Genetic variants modify susceptibility to atrial fibrillation in patients on thyroid hormone replacement therapy

Soto-Pedre E [1], Siddiqui MK [2], Doney AS [3], Palmer CN [2], Pearson ER [1], Leese GP [1,4]

1-Division of Molecular & Clinical Medicine, 2-Centre for Pharmacogenetics & Genomics, 3-Medicines Monitoring Unit (MEMO), 4-Department of Endocrinology and Diabetes. Ninewells Hospital & Medical School, Dundee DD1 9SY (Scotland, UK)

Introduction

Hypothyroidism is the most common thyroid disorder affecting about 3-5% of the general population. Treatment includes thyroid hormone replacement therapy, and levothyroxine (T4) is the treatment of choice for maintenance.

Some adverse health outcomes (cardiovascular disease, cardiac dysrhythmias, and bone fractures) have been described in patients receiving long-term replacement T4 therapy. Hypothyroidism has been associated with atrial fibrillation (AF) in some studies.

Over the last decade, great progress has been made in defining the genetic basis of AF, and there is now evidence that genetic factors may play a role in its pathogenesis.

Aims: to characterize thyroid related genetic variants that may change susceptibility to AF in patients on T4.

Methods

- A **case-control study** was done among patients of European Caucasian ethnicity from the Genetics of Diabetes Audit and Research Tayside Study (GoDARTS) recruited in Tayside (Scotland, UK)
- **Electronic medical records** (biochemistry, prescribing, hospital admissions and demographics) were used to ascertain patients with AF and their controls as well as patients with hypothyroidism, and **linked to genetic biobank data.**
- All patients with at least one serum TSH recording between 1994 and 2014 were considered for inclusion in this study:
  - At least one ICD 9th–10th edition code (ICD9: 427.31, 427.32; ICD10: I48) was required for AF (i.e. cases)
  - All-cause hypothyroidism was defined as having been issued at least two prescriptions of T4 (BNF code 6.2.1) . Patients with a history of thyroid cancer or probable hyperthyroidism were excluded.
- Genetic tests of association were performed by **logistic regression models** under the assumption of an additive genetic model. STATA/SE® v13.1 was used for statistical analysis and determination of statistical significance (P <0.05)

Results (I)

Table 1. *Description of patients included in the study.*

Variable	ATRIAL FIBRILLATON (n= 1,031)	CONTROLS (n= 10,757)	P
Age (years)	63.9 (9.6)	57.1 (12.6)	<0.001
Gender-male (%)	61.3	52.8	<0.001
SIMD quintile (%):			
1 most deprived	15.6	18.1	=0.270
2	15.8	15.4	
3	16.1	16.0	
4	31.8	31.8	
5 most affluent	20.5	18.6	
Serum TSH (mU/L)*	1.8 (1.2- 2.6)	1.7 (1.2- 2.4)	<0.01

SIMD= Scottish Index of Multiple Deprivation
TSH= thyroid-stimulating hormone
(*) Median (interquartile range).

Results (II)

Table 2. *Association between T4 treatment and atrial fibrillation risk by genotype. Treatment- genotype interaction of selected SNPs .*

#	SNP	Gene	Chromosome	Position	Coded allele	MAF	N *	OR (95%CI) †	P †
1	rs2234919	*TSHR*	14	81422178	A	0.05	9908	0.48 (0.24- 0.97)	4.2e-02
2	rs2517532	*HLA*	6	31018407	A	0.43	11578	1.32 (1.03- 1.67)	2.6e-02
3	rs2067499	*THRß*	3	24192161	T	0.21	8199	0.73 (0.53- 0.99)	4.6e-02
4	rs4241527	*THRß*	3	24487305	A	0.10	8290	0.60 (0.39- 0.92)	2.0e-02
5	rs6777133	*THRß*	3	24202111	G	0.23	8235	1.35 (0.99- 1.84)	5.0e-02
6	rs7622481	*THRß*	3	24351871	T	0.26	8223	0.69 (0.51- 0.94)	2.0e-02
7	rs7652234	*THRß*	3	24190459	G	0.05	8238	2.00 (1.11- 3.59)	2.1e-02
8	rs2596623	*THRß*	3	24204984	T	0.31	8302	1.42 (1.08- 1.88)	1.3e-02
9	rs2683540	*THRß*	3	24221947	T	0.21	8282	1.41 (1.03- 1.92)	2.7e-02
10	rs2683544	*THRß*	3	24205251	C	0.32	8306	1.33 (1.01- 1.75)	4.2e-02
11	rs2683545	*THRß*	3	24192584	T	0.20	8217	1.44 (1.05- 1.99)	2.2e-02
12	rs826229	*THRß*	3	24236613	T	0.27	8305	1.32 (0.98- 1.76)	6.0e-02
13	rs1158265	*THRß*	3	24336162	C	0.29	8243	0.71 (0.53- 0.95)	2.4e-02
14	rs1354605	*THRß*	3	24262065	G	0.20	8271	1.55 (1.13- 2.14)	5.9e-03
15	rs826219	*THRß*	3	24269601	A	0.08	8294	1.93 (1.27- 2.93)	2.0e-03
16	rs1667735	*THRß*	3	24257306	C	0.18	8310	1.55 (1.11- 2.16)	9.1e-03
17	rs1667739	*THRß*	3	24230196	A	0.22	8310	1.46 (1.07- 1.98)	1.4e-02

HLA= Human Leukocyte Antigen. SNP= Single nucleotide polymorphism. THRß= Thyroid Hormone Receptor Beta. TSH= thyroid-stimulating hormone . TSHR= Thyroid Stimulating Hormone Receptor. T4= levothyroxine.
Logistic regression models adjusted for age, gender and average TSH.
(*) Number of individuals used for the association test..
*(†) For the interaction term (T4*SNP)*

Conclusions

- **This study provides evidence that genetic factors, such as polymorphisms in the *THRß*, *HLA*, and *TSHR* genes, might contribute to inter-individual variations in susceptibility to AF in patients on T4.**
- **There appears to be a consistent signal from *THRß* and further analyses are necessary to determine their independence.**
- Further investigations are necessary to understand the gene-drug interaction/stratification effect observed.

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For further information email:

e.soto@dundee.ac.uk or grahamleese@nhs.net