Homology between TSH-R/Tg/TPO and Hashimoto's encephalopathy autoantigens

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1. ABSTRACT

Hashimoto's encephalopathy (HE) is a syndrome occurring in some patients with Hashimoto's thyroiditis or, less frequently, Graves' disease. Three known autoantigens are involved in HE: alpha-enolase, dimethylargininase-I (DDAHI) and aldehyde reductase-I (AKRIAI). We searched for amino acid sequence homologies between these proteins and the three classical thyroid autoantigens (thyroperoxidase (TPO), thyroglobulin (Tg), TSH-receptor (TSH-R)), which are also expressed in the central nervous system (CNS). TSH-R shows homologies with alpha-enolase (n=4), DDAHI (n=2) and AKRIAI (n=5); of these segments, two, two and four, respectively, overlap totally or partially with epitope-containing TSH-R segments. Tg has 10 homologies with alpha-enolase, five with DDAHI, and eight with AKRIAI; epitope-containing segments of Tg overlap four, three and four segments, respectively. TPO has six segments homologous to alpha-enolase, three to DDAHI and seven to AKRIAI; of these segments, five, one and four, respectively, are located in epitope-containing parts. These data suggest that cross-reactivity between CNS autoantigens and thyroid autoantigens might contribute to the HE pathogenesis, together with other proposed mechanisms, including autoimmunity involving autoantigens common to CNS and thyroid.

2. INTRODUCTION

The 3 September 1966 issue of The Lancet published back-to-back two important papers on autoimmune thyroiditis (AIT) (1, 2). The second of these papers was the first description of a syndrome that later on was termed "Hashimoto's encephalopathy" (HE) (3) and, more recently, "steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)" (4). The described patient presented with recurrent neuropsychiatric symptoms, was euthyroid and tested positive for serum anti-thyroid antibodies (TAb) (2). Encephalopathy may precede AIT even by years. As of December 2018, 418 papers on SREAT were deposited in PubMed. In detail, Hashimoto's thyroiditis-related encefalopathy was the topic of 335 papers, of which 202 (~60%) published from 2008; some articles are important reviews (5-8). Graves' disease-related encephalopathy was instead

discussed in 83 papers.

Since clinical features of HE are unspecific, other etiologies such as infectious, metabolic, toxic, vascular, neoplastic, and paraneoplastic causes have to be excluded. Kothbauer-Margretier *et al.* (5) noticed that two types of initial clinical presentation are identifiable in 20 well-documented cases (6/20 personal ones, female:male ratio 18:2 or 9:1). One is the vasculitic type, with stroke-like episodes and mild cognitive impairment; the other is the diffuse progressive type, with dementia, seizures, psychotic episodes or altered consciousness. These types may overlap, particularly in the long-term course without treatment. Response to steroids is usually excellent, with complete remission in 80% of patients. Characteristic, though unspecific findings are abnormal electroencephalography (EEG) (90% of patients) and increased concentration of proteins/immunoglobulins G (IgG) in the cerebrospinal fluid (CSF) (80% of patients). Serum TAb are the main indicators of HE, though their serum levels do not correlate with the severity or type of clinical presentation. The authors concluded that a link between HE and Hashimoto's thyroiditis (HT) is unclear, and that a pathogenetic role for TAb in the central nervous system (CNS) seems unlikely.

Another review (6) retrieved 85 patients with properly documented HE (female:male ratio of 4.3:1; age 9 to 78 years, mean 44). The rate of abnormal EEG, CSF, unspecific brain imaging (most frequently diffuse or focal subcortical white matter lesions) and responsiveness to therapy with corticosteroids was 98%, 78%, 49% or 96%, respectively. Subclinical hypothyroidism, euthyroidism or overt hypothyroidism were the functional states mostly represented (35%, 22% or 20%), and serum TAb were frequently positive: thyroglobulin Ab (TgAb, 73%), microsomal Ab (MAb, 95%), thyroperoxidase Ab (TPOAb, 100%). Again, there was no relationship between the neurologic symptoms/signs and the type or serum concentration of TAb. Chong *et al.* (6) underscored that "There is no evidence that any antithyroid antibody reacts with brain tissue or affects nerve function", and concluded that "The combination of encephalopathy, high serum

antithyroid antibody concentrations, and responsiveness to glucocorticoid therapy seems unlikely to be due to chance".

Japanese authors were the first to identify autoAb against brain-expressed autoantigens. Ochi *et al.* (9) found anti-alpha-enolase autoAb in 3/5 HE patients, 3/54 patients with Hashimoto's thyroiditis but not encephalopathy (faint positivity), as opposed to none of 20 patients with other neurological disorders and none of 25 healthy controls. Subsequently, Yoneda *et al.* (10) found autoAb against the N-terminal region of alpha-enolase in 17/25 HE patients and 2/20 patients with Hashimoto's thyroiditis without encephalopathy. Two new autoantigens involved in HE, namely dimethylargininase-I (DDAHI) and aldehyde reductase-I (AKRIAI), were identified by Gini *et al.* in a study on six patients (11). In detail, the two isoforms of DDAHI, which is localized in the endothelial cells of normal human CNS, were recognized by autoAb present in the serum of five and four HE patients, respectively, while AKRIAI, which is widely distributed on neurons and endothelia, was recognized by autoAb present in the CSF of three HE patients (11).

Of interest, alpha-enolase, DDAHI and AKRIAI are expressed not only in the CNS, but also in the thyroid among other tissues. Hence, an autoimmune process involving autoantigens common to CNS and thyroid was proposed as one of the pathogenetic mechanisms of SREAT.

To corroborate this mechanism, we hypothesized that human AE, AKRIA-I and DDAH-1 share amino acid sequence homology with at least one of the classical human thyroid autoantigens (thyroperoxidase (TPO), thyroglobulin (Tg), TSH-receptor (TSH-R)). We aimed at verifying this hypothesis by bioinformatic methods.

3. MATERIALS AND METHODS

We followed our usual procedure, as consolidated in previous bioinformatics papers (12-17). Thus, in the present paper, we first retrieved the amino acid sequence of the six proteins under study (TSH-R (accession number
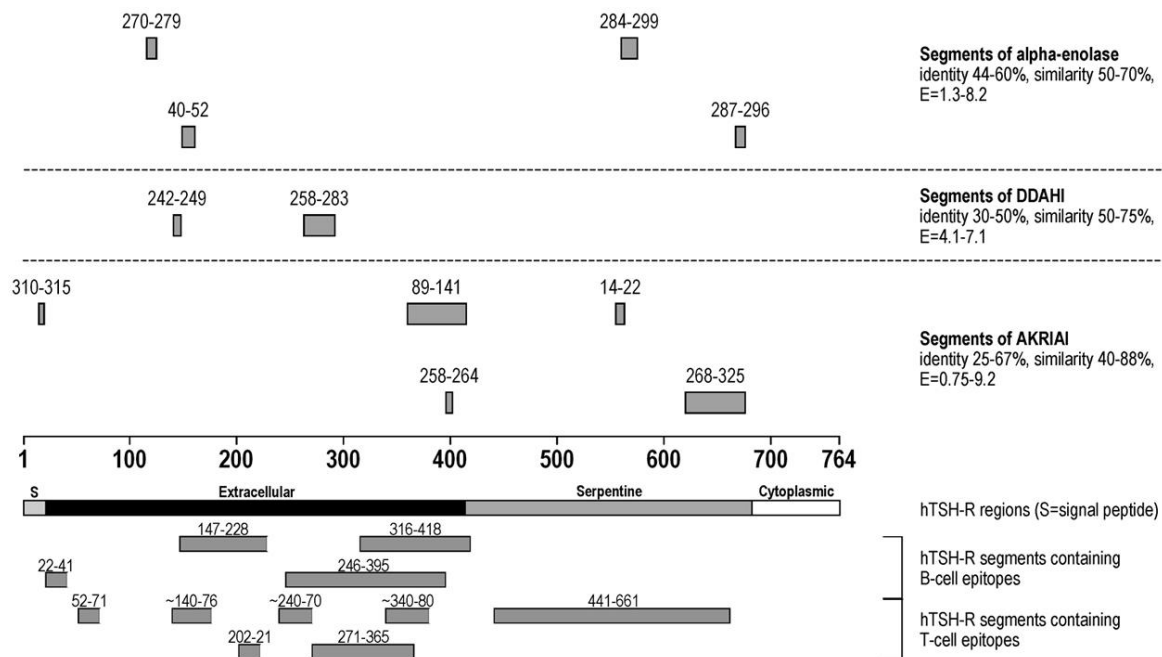
Figure 1. Homologies between human thyroid stimulating hormone receptor (TSH-R) and alpha-enolase, dimethylargininase-I (DDAHI) and aldehyde reductase-I (AKRIAI).

P16473), Tg (accession number NP_003226), TPO (accession number AAA61217), alpha-enolase (accession number P06733), AKRIAI (accession number AAF01260) and DDAHI (accession number O94760)) from the Entrez Protein database (https://www.ncbi.nlm.nih.gov/protein), and then probed for amino acid sequence homology each of the three thyroid autoantigens with each of alpha-enolase, AKRIAI and DDAHI in a pairwise sequence alignment. The Protein BLAST (Basic Local Alignment Search Tool) software version 2.8.0.+ (18) was used to compare each thyroid autoantigen to each HE autoantigen. Search for homology was made using the standard parameters of the software, and only results with E<10 were considered. As also done previously (12-17), we also ascertained whether the regions of homology found were immunologically relevant because containing T- and B-cell epitopes. Position of the epitopes for TSH-R, Tg and TPO along the primary structure of the corresponding proteins was reported elsewhere (12-17, 19-21). Position of the epitopes for alpha-enolase was derived from the literature (10, 22), whereas there

are no data available for AKRIAI and DDAHI.

4. RESULTS

Figure 1 shows the homologies between TSH-R and alpha-enolase (n=4), DDAHI (n=2) and AKRIAI (n=5). Two segments homologous to alpha-enolase, two homologous to DDAHI and four homologous to AKRIAI overlap totally or partially with segments of TSH-R that contain T-cell or B-cell epitopes. A higher number of homologies was found in the case of Tg (Figure 2): 10 with alpha-enolase, five with DDAHI, and eight with AKRIAI. Overlaps with epitope-containing segments of the thyroid autoantigen were observed for four, three and four segments, respectively. Finally, TPO had six segments homologous to alpha-enolase, three to DDAHI and seven to AKRIAI (Figure 3); of these segments, five, one and four, respectively, were located in epitope-containing parts. A detailed list of the above homologies is shown in Figure 4.

Figures 5, 6 and 7 present data from the opposite perspective, namely they show the position of homologies with thyroid autoantigens in
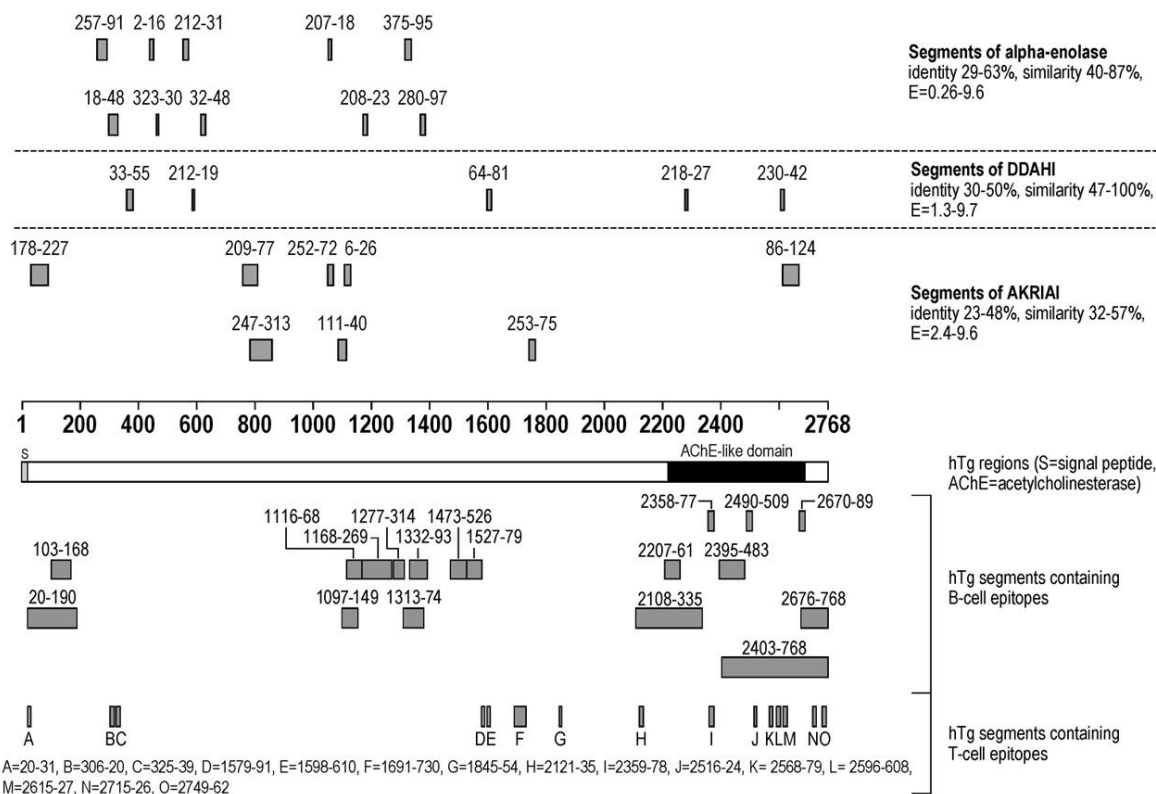
Figure 2. Homologies between human thyroglobulin (Tg) and alpha-enolase, dimethylargininase-I (DDAHI) and aldehyde reductase-I (AKRIAI).

the amino acid sequence of alpha-enolase, DDAHI and AKRIAI, respectively. A comment can be reserved to the homologies with alpha-enolase, because (i) it is the N-terminal part of alpha-enolase (aa 1-157) that was found to react with sera of HE patients (10, 22); (ii) major epitopes have been reported in given regions of this protein (23-25). These alpha-enolase epitopes include amino acids 31-38, 56-63, 53-87, 176-183, 207-238 and 421-428. Thus, it is worthy of note that the following seven segments of alpha-enolase having homology with thyroid autoantigens fall within or adjacent the said epitopes. We are referring to aa 40-52 (homologous to aa. 149-161 of TSH-R), aa 18-48 and 32-48 (homologous to aa. 298-329 and 614-630 of Tg), aa 207-218, 208-223 and 212-231 (homologous to aa. 1052-1063, 1171-1186 and 553-572 of Tg), and aa. 227-241 (homologous to aa. 609-623 of TPO).

The position of autoreactive epitopes in DDAHI and AKRIAI is still unknown, thus precluding any comment.

Examples of the homologies found are illustrated in Figure 8. Here results are presented in a multiple alignment to highlight that a given region of the thyroid autoantigen was homologous to more than one HE-associated autoantigen, and that the local region of homology contained one epitope in the thyroid autoantigen and one epitope in the HE-autoantigen counterpart.

5. DISCUSSION

As reviewed by Terrier *et al. (26),* Ab against alpha-enolase were detected in a large variety of infectious and autoimmune diseases. Among endocrine autoimmune diseases, anti-alpha-enolase Ab were reported in Hashimoto's thyroiditis (with our without encephalopathy), lymphocytic hypophysitis, and autoimmune polyglandular
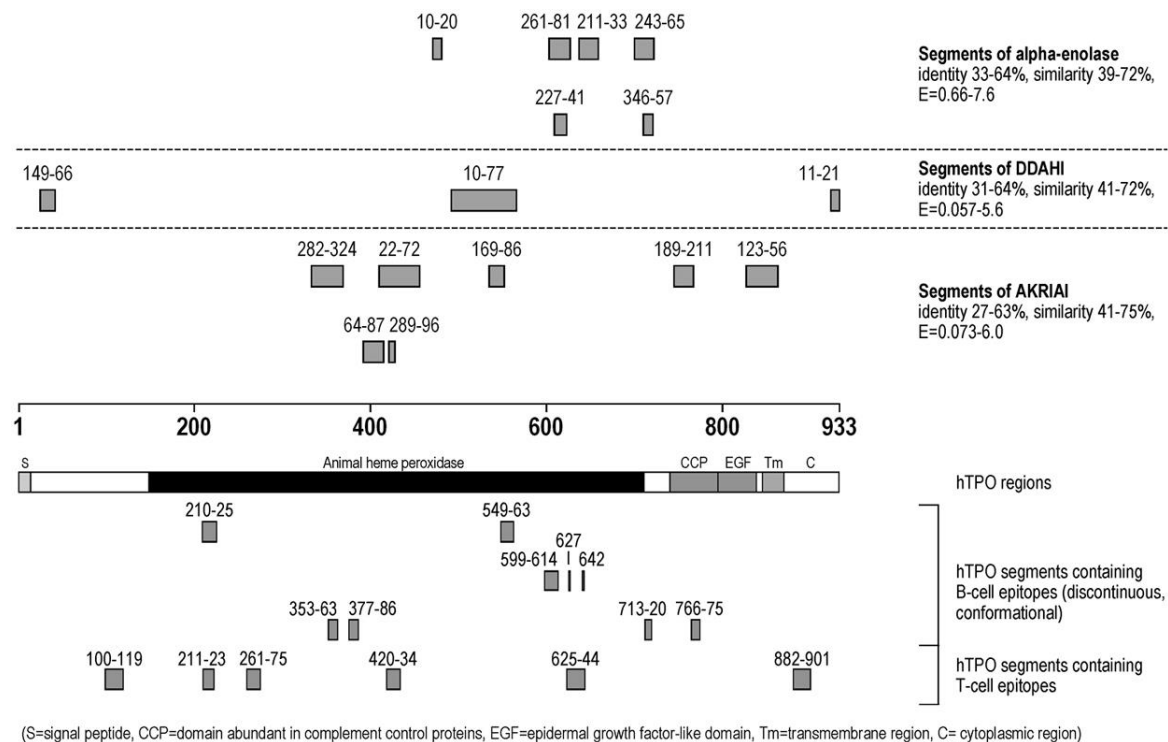
Figure 3. Homologies between human thyroperoxidase (TPO) and alpha-enolase, dimethylargininase-I (DDAHI) and aldehyde reductase-I (AKRIAI).

syndrome I (APS-1; chronic muco-cutaneous candidiasis, hypoparathyroidism, and Addison's disease). Interestingly, most of the autoimmune diseases in which alpha-enolase can be detectable (rheumatoid arthritis, celiac disease, Sjögren disease, multiple sclerosis, systemic lupus erythematosus, systemic sclerosis) coincide with those that relatively more frequently are associated with Hashimoto's thyroiditis (27) or Graves' disease (28). In autoimmune diseases, alpha-enolase Ab could induce endothelial injury through the generation of immune complexes and activation of the complement cascade, inhibit the binding of plasminogen to alpha-enolase with perturbations of the intravascular and pericellular fibrinolytic system, and induce cell death through an apoptotic process (25).

The data that we report in the present paper are to be evaluated also in light of other recent and very interesting data from the literature (28-30). Crisanti *et al.* (28) demonstrated TSH-R expression in both neuronal cells (cell body, not axon-specific neurofilament) and astrocytes of rat brain. TSH-R predominated in neuron-rich areas (pyriform and postcingulate cortex, hippocampus, and hypothalamic nuclei) and was mostly colocalized with neuron-specific enolase. In astrocytes, TSH-R mRNA was detected in the ependymal cell layer and the subependymal zone, and several isolated cells were also found in the brain parenchyma and blood vessels. The choroid plexus, cerebellum (at the level of the Purkinje cell layer) and meninges also expressed TSH-R. TSH-R mRNA and protein were found in primary cultured human astrocytes. The protein was detected as well in both rat and human embryonic brain cryoslices.

Using immunohistochemistry with two rabbit polyclonal Ab, one against human TSH-R and one against human Tg, Moodley *et al.* (29) evaluated the presence of TSH-R and Tg in the brain tissue obtained at post mortem from 3 males (mean age=36.7 years) and 2 females (mean age=28.0

	Alpha-enolase	AKRIAI	DDAHI
TSH-R	149-161 / 40-52 *(TSH-R T-cell epitope at aa ~140-176,* *B-cell epitope at aa 147-228)* 560-575 / 284-299 *(TSH-R T-cell epitope at aa 441-661)*	620-676 / 268-325 *(TSH-R T-cell epitope at aa 441-661)* 555-563 / 14-22 *(TSH-R T-cell epitope at aa 441-661)* 396-402 / 258-264 *(TSH-R B-cell epitope at aa 316-418)* 360-415 / 89-141 *(TSH-R T-cell epitopes at aa ~340-380* *and 271-365,* *B-cell epitopes at aa 316-418* *and 246-395)*	263-292 / 258-283 *(TSH-R T-cell epitopes at aa 271-365* *and ~240-270,* *B-cell epitope at aa 246-395)* 141-148 / 242-249 *(TSH-R T-cell epitope at aa ~140-176)*
Tg	298-329 / 18-48 *(Tg T-cell epitopes at aa 306-320 and* *325-339)* 1368-1385 / 280-297 *(Tg B-cell epitopes at aa 1332-1993 and* *1313-1374)* 1315-1337 / 375-395 *(Tg B-cell epitopes at aa 1313-1374* *and 1332-1393)* 1171-1186 / 208-223 *(Tg B-cell epitope at aa 1168-1269)*	1107-1129 / 6-26 *(Tg B-cell epitopes at aa 1097-1149 and* *1116-1168)* 2612-2668 / 86-124 *(Tg T-cell epitope at aa 2615-2627,* *B-cell epitope at aa 2403-2768)* 31-90 / 178-227 *(Tg B-cell epitope at aa 20-190)* 1086-1114 / 111-140 *(Tg B-cell epitope at aa 1097-1149)*	2605-2617 / 230-242 *(Tg T-cell epitopes at aa 2596-2608* *and 2615-2627,* *B-cell epitope at aa 2403-2768)* 2277-2286 / 218-227 *(Tg B-cell epitope at aa 2108-2335)* 1597-1612 / 64-81 *(Tg T-cell epitope at aa 1598-1610)*
TPO	700-722 / 243-265 *(TPO B-cell epitope at aa 713-720)* 637-659 / 211-233 *(TPO T-cell epitope at aa 625-644,* *part of B cell epitope at aa 599-642)* 710-721 / 346-357 *(TPO B-cell epitope at aa 713-720)* 609-623 / 227-241 *(TPO T-cell epitope at aa 625-644,* *B-cell epitope at aa 599-642)* 603-627 / 261-281 *(TPO T-cell epitope at aa 625-644,* *B-cell epitope at aa 599-642)*	333-369 / 282-324 *(TPO B-cell epitope at aa 353-363)* 535-552 / 169-186 *(TPO B-cell epitope at aa 549-563)* 410-456 / 22-72 *(TPO T-cell epitope at aa 420-434)* 421-428 / 289-296 *(TPO T-cell epitope at aa 420-434)*	492-566 / 10-77 *(TPO B-cell epitope at aa 549-563)*

Figure 4. Segments of human alpha-enolase, aldehyde reductase (AKRIAI) or dimethylarginine dimethylaminohydrolase 1 (DDAHI) that are homologous to segments of TSH-R, Tg or TPO totally or in part coinciding with experimentally demonstrated epitope-containing regions. For each pair of matching segments, the sequence belonging to the thyroid autoantigen is typed in *italics*.

years). All five persons had succumbed to unnatural causes other than head injury, with no apparent indication of psychological abnormality. Anti-TSH-R IgG immunolocalized to cell bodies and axons of large neurons in all investigated regions of all five brains, and also in vascular endothelial cells in the cingulate gyrus. Neither astrocytes nor oligodendrocytes labelled for TSH-R. Again, in all six regions of the five brains, Tg was detected. However, Tg localized exclusively in vascular smooth muscle cells; no immunoreactivity was present in neurons.

Concerning TSH-R, unlike the selective neuronal body presence of TSH-R reported by Crisanti *et al.* (28), the presence of TSH-R also in the axon was explained by difference in human brains (embryonic vs adult) and TSH-R Ab used. Concerning Tg, unlike its vascular and neuronal expression reported by Gini *et al.* (11), the vascular-restricted expression was explained by difference in the TgAb used and by Gini *et al.* (11), having used brain from patients with HE. Moodley *et al.* (29) speculated that "the circulating anti-Tg IgG could bind to Tg in the tunica media
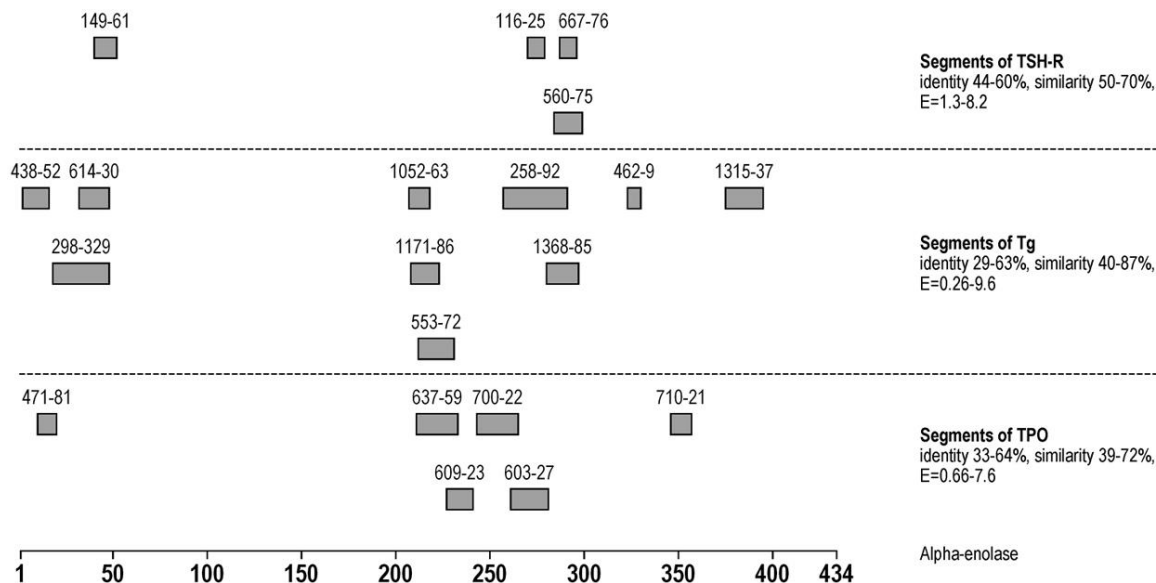
Homology between TSH-R/Tg/TPO and HE autoantigens

Figure 5. Homologies between human alpha-enolase and thyroid stimulating hormone receptor (TSH-R), thyroglobulin (Tg) and thyroperoxidase (TPO).
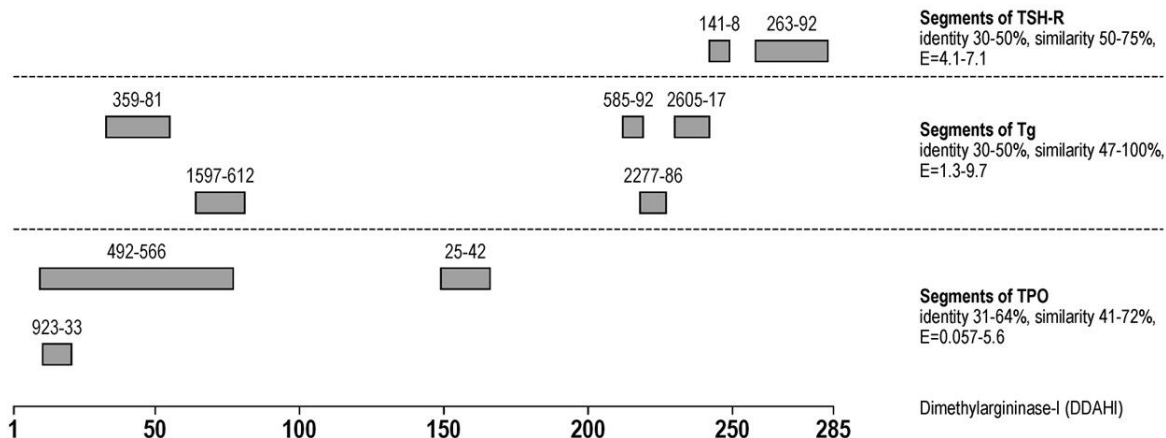

Figure 6. Homologies between human dimethylargininase-I (DDAHI) and thyroid stimulating hormone receptor (TSH-R), thyroglobulin (Tg) and thyroperoxidase (TPO).

causing sub-clinical vasculitis", with subsequent cerebral hypoperfusion.

In a subsequent study, this South African group extended this investigation on the expression of TSH-R and Tg specifically in limbic regions of normal human brain (30). Forensic human samples of six limbic regions (amygdala, cingulate gyrus, frontal cortex, hippocampus, hypothalamus, and thalamus) were obtained post mortem from the

above five individuals (29). The authors demonstrated neuronal expression of TSH-R in all limbic regions examined. The frontal cortex and cingulate gyrus displayed the most intense staining. There was no evidence of TSH-R immuno-labelling within the cerebral vasculature and neuronal support cells such as the oligodendrocytes, astrocytes, neuroglia and satellite cells, for any of the limbic regions examined. They also demonstrated Tg expression in the cerebral vasculature (vascular

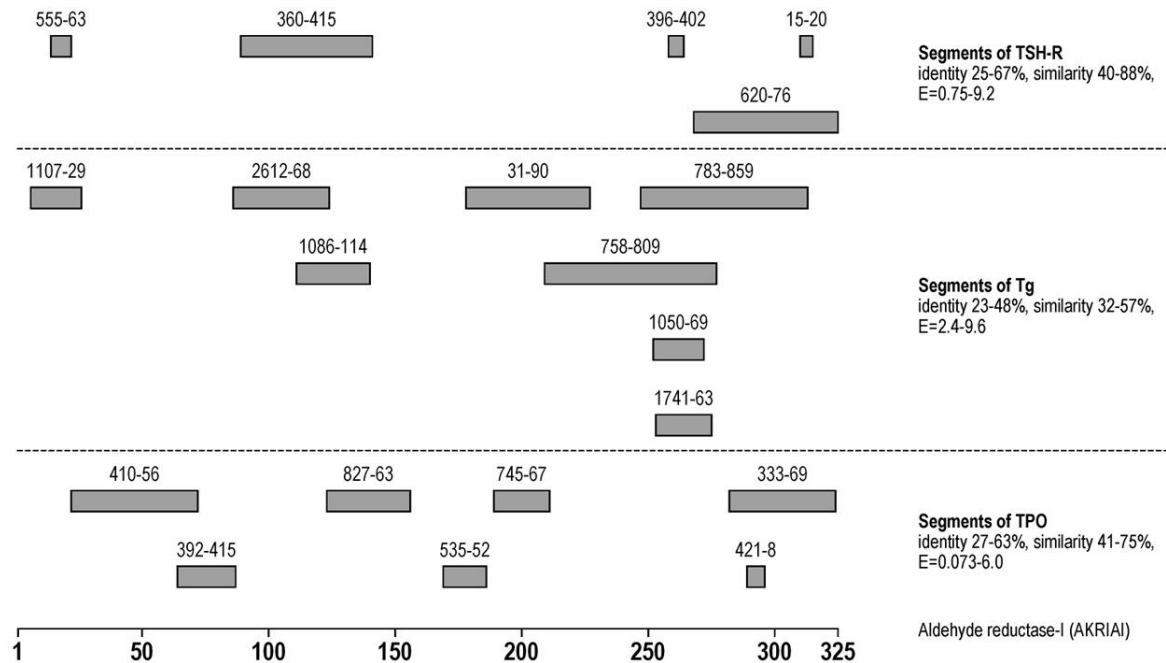**Homology between TSH-R/Tg/TPO and HE autoantigens**

Figure 7. Homologies between human aldehyde reductase-I (AKRIAI) and thyroid stimulating hormone receptor (TSH-R), thyroglobulin (Tg) and thyroperoxidase (TPO).

smooth muscle of the *tunica media* and tunica *adventitia)* of all limbic regions, with the cingulate gyrus and amygdala displaying the highest intense staining, and in some neurons. Intense immunoreactive Tg was demonstrated in most neuronal cell bodies and axons of the cingulate gyrus, while similar cellular structures in the frontal cortex exhibited less staining; no staining was observed in the other four limbic regions. The authors concluded "cerebro-limbic localisation of thyroid proteins may have potential roles in neuro-psycho-pharmacology", without mentioning pathophysiology implications for HE, but rather mentioning "the association between thyroid disorders and psychiatric illness".

Though a demonstration of the CNS expression of TPO similar to that provided for both Tg and TSH-R (28-30) is lacking, nevertheless the brain expression of TPO was inferred by the observed binding of TPOAb to astrocytes (30). Blanchin *et al.* (31) studied sera and CSF from 10 HE patients, 33 control patients (i.e., patients who were referred to the emergency ward with meningitis (n= 15), intractable headache (n= 8), peripheral neuropathy

(n= 4), multiple sclerosis (n= 6)). They were free of AITD except two who were diagnosed with Hashimoto's thyroiditis. Other controls were sera from 12 patients with a HT, but not HE, and 4 healthy adult volunteers without AITD or CNS disease. Sera immunoreactivity was tested on cerebrum and cerebellum from *Macacus rhesus* monkeys and normal human astrocyte coverslips. Normal primary human astrocytes were derived from the whole brain of one donor, 18 weeks old fetus. All 10 HE patients exhibited high serum levels (>50 IU/mL; normal values < 25) of TPOAb or Tg Ab, or both. High levels of TPOAb and TgAb were detected in all the HE patients' CSF. The 10 sera from HE patients but not the 12 from HT patients or the 4 from healthy subjects bound to structures in primate cerebellar tissues. Experiments demonstrated that this binding was accounted for by the TPOAb, not the TgAb, and the reactive cells were the astrocytes. Stained cells were mostly located in the subcortical cerebellar white matter, near the granular cell layer. No staining of cerebellar neuronal cells, including granular and Purkinje cells, was observed. Because none of the sera bound to primate cerebrum tissues, the authors inferred that the TPO Ab electively recognize primate

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TSH-R          149  STDIFFILEITDN  161
                    ST I+   LE+ DN
Alpha-enolase   40  STGIYEALELRDN   52


TPO            700  GLTRVPM-DAFQVGKFPEDFESCD  722
                    G+   V   + F+ GK+  DF+S D
Alpha-enolase  243  GMD-VAASEFFRSGKYDLDFKSPD  265


Tg            1597  EFPVMQCLTDC--TEDEA  1612
                    E P  + L DC    ED A
DDAHI           64  ELPADESLPDCVFVEDVA   81
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Figure 8. Examples of amino acid sequence alignments between epitope-containing segments of thyroid autoantigens and their homologous counterparts of HE-associated autoantigens.

cerebellum structures. The authors concluded that "Although not excluding the role of other neuropathogenic antibody(ies) in HE, present data prompt identification of the astrocytic antigenic target(s) of HE anti-TPO aAb".

6. CONCLUSION

We think that our work represents a significant advance in the pathogenesis of SREAT, upon keeping in mind the possible mechanism of SREAT as deriving by thyroid Ab that circulate in the CSF, because either synthesized intrathecally (11) or, more likely, systemically derived and crossing the damaged blood–brain barrier, and that may react with intracranial antigens (32-35). The homologies that we report here for the first time validate the hypothesis that we had formulated, support the mechanism of autoantigens expressed in CNS and thyroid (alpha-enolase, DDAHI and AKRIAI) that share homology with the classic thyroid autoantigens (Tg, TPO and TSH-R). Thus, some HT or GD patients might develop SREAT because they produce anti-thyroid Ab that, after crossing the blood-brain barrier, may react with regions of SREAT-associated CNS autoantigens that share local homology with thyroid Ag. This cross-reaction possible mechanism is not mutually exclusive with respect to the other more straightforward possible mechanism of binding of TgAb and TSH-RAb to the corresponding autoantigens (Tg and TSH-R) that are expressed in neuronal, glial and vascular cells, as summarized at the beginning of the Discussion. Though demonstration of the CNS expression of TPO

similar to that provided for both Tg and TSH-R (28-30) is lacking, nevertheless binding of TPOAb to brain TPO cannot be excluded based on binding of TPOAb to astrocytes (31). However, the synthesis of Ab against epitopes of any of Tg, TPO and TSH-R that would cross-react with any of epitopic regions of alpha-enolase, AKRIA and DDAHI sharing amino acid homology with thyroid autoantigen(s) is probabilistically rare, thus explaining why SREAT is rare in the universe of patients with HT or GD. Furthermore, we think that the involvement of TSH-R in the homologies with alpha-enolase, DDAHI and AKRIAI is of relevance. Such homologies could explain why encephalopathy may occur also in GD patients, and not solely in Hashimoto's thyroiditis patients. Finally, it cannot be excluded that other proteins expressed in the CNS share local amino acid sequence homology with at least one of the thyroid autoantigens. Indeed, this possibility plus the herein demonstrated existence of multiple segments of homology between each CNS-protein and each thyroid autoantigen, fits well the multiform clinical phenotype of SREAT.

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