No effect of the Thr92Ala DIO2 polymorphism on thyroid parameters, health-related quality of life and cognitive functioning

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Background

The Thr92Ala polymorphism of deiodinase 2 (DIO2) is associated with increased expression in the brain of genes associated with oxidative stress and inflammation (1), and may predict favourable response to combination therapy of thyroxine (LT4) plus triiodothyronine (T3).

Aim

We examined whether the Thr92Ala polymorphism (rs225014) was associated with differences in thyroid hormone parameters, health-related quality of life (HR-QOL) and cognitive functioning in a large population-based study.

Results

Mean (±SD) age was 56±10 years and BMI 27.3±4.4 kg/m^2 in the LT4 users vs. 51±11 years and 26.4±4.1 kg/m^2 in non-LT4 users; 3,847 subjects had normal TSH (0.4-4.5 mU/l), and 90% of LT4 users were females. Only 58% of LT4 users had a TSH within normal limits.

The rarer Thr92Alaa-D2 polymorphism in DIO2 was present in 10.2% of the total study population. In non-LT4 users, the Thr92Ala-D2 polymorphism was not associated with differences in TSH, FT4, FT3, and the FT3/FT4-ratio, and there were no differences in any of the eight HR-QOL domains or the RFFT scores. LT4 users had higher FT4, lower FT3 and lower FT3/FT4-ratio, lower scores on the HR-QOL domains physical functioning, general health and vitality (all p<0.001) and lower RFFT scores (p=0.004). Also, their thyroid hormone parameters, HR-QOL and cognitive functioning were not influenced by the Thr92Ala genotype.

Table 1. Distribution of the Thr92Ala DIO2 polymorphism

Thr92Ala	Thr/Thr	Thr/Ala	Ala/Ala	Total
TSH-class 1 (TSH<0.4)	36 (1.8%)	26 (1.3%)	4 (0.0%)	66 (1.5%)
TSH-class 2 (TSH 0.4-4.5)	1,781 (89.5%)	1,747 (90.6%)	401 (89.9%)	3,929 (90.0%)
TSH-class 3 (TSH 4.5-10.0)	154 (7.7%)	134 (6.9%)	34 (7.6%)	322 (7.4%)
TSH-class 4 (TSH>10)	18 (0.9%)	22 (1.1%)	7 (1.6%)	47 (1.1%)
	1,989	1,929	446	4,364

Major findings

We conclude that the Thr92Ala polymorphism of DIO2 was not associated with thyroid parameters, HR-QOL and cognitive functioning in the general population and subjects with hypothyroidism.

References

1. McAninch EA, et al. JCEM 2015; 2. Stolk RP, et al. Eur J Epid 2008; 3. Hays RD, et al. The Psychological Corporation 1998. 4. Ruff RM, et al. Dev Neuropsychol 1987.

Methods

In total, 4,364 subjects from the LifeLines Cohort study (2), aged 18-80 years and from Western European descent (141 using LT4), thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free T3 (FT3) levels were measured with electrochemiluminescent immunoassay on the Roche Modular E170 Analyzer. HR-QOL was assessed with the Short Form-36 questionnaire (3). Scores in the individual HR-QOL domains range between 0-100 (best), and we calculated the number of participants with an abnormal score. The Ruff Figural Fluency Test (RFFT) was used as a sensitive cognitive test for general frontal lobe function (4). Linear regression with an additive model was used to analyze association between the Thr92Ala polymorphism and phenotypes of interest.

Table 2. The Thr92Ala DIO2 polymorphism and thyroid function parameters in participants with normal TSH

Thr92Ala	Thr/Thr	Thr/Ala	Ala/Ala	P-value
N of non-LT4-users	1,740	1,714	393	
Age (years)	51 ± 11	51 ± 11	52 ± 11	0.75
BMI (kg/m^2)	26.4 ± 4.1	26.3 ± 4.1	26.4 ± 4.0	0.67
TSH	2.18 ± 0.88	2.18 ± 0.91	2.11 ± 0.89	0.38
FT4	15.9 ± 1.9	15.7 ± 2.0	15.7± 2.0	0.09
FT3	5.2 ± 0.7	5.2 ± 0.6	5.2 ± 0.6	0.98
FT3/FT4 ratio	0.33 ± 0.05	0.34 ± 0.05	0.34 ± 0.05	0.08
N of subjects using LT4	41	33	8	
Age (years)	54 ± 9	56 ± 12	59 ± 8	0.31
BMI (kg/m^2)	27.9 ± 4.2	26.9 ± 4.4	24.3 ± 3.2	0.08
TSH	2.15 ± 1.19	2.37 ± 1.12	2.21 ± 1.07	0.71
FT4	18.4 ± 2.9	18.7 ± 2.7	18.5± 3.1	0.92
FT3	4.5 ± 0.8	4.4 ± 0.5	4.8 ± 0.3	0.18
FT3/FT4 ratio	0.25 ± 0.05	0.24 ± 0.04	0.27 ± 0.04	0.29

Table 3. The Thr92Ala DIO2 polymorphism, HR-QOL and RFFT scores

Thr92Ala	Thr/Thr	Thr/Ala	Ala/Ala	P-value
N of non-LT4-users	1,740	1,714	393	
Physical functioning < 85 (%)	20.6	22.5	22.2	0.336
Bodily pain < 70 (%)	27.5	27.6	25.5	0.667
General health < 65 (%)	25.7	26.4	23.8	0.533
Vitality < 60 (%)	24.7	23.4	22.9	0.548
RFFT unique designs	78 ± 23	78 ± 23	80 ± 25	0.098
N of subjects using LT4	41	33	8	
Physical functioning < 85 (%)	40.6	45.8	38.5	0.799
Bodily pain < 70 (%)	41.2	37.3	50	0.700
General health < 65 (%)	43.5	37.3	23.1	0.361
Vitality < 60 (%)	33.3	35.6	23.1	0.687
RFFT unique designs	74 ± 21	75 ± 22	75 ± 20	0.974

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LifeLines

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