Topic: POLYMORPHISMS IN THYROID HORMONE RECEPTORS

Title: Identification and consequences of polymorphisms in the thyroid hormone receptors alpha and beta genes.

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Reference: Thyroid 18: 1087-1094, 2008

SUMMARY

Objective: Genetic factors exert considerable influence on thyroid function variables. Single nucleotide polymorphisms (SNPs) in thyroid hormone pathway genes have been associated with serum thyroid parameters implying small alterations in the hypothalamus-pituitary-thyroid axis. However, little is known about SNPs in the THR-alpha and THR-beta genes. The aim of this study was to map THRA and THRB for the occurrence and frequencies of SNPs and relate these to thyroid parameters.

Design & Methods: SNPs were identified by sequencing all THRA and THRB exons and flanking regions in 52 randomly selected subjects. SNPs were genotyped in 1,116 healthy Danish twins by TaqMan assays and related to thyroid parameters. One SNP in THRB was additionally genotyped in the elderly population of the Rotterdam Scan Study (N=940).

Results: 15 SNPs (7 novel) in THRA and THRB were identified. Two SNPs in the 3' untranslated region of THRA were genotyped: a novel SNP (2390A/G) and 1895C/A (rs12939700). In THRB, a synonymous (735C/T; rs3752874) and an intronic SNP (in9-G/A; rs13063628) were genotyped. No association between SNPs and thyroid hormone levels was found. THRB-in9-G/A was significantly associated with higher serum TSH in the Danish twins, but not in subjects of the Rotterdam Scan Study, although it showed a similar trend.

Conclusions: Analysis of the T3 receptor genes revealed 15 SNPs, including 7 novel ones. Only THRB-in9-G/A was associated with higher serum TSH in a large population of Danish twins.

COMMENT

A few definitions are given for those readers who (like me) are not too familiar with the genetic terminology. The Human Genome Project resulted in the sequencing of the 3 billion base pairs of DNA that comprise the human genome, estimated to contain 50,000 to 100,000 genes. Over 99% of DNA is identical between individuals. However, every 100-500 base pairs, the nucleotide sequence varies and these differences are called ‘single nucleotide polymorphisms’ (SNPs). By definition, a sequence variation is a SNP if it occurs in at least 1% of the population. Normal genetic variation in the population is due to these SNPs (or changes in the DNA sequence of genes). Genes are composed of introns & exons. While exons represent the portion of a gene that codes for amino acids, introns represent intervening sequences between the exons. Within the population, one gene may have different sequences. Genotype refers to the alleles of a gene that a person carries. Phenotype refers to the physical expression of the genotype, which is modified by
environmental factors as well as by other genes. Although a person has only 2 chromosomes and thus cannot have more than 2 alleles for 1 gene, most often there are more than 2 alleles for each gene in the population. When the frequency of 2 or more alleles at a gene locus is greater than 1% in the population, that locus is said to be polymorphic.

Thyroid hormone receptors (TRs) are encoded by two genes, respectively the THRA & THRB genes. TRs are composed of 2 main variants (TRα & TRβ), and TRs exist in several isoforms. TRα1 is most abundant in heart & brain; TRβ1 is highly expressed in liver, kidney, & thyroid; TRβ2 expression is restricted to specific brain areas, reflecting its function in the negative feed-back loop of the hypothalamo-pituitary-thyroid axis.

Recently, several SNPs in thyroid hormone receptor genes have been identified and associated with variation in serum thyroid function parameters. The questions therefore raised in present work were: a) to ascertain the degree of variability in TR genes in the population; and b) to investigate whether such polymorphism might alter thyroid function parameters, to help explain perhaps why we all have our own ‘genetically-determined’ set point for normal serum TSH & free T4 values.

The authors mapped THRA & THRB for the occurrence and frequency of SNPs. Then, they evaluated the influence of the SNPs on thyroid hormone parameters in a population of Danish twins and participants to the ‘Rotterdam Scan’ study. The main results were that the sequence analyses of all exons and flanking regions of THRA & THRB identified 15 SNPs, including 7 novel variants. Except for one SNP (THRB-in9-G/A), there was no significant association between SNPs and serum thyroid parameters. Concerning THRB-in9-G/A specifically, this SNP was associated with a phenotypic variance in serum TSH levels in Danish twins, but not statistically in Dutch subjects (although there was a similar trend).

In summary, the authors have identified several previously unknown SNPs in THRA & THRB genes. The SNPs in THRA were not associated with serum thyroid parameters. One genetic marker - THRB-in9-G/A - was associated with increased serum TSH in a large Danish twin population, although this association accounted only for a limited proportion in the inter-individual variability of serum TSH.

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See Figure below