THE PREVALENCE OF IODOTHYRONINE DEIODINASE GENES AND THEIR ASSOCIATION WITH NEUROPSYCHOLOGICAL STATUS IN KOREAN HYPOTHYROID PATIENTS

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BACKGROUND

Three deiodinase genes (DIO) play an important role in thyroid hormone metabolism. Among them, type 2 iodothyronine deiodinase (DIO2) converts T4 to T3 in brain and impaired psychological well-being was reported in minor variants of DIO2. However, the prevalence of three DIOs and their relation to neuropsychological status has not been evaluated in Asian hypothyroid subjects.

OBJECTIVE

We aim to identify the prevalence of iodothyronine deiodinase genes and their association with neuropsychological status in Korean hypothyroid patients

METHODS

We prospectively enrolled 196 subjects who were taking levothyroxine between Nov. 2012 and May 2015 at Samsung Medical Center. We analyzed 19 single nucleotide polymorphisms (SNPs) in the three deiodinase genes using MassARRAY matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Sequenom, San Diego, CA, USA). We assessed the neuropsychological status by the six questionnaires (SF-36-PCS, SF-36-MCS, HADS-Anxiety, HADS-Depression, Brief Fatigue Inventory and Thyroid Symptom Questionnaire) and identified the association between DIO variants and well-being scores.

RESULTS

Prevalence of studied SNPs for DIO in patients with thyroid disease

	No. of samples	Allele		Common Homo-zygous (AA)		Hetero-zygous (AB)		Minor Homo-zygous (BB)	
		A	B	n	%	n	%	n	%
DIO1									
rs11206237	194	C	A	126	65	64	33	4	2
rs11206244	194	C	T	145	75	45	23	4	2
rs2235544	193	C	A	64	33	101	52	28	15
rs2268181	194	T	C	126	65	64	33	4	2
rs2294511	196	A	T	105	54	83	42	8	4
rs2294512	192	G	A	85	44	83	43	24	17
rs4926616	194	C	T	146	75	45	23	3	2
rs731828	193	A	C	65	34	92	48	36	18
rs7527713	193	G	A	89	46	88	45	16	8
DIO2									
rs12885300	192	C	T	145	76	43	22	4	2
rs225011	193	C	T	113	58	74	38	6	4
rs225014	196	T	C	61	31	108	55	27	14
rs225015	196	G	A	63	32	106	54	27	14
DIO3									
rs1190715	194	G	A	56	29	87	45	51	26
rs1190716	196	C	T	195	99	1	1	0	0
rs17716499	194	T	C	96	49	84	43	14	8
rs7150269	193	C	A	72	37	87	45	34	18
rs8011440	196	C	T	50	26	91	46	55	28
rs945006	194	T	G	193	99	1	1	0	0

Relationship between DIO2 genotype and scores of six questionnaires

	Common homozygous		Heterozygous		Minor homozygous		P-value
	n	Median	n	Median	n	Median	
SF-36-PCS							
rs12885300	145	47.0 (42.3, 52.1)	43	48.1 (41.6, 53.9)	4	55.5 (42.9, 57.5)	0.29
rs225011	113	47.3 (42.7, 52.0)	74	47.6 (40.6, 53.6)	6	54.3 (40.1, 56.9)	0.43
rs225014	61	48.2 (42.7, 54.3)	108	47.4 (41.3, 52.1)	27	45.5 (42.2, 51.6)	0.41
rs225015	63	48.2 (42.4, 54.3)	106	47.4 (41.4, 51.9)	27	45.5 (42.2, 51.7)	0.62
SF-36-MCS							
rs12885300	145	45.1 (37.2, 53.5)	43	42.3 (34.7, 52.7)	4	37.7 (25.4, 52.7)	0.47
rs225011	113	46.4 (36.8, 53.8)	74	43.2 (36.7, 50.7)	6	31.3 (27.5, 44.6)	0.08
rs225014	61	44.3 (37.4, 54.7)	108	45.0 (35.0, 53.3)	27	43.9 (35.5, 47.8)	0.76
rs225015	63	46.0 (37.7, 55.3)	106	44.3 (34.8, 52.6)	27	44.0 (35.9, 51.7)	0.48
HADS-Anxiety							
rs12885300	145	8.0 (4.0, 11.0)	43	8.0 (5.0, 11.0)	4	10.0 (5.3, 12.5)	0.61
rs225011	113	7.0 (4.0, 10.0)	74	8.0 (5.0, 11.0)	6	9.0 (7.0, 11.5)	0.30
rs225014	61	8.0 (4.0, 11.0)	108	7.0 (5.0, 10.7)	27	9.0 (5.0, 11.0)	0.53
rs225015	63	8.0 (3.0, 11.0)	106	8.0 (5.0, 11.0)	27	7.0 (5.0, 11.0)	0.26
HADS-Depression							
rs12885300	145	6.0 (3.0, 8.5)	43	6.0 (3.0, 9.0)	4	10.0 (3.5, 14.3)	0.37
rs225011	113	6.0 (3.0, 8.0)	74	7.0 (3.0, 9.0)	6	9.0 (6.5, 11.3)	0.11
rs225014	61	6.0 (2.5, 9.5)	108	6.0 (3.0, 8.0)	27	7.0 (5.0, 10.0)	0.44
rs225015	63	6.0 (3.0, 9.0)	106	6.0 (3.0, 8.0)	27	7.0 (4.0, 10.0)	0.62
BFI							
rs12885300	145	5.0 (3.1, 6.2)	43	5.4 (2.1, 6.4)	4	6.9 (2.8, 7.2)	0.41
rs225011	113	5.0 (3.1, 6.2)	74	5.1 (2.4, 6.6)	6	6.5 (4.7, 7.3)	0.22
rs225014	61	4.7 (2.7, 6.3)	108	4.9 (3.0, 6.3)	27	5.4 (3.8, 6.2)	0.87
rs225015	63	4.6 (2.4, 6.0)	106	5.1 (3.1, 6.4)	27	5.4 (3.4, 6.2)	0.81
TSQ							
rs12885300	145	11.0 (8.5, 15.0)	43	11.0 (9.0, 15.0)	4	15.5 (9.3, 18.0)	0.51
rs225011	113	11.0 (8.0, 15.0)	74	11.5 (9.0, 15.0)	6	15.5 (9.5, 19.3)	0.31
rs225014	61	11.0 (8.5, 15.0)	108	11.0 (8.0, 15.0)	27	13.0 (9.0, 15.0)	0.66
rs225015	63	11.0 (8.0, 15.0)	106	11.0 (8.8, 15.0)	27	13.0 (9.0, 15.0)	0.81

Thyroid cancer patients (n=60) who underwent total thyroidectomy and patients with chronic autoimmune thyroiditis (n=136) showed similar distributions of DIO variants and questionnaire scores. The prevalence of minor homozygote in four DIO2 SNPs tested was 2% (rs12885300), 4% (rs225011), 14% (rs225014) and 14% (rs225015). Questionnaire scores (HADS-Anxiety, HADS-Depression and Brief Fatigue Inventory) in minor homozygote of DIO2 SNPs were worse than common homozygote and heterozygote, but not significant.

CONCLUSION

Worse neuropsychological scores seemed to be related to minor variants of DIO2 SNPs in subjects with thyroid disease. This issue should be validated in further larger studies to clarify the relevance between psychological status and DIO variants as well as the improvement of well-being using T3/T4 combination or T4 monotherapy in subjects with minor variants.

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Thyroid (non-cancer)

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