substitution in exon 6. This variant was found at very low level (only 8% of patients, all heterozygous) and was not linked to FT3 post surgical levels. For rs17606253, both wild-type and heterozygous patients had statistically significant lower post surgical FT3 levels. However, no significant difference in rs17606253 distribution was observed both at genotype and allele levels when we applied a cutoff of 0.5 pg/ml as a significant variation between pre- and post surgical FT3 values. We, then, hypothesized that the significant reduction observed in rs17606253 wild-type and heterozygous patients was related to the concomitant presence of *DIO2* variation in these patients. In fact, results of the present study confirmed the effect of *DIO2* Thr92Ala on TH levels. In addition to our previous work [14], data on Thr92Ala were also analyzed assuming both dominant and recessive models. When we combined the two SNPs, a statistically significant difference ($p = 0.017$) in allele distribution was observed but this difference was only linked to allele distribution of *DIO2* polymorphism and to the absence of the rs17606253. The fact that MCT10 protein seems not to be linked with an impairment of TH levels was also concluded in another study in which a different SNP, the rs14399-C/A was analyzed in 3000 subjects [25].

The strength of our study is that it was conducted in patients that had similar pre- and post surgery TSH levels thus enabling us to evaluate putative changes in circulating TH levels with the same feedback set-point. One limit of our study is that FT3 does not directly represent intracellular T3 but only the level of T3 that is biologically available to enter cells and initiate thyroid hormone action [26]. Tissue T3 availability depends on conversion but also on other factors such as uptake, transport, degradation of thyroid hormones as well as activation/inactivation of thyroid hormone receptors and their co-regulators [26]. In addition, the balance of FT3 and FT4 levels is markedly influenced by thyroid hormone binding proteins.

In conclusion, we confirm that the lower plasmatic FT3 level is associated with the Thr/Ala or Ala/Ala D2 genotypes while, *SLC16A10* gene polymorphism rs17606253 seems do not have any effects on serum FT3 in athyreotic patients treated with LT4-replacement therapy. It is reasonable to speculate that in the "FT3 reduced" group of patients, restoration of pre-surgery FT3 values would be obtained by adding T3. The next challenge will be to treat the subgroup of patients with low FT3 carrying D2-Ala mutants, with the monotherapy first and then shift to the combined therapy to verify whether the addition of T3 is able to normalize T3 levels and also to improve the quality of life of these patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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