Introduction

Hashimoto’s encephalopathy (HE) was initially described in 1966 in association with Hashimoto’s thyroiditis (HT) [1], and later found to be associated, although less frequently, with the other autoimmune thyroiditis (AT): Graves’ disease (GD). Because, regardless of the HT or

A few patients with Hashimoto’s thyroiditis or Graves’ disease develop a polymorphic syndrome of the central nervous system (CNS) termed Hashimoto’s encephalopathy or steroid-responsive encephalopathy associated with autoimmune thyroid disease (HE/SREAT). They have high levels of thyroid autoantibodies (TgAb, TPOAb and/or TSH-R-Ab) in blood and cerebrospinal fluid. Autoantibodies against alpha-enolase, aldehyde reductase-I (AKRIA) and/or dimethylargininase-I (DDAHI), proteins expressed in the CNS among other tissues, were detected in the blood and, when searched, in the cerebrospinal fluid of HE/SREAT patients. Recently, we reported that alpha-enolase, AKRIA and DDAHI share local sequence homology with each of the three autoantigens (TgAb, TPOAb, TSH-R-Ab), often in epitope-containing segments of the thyroid autoantigens. We hypothesized that there might be additional CNS-expressed proteins homologous to thyroid autoantigens, possibly overlapping known epitopes of the thyroid autoantigens. We used bioinformatic methods to address this hypothesis.

Six, 27 and 47 of 46,809 CNS-expressed proteins share homology with TSH-R, Tg and TPO, respectively. The homologous regions often contain epitopes, and some match regions of thyroid autoantigens which have homology with alpha-enolase, AKRIA and/or DDAHI. Several of the aforementioned proteins are present in CNS areas that show abnormalities at neuroimaging in HE/SREAT patients. Furthermore, autoantibodies against some of the said six, 27 and 47 proteins were reported to be associated with a number of autoimmune diseases.

Not only we validated our hypothesis, but we think that such a variety of potential CNS targets for thyroid Ab against epitopes contained in regions that have local homology with CNS proteins may explain the polymorphic phenotypes of HE/SREAT. Only when elevated amounts of these Ab are synthesized and trespass the blood-brain barrier, HE/SREAT appears. This might explain why HE/SREAT is so relatively rare.
GD association, encephalopathy is very sensitive to corticosteroid therapy, another denomination is steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT). SREAT represents a rare complication of autoimmune thyroiditis [2] and may precede it even by years, similar to thyroid eye disease in patients with Graves disease [3–4]. SREAT patients have abnormal electroencephalography and increased concentration of proteins/immunoglobulins G (IgG) in the cerebrospinal fluid, which can be observed in 90% and 80% of patients, respectively, but these findings are not specific of the disease [5]. Serum anti-thyroid antibodies (TAb) are typically elevated in SREAT patients, but their levels do not correlate with either severity or any specific clinical presentation.

Between 2002 and 2008, three autoantigens shared by the central nervous system (CNS) and the thyroid, and targeted by autoantibodies specifically present in SREAT patients, were identified: alpha-encephalase, dimethylargininase-1 (DDAH) and aldehyde reductase-1 (AKRIAI) [6–8]. This discovery led to the idea that autoimmunity against autoantigens common to CNS and thyroid could be one of the pathogenetic mechanisms of SREAT, in addition to the action of antithyroid autoantibodies on Tg, TPO and TSH-R expressed in the central nervous system [9].

In 2003, a paper described one patient with HE and reviewed the HE literature (85 patients who met their inclusion criteria out of “105 patients with brain dysfunction associated with possible Hashimoto thyroiditis”) [10]. This paper reported that pathologic findings were available for only three HE patients (one based on necropsy and two based on brain biopsy) [10]. In one patient, autopsy revealed lymphocytic infiltration in the brainstem (including its veins and venules), leptomeninx of the biopsy) [10]. In one patient, autopsy revealed lymphocytic infiltration in the brainstem (including its veins and venules), leptomeninx of the biopsy) [10]. In one patient, autopsy revealed lymphocytic infiltration in the brainstem (including its veins and venules), leptomeninx of the biopsy) [10]. In one patient, autopsy revealed lymphocytic infiltration in the brainstem (including its veins and venules), leptomeninx of the biopsy) [10]. This discovery led to the idea that autoimmunity against autoantigens common to CNS and thyroid could be one of the pathogenetic mechanisms of SREAT, in addition to the action of antithyroid autoantibodies on Tg, TPO and TSH-R expressed in the central nervous system [9].

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For sake of completeness, we should note that Chong et al. [10] missed three patients. One was a French patient [13], in whom post-mortem neuropathology demonstrated non-specifically activated microglia. The second was a Japanese patient [14], in whom autopsy revealed no evidence of CNS vasculitis or other brain abnormalities. The third was an American patient with a questionable 7-mm area of the left parietal lobe [15]. Biopsy revealed moderate gliosis, some perivascular lymphoid cells and macrophages, scattered microgliosis in the parenchyma, but not vasculitis or microglial nodules [15].

In subsequent years, post-mortem examination in HE patients demonstrated “mild perivascular lymphocytic infiltration throughout the brain and leptomeninges plus diffuse gliosis of gray matter in the cortex, basal ganglia, thalami, hippocampi, and, to a lesser extent, the parenchymal white matter” [16]. Biopsy of other HE patients revealed: (i) “patchy myelin pallor, scant perivascular chronic inflammation, mild gliosis, and microglial activation” [17]; (ii) primary vasculitis of the CNS [18]; (iii) diffuse gliosis and perivascular lymphocyte infiltration with CD3 + T-cell predominance, “... with no signs of a brain tumor” in a patient with a tumor-like lesion of the left caudate nucleus, “suggesting cerebral vasculitis as an underlying etiology” [19]; (iv) non-vasculitic autoimmune inflammatory meningoencephalitis [20]; (v) reactive gliosis, angiogenesis, swollen vascular endothelial cells, mild lymphocyte infiltration (almost exclusively T cells) around small vessels [21].

Molecular mimicry between thyroid autoantigens and other autoantigens was mentioned by several authors as a possible clinically relevant causal mechanism of extrathyroid manifestations of thyroid autoimmunity, including some neurological and psychiatric disorders [22–24].

Just very recently, we demonstrated that there is striking local homology between thyroid autoantigens and the three HE/SREAT-autoantigens [25]. Particularly, Tg was homologous to 10 regions of alpha-encephalase, 8 regions of AKRIAI, and 5 regions of DDAHI. TPO was homologous to 6 regions of alpha-encephalase, 7 regions of AKRIAI, and 3 regions of DDAHI. Finally, TSH-R was homologous to 4 regions of alpha-encephalase, 5 regions of AKRIAI, and 2 regions of DDAHI. Importantly, in regard to alpha-encephalase (the sole of the three HE/SREAT autoantigens for which epitopes have been characterized), a total of 5 regions homologous to Tg, one region homologous to TPO, and one region homologous to TSH-R fell within, or adjacent to, epitopes of the protein. From the opposite perspective, a total of 4 regions of Tg, 5 of TPO and 2 of TSH-R homologous to alpha-encephalase contained epitopes. Epitopes in each of the three thyroid autoantigens were present also in their regions that were homologous to regions of AKRIAI and DDAHI [25]. In brief, we provided some indirect evidence that a number of regions of homologies were relevant for the autoimmunity associated with HE/SREAT.

We hypothesized that alpha-encephalase, AKRIAI and DDAHI might be the classic “tip of the iceberg”, viz. we hypothesized that there could be more proteins expressed in the CNS, not necessarily in a CNS-restricted expression mode, which share homology with at least one of the three thyroid autoantigens. Applying the same bioinformatic approach used for alpha-encephalase, AKRIAI and DDAHI, we searched for such homologies.

Material and methods

We used our standard procedure, as in previous bioinformatic papers [25–31]. We retrieved the amino acid sequence of the precursors of the three “classical” human thyroid autoantigens, i.e. TSH-R (accession number P16473), Tg (accession number NP_003226) and TPO (accession number AAA61217) from the Entrez Protein database (https://www.ncbi.nlm.nih.gov/protein). Next, we probed each of these three autoantigens for amino acid sequence homology with human proteins of the same database whose records contained the term “brain” or “central nervous system”. Proteins labeled as “incomplete” or “hypothetical” were excluded. We also excluded alpha-encephalase, AKRIAI and DDAHI, since they were investigated in our previous paper [25]. The Protein BLAST (Basic Local Alignment Search Tool) software version 2.8.0+ [32] was used to perform the comparison. Analysis was made with the standard parameters of the program, and only results with E < 10 were considered. Finally, the records of the proteins identified were manually reviewed, to exclude those not expressed in the CNS (the presence of the term “brain” and/or “central nervous system” in the record was sometimes incidental, not related to the actual localization of the protein).

As also done previously [25–31], we verified the immunological relevance of the homologies selected, checking for their possible overlap (s) with known epitopes of TSH-R, Tg and TPO [26–31,33–36]. To strengthen the immunological relevance of the homologies that we found, we searched the literature for the presence of serum autoantibodies against each of the thyroid autoantigen-homologous proteins in autoimmune diseases, including thyroid autoimmune diseases. To this aim, we searched in the PubMed database using the search string “autoantibody OR autoimmune OR autoreact*” AND followed by the name of each protein, and manually revised the results to select only relevant original articles.

To quickly know (i) which areas of the CNS express each of the proteins that we found to be thyroid autoantigen-homologous, and (ii) whether the thyroid gland also expressed these proteins, we probed the Expression Atlas (https://www.ebi.ac.uk/gxa/home) [37].

Results

CNS-expressed proteins found to be homologous to thyroid autoantigens

Table 1, Table 2 and Table 3 list which of the 46,809 CNS-expressed
### Table 1
Homologies between TSH-R and proteins from brain or central nervous system.

| Protein [Entrez Protein GI accession number] | Protein segment | TSH-R segment | Identity | Overall homology* | E value | Coincidences with** |
|---------------------------------------------|-----------------|---------------|----------|-------------------|---------|---------------------|
| 1 Leucine-rich repeat-containing G-protein coupled receptor 4 (LRG4) [157694513] | 20-253 | 20-252 | 24% | 39% | 1.19 × 10^{-4} | Eno | D |
| | | | | | 177-815 | 52-692 | 24% | 44% | 6.95 × 10^{-5} | Eno | A | D |
| 2 Leucine-rich repeat-containing G-protein coupled receptor 5 (LRGS) [4504379] | 234-868 | 32-732 | 24% | 42% | 1.25 × 10^{-4} | Eno | A | D |
| 3 Relaxin receptor 2/Leucine-rich repeat-containing G-protein coupled receptor 8 (LRGB) [1867729] | 115-708 | 29-695 | 22% | 40% | 7.82 × 10^{-5} | Eno | A | D |
| 4 Relaxin receptor 1/Leucine rich repeat-containing G protein-coupled receptor 7 (LRGR) [359279868] | 182-738 | 182-710 | 25% | 44% | 1.75 × 10^{-3} | Eno | A | D |
| 5 Chondroadherin [153251229] | 24-219 | 28-250 | 21% | 44% | 0.013 | Eno | D |
| 6 Leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 2 precursor (LINGO2) [22749183] | 26-205 | 22-254 | 25% | 43% | 0.028 | Eno | D |
| 7 Somatostatin receptor type 2 [5578559] | 24-322 | 395-685 | 23% | 41% | 1.14 × 10^{-5} | Eno | A |
| 8 Neuropeptide Y receptor type 1 [4505445] | 50-331 | 424-689 | 24% | 41% | 2.07 × 10^{-5} | Eno | A |
| 9 Apelin receptor [4885057] | 38-318 | 424-687 | 25% | 42% | 2.78 × 10^{-5} | Eno | A |
| 10 Neuromedin-K receptor/Neurokinin B receptor/Tachykinin receptor 3 [7669548] | 84-382 | 418-696 | 26% | 43% | 4.26 × 10^{-4} | Eno | A |
| 11 Free fatty acid receptor 3 [4885329] | 88-334 | 494-731 | 20% | 41% | 5.11 × 10^{-5} | Eno | A |
| 12 Melanopin/Opsin-4 [15150803] | 73-386 | 417-710 | 22% | 36% | 1.60 × 10^{-5} | Eno | A |
| 13 G-protein coupled estrogen receptor 1/Membrane estrogen receptor [4504901] | 68-332 | 423-686 | 23% | 41% | 5.02 × 10^{-6} | Eno | A |
| 14 Alpha-1A adrenergic receptor [111118992] | 9-354 | 393-706 | 20% | 38% | 1.71 × 10^{-5} | Eno | A |
| 15 Vasopressin V1a receptor [4502331] | 64-358 | 427-688 | 21% | 39% | 3.46 × 10^{-5} | Eno | A |
| 16 Probable G-protein coupled receptor 34 [4885319] | 26-367 | 370-727 | 19% | 40% | 3.86 × 10^{-5} | Eno | A |
| 17 G-protein coupled receptor 26 [23592220] | 79-200 | 494-609 | 26% | 47% | 7.64 × 10^{-5} | Eno | A |
| 18 Orexin 2 receptor [1285033761] | 71-163 | 424-523 | 28% | 50% | 8.46 × 10^{-5} | Eno | A |
| 19 Oxytocin receptor [32307152] | 56-357 | 431-711 | 23% | 40% | 1.28 × 10^{-5} | Eno | A |
| 20 Orexin receptor type 1 [222080095] | 63-169 | 431-546 | 28% | 44% | 4.14 × 10^{-4} | Eno | A |
| 21 Galanin receptor type 2 [4503905] | 37-302 | 426-688 | 22% | 39% | 6.07 × 10^{-4} | Eno | A |
| 22 GPER protein [52350636] | 68-274 | 423-639 | 24% | 42% | 6.90 × 10^{-4} | Eno | A |
| 23 N/O/FQ opioid receptor [385252102] | 135-401 | 424-686 | 22% | 41% | 0.002 | Eno | A |
| 24 Type 2 angiotensin II receptor [23238240] | 103-350 | 481-707 | 24% | 41% | 0.002 | Eno | A |
| 25 Alpha-1B adrenergic receptor [4501959] | 57-357 | 426-687 | 19% | 37% | 0.006 | Eno | A |
| 26 Ms opioid receptor [119568960] | 142-451 | 424-744 | 20% | 39% | 0.021 | Eno | A |
| 27 Melanin-concentrating hormone receptor 1 [397487122] | 119-393 | 424-691 | 22% | 40% | 0.013 | Eno | A |
| 28 Bombesin receptor subtype-3 [4502455] | 60-339 | 427-687 | 19% | 40% | 0.023 | Eno | A |
| 29 Neuropeptide Y receptor type 5 [5453796] | 5-93 | 381-466 | 27% | 50% | 0.029 | A |
| 30 C3a anaphylatoxin chemotactic receptor [4757888] | 331-444 | 576-687 | 22% | 44% | 0.151 | A |
| 31 Substance-P receptor/Tachykinin receptor 1 [4507343] | 54-163 | 436-554 | 25% | 41% | 0.365 | A |
| 32 Proteasome-activated receptor 2 [34577052] | 77-352 | 416-686 | 21% | 39% | 0.394 | Eno | A |
| 33 Trace amine-associated receptor 6 (TaR-6) [28173558] | 35-135 | 417-524 | 30% | 53% | 0.463 | A |
| 34 Urotensin-2 receptor/G-protein coupled receptor 14 [9506745] | 115-323 | 487-686 | 23% | 42% | 0.515 | Eno | A |
| 35 Nicotinrev receptor [974065167] | 132-322 | 508-686 | 25% | 44% | 0.779 | Eno | A |
| 36 G-protein coupled receptor 24 [56554976] | 149-267 | 584-691 | 24% | 47% | 0.812 | A |
| 37 C-C chemokine receptor type 7/Epstein-Barr virus-induced G-protein coupled receptor 1/MIP-3 beta receptor [4502641] | 320-374 | 672-725 | 29% | 49% | 0.941 | A |

*Identical plus similar amino acids.

**Coincidences with segments of TSH-R homologous to known autoantigens of Hashimoto’s encephalopathy, i.e. alpha-enzyme (Eno), AKRIIA (A) and DDAH (D). Segments 149–161 and 560–575 of TSH-R are homologous to segments 40–52 and 284–299 of alpha-enzyme, respectively. Segments 360–415, 396–402, 555–563 and
proteins in our databank, were homologous to TSH-R, Tg and TPO, respectively. There were 46 proteins (~0.1%), 27 (~0.06%) and 47 proteins (~0.1%) that shared homology with TSH-R, Tg and TPO, respectively. Tables 1-3 illustrate the span of the homologous segments, the degree of amino acid identity and overall amino acid homology (namely, identity plus similarity).

Making reference to Table 2 as an example for describing the other two Tables (Table 1 and Table 3), there are proteins with a single segment of homology each, such as butyrylcholinesterase (aa 9–527 matching aa 2204–2722 of Tg), and other proteins with multiple segments of homology (which are listed from the most N-terminal to the most C-terminal position). Examples of this multiplicity are the nine segments of SPARC-1/SMOC-1 that are homologous to Tg. Close inspection of these nine segments (Table 2) shows that they fall within the long region 54–340 of SPARC-1/SMOC-1, which matches a discontinuous and much longer region of Tg comprised between aa 34 and 1212. Indeed, two long stretches of Tg (aa 359–608 and 662–880) did not match any segment of aa 54–340 of SPARC-1/SMOC-1. The extent of amino acid identity with Tg segments ranges from 22% (KIAA1366 protein) to 50% (aa 333–372 of testican-1 and aa 333–374 of testican-2), and overall homology from 36% (aa 636–752 of signal peptide, CUB and EGF-like domain-containing protein 1) to 67% (aa 333–372 of testican-1). Of interest, the group of Tg segments homologous to CNS-expressed proteins (Table 2) and the group of Tg segments homologous to alpha-enolase, AKRIAI or DDAHI [25] showed several overlaps. In detail, Tg segments of the first group fully contained a Tg segment of the second group in 59 cases (with some multiple matches) and were fully contained in a Tg segment of the second group in 3 cases, while a partial overlap of more than 10 residues was observed in 10 cases.

This pattern of proteins having a single segment of homology (for instance, protacderhin Fat 4) or other proteins having multiple segments of homology (for instance, fibrillin-1 and fibrillin-3) applied to TPO (Table 3). Identity with TPO ranges from 22% (prostaglandin G/H synthase 1/cyclooxygenase-1) to 54% (aa 158–191 of Adhesion G protein-coupled receptor E2/EGF-like module receptor 2/CD312), and overall homology from 36% (aa 1621–1706 of LTBP-1) to 64% (thrombospondin-3 and aa 2204–2236 of fibrillin-3). TPO segments homologous to CNS-expressed proteins (Table 3) fully contained a Tg segment homologous to alpha-enolase, AKRIAI or DDAHI [25] in 36 cases (with many multiple matches), and two partial overlaps of more than 10 residues were also observed.

In the case of TSH-R (Table 1), with the only exception of LGR4, all proteins (which were cell receptors, except chondroadherin) had a single segment of homology with the thyroid autoantigen. Identity with TSH-R ranges from 19% (probable G protein-coupled receptor 34, alpha-B adrenergic receptor and bombesin receptor subtype-3) to 55% (G protein-coupled receptor), and overall homology from 36% (Melanop- sin/Opsin-4 and 5-hydroxytryptamine receptor 7) to 75% (G protein-coupled receptor). TSH-R segments homologous to CNS-expressed proteins (Table 1) fully contained a Tg segment homologous to alpha-enolase, AKRIAI or DDAHI [25] in 122 cases (with many multiple matches), while the partial overlaps of more than 10 residues were five.

Topographic position of the homologous proteins with respect to domains and epitopic regions of each thyroid autoantigen

Fig. 1 provides illustrative examples for TSH-R, Tg and TPO (top, middle and bottom panel, respectively), with their epitopes highlighted. The position of sequence homology within given domains of the three thyroid autoantigens can be appreciated in Figs. 2-4. Of the 46 proteins homologous to TSH-R (Fig. 2), only the first 6 (LGR4, LGR5, relaxin receptor 1, relaxin receptor 2, chondroadherin and LINGO2) match the whole length of TSH-R, while the others match the serpentine domain, most frequently for its whole length. A few proteins match the C-terminus of the extracellular domain, and a few match the intracellular domain. With the single exception of G protein-coupled receptor and C-C chemokine receptor type 7 (whose homology with TSH-R starts at aa 670 and 672, respectively, of the thyroid autoantigen), all other 44 proteins matched TSH-R regions containing at least one epitope (Fig. 2).

Concerning Tg (Fig. 3), of the 27 homologous proteins, 7 matched a long N-terminal region, 4 a very short central region, and the remaining 11 the acetycholinesterase-like domain at the C-terminus of Tg. Note- worthy, all 27 proteins matched regions of Tg containing at least one epitope, including the short Tg segment 1470–1494 matched by Ephrin type-B receptor 6, since the aa sequence 1473–1526 of Tg is epitopic (Fig. 3).

Concerning TPO (Fig. 4), of the 48 homologous proteins, 2 (perox- idasin homolog, and peroxidasin-like protein) matched the long whole heme-peroxidase domain (residues 142–738) and the N-terminal segment ahead of it, 3 matched part of the heme-peroxidase domain (prostaglandin G/H synthase 1, prostaglandin G/H synthase 2, and dual oxidase 2 precursor variant), while the remaining 43 matched the complement control protein-like domain (CCP-like domain at residues 740–795) and/or the epidermal growth factor (EGF)-like domain (EGF-like domain, residues 786–946), with a few matching also the end of the heme-peroxidase and a few matching part of the transmembrane domain (residues 847–871). Noteworthy, one CNS-protein (nudigen-1/entactin), shared homology also with Tg. The segment 800–840 of nudigen-1/entactin was 43% identical and 50% homologous to the segment 794–839 of TPO (Table 3 and Fig. 4). On the other hand, 6 segments of nudigen-1/entactin spanning aa 847–925 were 35–45% identical and 50–58% homologous to six segments of Tg: 96–161, 315–358, 660–726, 882–921, 1015–1076 and 1159–1216 (Table 2 and Fig. 3). While the segment 794–839 of TPO, and 315–358, 660–726, 882–921 and 1015–1076 of Tg do not contain epitopes, the Tg segment 96–161 and 1159–1216 contain epitopes at aa 20–190, 1116–1168 and 1168–1269 (Fig. 3 and Fig. 4).

For 18 of the proteins shown in Table 3, all homologies were with segments of TPO which do not contain epitopes or had 6 or less amino acids of overlap with TPO epitopes. These proteins were, in alphabetical order: adhesion G protein-coupled receptor E2, C-type lectin domain family 14 member A, dual oxidase 2 precursor variant, EGF-containing fibulin-like extracellular matrix protein 1, EGF-containing fibulin-like extracellular matrix protein 2, EGF-like protein 6, EGF-like protein 7, fibrillin 1 variant, KIAA1237 protein, mutant p53 binding protein 1, nephroenctin, nudigen-1, protein HEG homolog 1, protein kinase C-binding protein NELL2, signal peptide, CUB and EGF-like domain-containing protein 1, thrombospondin-3, tolidoid-like protein 1, vitamin K-dependent protein S. For 16 other proteins, homologies included only segments belonging to IDR-B: this was the case of fibrillin-1, proto- cadherin Fat 4, low-density lipoprotein receptor-related protein 4, latent-transforming growth factor beta-binding protein 4, seizure related 6-like protein 2, CUB and sushi domain-containing protein 1, multiple epidermal growth factor-like domains protein 6, seizure 6-like protein, complement component CIq receptor, low-density lipoprotein receptor-related protein 1B, P-selectin, fibulin-1, NOTCH4 protein, complement receptor type 2, endostatin, CUB and sushi domain-containing protein 3.

The thyroid-autoantigens-homologous proteins are expressed in given areas of the CNS, and almost all of them are expressed in the thyroid

Supplementary Tables 1–3 summarize information from the Expression Atlas ([https://www.ebi.ac.uk/gxa/home] [37]) about the expression of the proteins homologous to TSH-R, Tg and TPO, respectively, in different areas of the CNS and in the thyroid.
Table 2
Homologies between thyroglobulin (Tg) and proteins from brain or central nervous system.

| Protein [Entrez Protein GI accession number] | Protein segment | Tg segment | Identity  | Overall homology* | E value | Coincidences with** |
|---------------------------------------------|-----------------|------------|-----------|-------------------|---------|---------------------|
| 1 Nidogen-1/Entactin [115298674]             | 847-919         | 660-726    | 35%       | 52%               | 1.23 × 10⁻⁵ |                     |
|                                             | 849-917         | 96-161     | 39%       | 50%               | 1.61 × 10⁻⁵ |                     |
|                                             | 859-922         | 1015-1076  | 43%       | 58%               | 8.51 × 10⁻⁷ |                     |
|                                             | 867-925         | 1159-1216  | 45%       | 53%               | 4.60 × 10⁻⁷ |                     |
|                                             | 874-919         | 315-358    | 45%       | 58%               | 0.002   |                     |
|                                             | 880-919         | 882-921    | 35%       | 52%               | 0.281   |                     |
| 2 Testican-1/Protein SPOCK [4759164]         | 281-368         | 972-1062   | 29%       | 46%               | 6.03 × 10⁻⁵ |                     |
|                                             | 312-385         | 298-367    | 37%       | 52%               | 2.42 × 10⁻⁵ |                     |
|                                             | 313-372         | 96-155     | 35%       | 51%               | 0.001   |                     |
|                                             | 333-372         | 616-653    | 50%       | 67%               | 7.80 × 10⁻⁵ |                     |
|                                             | 333-376         | 48-92      | 40%       | 62%               | 0.001   |                     |
| 3 Testican-2/SPARC/osteonectin, CWCV, and Kazal-like domains proteoglycan 2 (SPOCK2) [7662036] | 54-149         | 50-151     | 28%       | 40%               | 0.034   |                     |
|                                             | 54-158          | 1106-1210  | 30%       | 39%               | 1.39 × 10⁻⁴ |                     |
|                                             | 95-149          | 34-83      | 41%       | 54%               | 2.69 × 10⁻⁴ |                     |
|                                             | 114-294         | 1027-1212  | 28%       | 42%               | 1.03 × 10⁻⁸ |                     |
|                                             | 116-292         | 181-358    | 25%       | 39%               | 8.360   |                     |
|                                             | 119-317         | 881-1110   | 26%       | 38%               | 1.73 × 10⁻⁶ |                     |
|                                             | 227-272         | 34-73      | 30%       | 52%               | 6.927   |                     |
|                                             | 227-340         | 96-212     | 26%       | 39%               | 0.221   |                     |
|                                             | 239-295         | 609-461    | 40%       | 54%               | 0.031   |                     |
|                                             | 300-384         | 17-95      | 31%       | 43%               | 2.80 × 10⁻³ |                     |
| 4 SPARC-related modular calcium-binding protein 1/ Secreted modular calcium-binding protein 1 (SMOC-1) [11545873] | 311-373         | 652-717    | 30%       | 52%               | 0.029   |                     |
|                                             | 317-376         | 96-155     | 38%       | 46%               | 9.63 × 10⁻⁴ |                     |
|                                             | 318-372         | 999-1062   | 42%       | 51%               | 1.42 × 10⁻⁶ |                     |
|                                             | 337-376         | 315-353    | 45%       | 57%               | 0.018   |                     |
|                                             | 337-376         | 616-653    | 42%       | 62%               | 0.005   |                     |
|                                             | 337-376         | 1165-1205  | 48%       | 60%               | 5.46 × 10⁻⁴ |                     |
| 5 Testican-3 [3581970]                       | 91-154          | 598-659    | 34%       | 56%               | 1.05 × 10⁻⁵ |                     |
|                                             | 105-153         | 311-358    | 36%       | 51%               | 0.043   |                     |
|                                             | 109-156         | 116-163    | 39%       | 52%               | 0.002   |                     |
|                                             | 109-251         | 48-194     | 25%       | 40%               | 0.017   |                     |
|                                             | 109-301         | 1027-1230  | 28%       | 43%               | 4.21 × 10⁻³ |                     |
|                                             | 198-327         | 78-210     | 26%       | 40%               | 0.030   |                     |
|                                             | 233-395         | 613-672    | 33%       | 50%               | 0.012   |                     |
|                                             | 210-265         | 611-660    | 33%       | 51%               | 0.033   |                     |
|                                             | 215-253         | 315-348    | 41%       | 56%               | 0.581   |                     |
| 7 Insulin-like growth factor-binding protein 5 [10834982] | 636-752         | 1427-1532  | 29%       | 36%               | 0.106   |                     |
| 8 Signal peptide, CUB and EGF-like domain-containing protein 1 [120587029] | 269-312         | 1473-1531  | 35%       | 44%               | 2.342   |                     |
| 9 Ephrin type-B receptor 2 [822606583]       | 311-335         | 1470-1494  | 48%       | 60%               | 6.469   |                     |
| 10 Ephrin type-B receptor 6 [294862532]      | 260-319         | 1457-1531  | 28%       | 42%               | 7.379   |                     |
| 11 Ephrin type-A receptor 7 [568599847]      | 46-573          | 2211-2728  | 32%       | 50%               | 4.79 × 10⁻⁶ |                     |
| 12 Acetylcholinesterase (Y1 blood group) [219518823] | 9-527           | 2204-2722  | 29%       | 47%               | 2.43 × 10⁻⁶ |                     |
| 13 Butyrylcholinesterase [1073548962]        | 66-596          | 2225-2730  | 30%       | 46%               | 10⁻⁴    |                     |
| 14 Neurologin-3 [262359974]                  | 1062 6596       | 2225-2730  | 30%       | 46%               | 10⁻⁴    |                     |

(continued on next page)
The same Supplementary Tables also show, highlighted in gray, which areas of CNS expressing thyroid autoantigen-homologous proteins were found to show abnormalities at diagnostic neuroimaging in patients with HE/SREAT (references about these data are available upon request). Of these areas, those with the highest number of TSH-R-homologous proteins expressed were frontal lobe (n = 33 each); those with the highest number of Tg-homologous proteins expressed were frontal lobe and temporal lobe (n = 26 each) followed by brain, cerebral cortex and frontal cortex (n = 25 each); those with the highest number of TPO-homologous proteins expressed were brain (n = 47), temporal lobe (n = 45), cerebral cortex, frontal cortex and frontal lobe (n = 44 each).

For a few proteins homologous to TSH-R (free fatty acid receptor 3, trace amine-associated receptor 6, olfactory receptor 2A14, trace amine-associated receptor 8, olfactory receptor 2 J3), the Expression Atlas provides no details on which CNS areas express these proteins. Also for a few proteins, the same Atlas provides no details as to whether the thyroid gland expresses these proteins, or reports that their expression is below the cutoff value considered (Supplementary Tables 1–3). Supplementary Table 4 shows data reported in the Expression Atlas about the expression of the three currently known autoantigens of HE/SREAT in the thyroid and in the brain/CNS.

Autoantibodies against the thyroid-autoantigen-homologous CNS-expressed proteins have been detected in a number of autoimmune diseases

As explained under Materials and Methods, we probed the literature for articles on the presence of serum autoantibodies against each of the thyroid autoantigen-homologous proteins in autoimmune diseases, including thyroid autoimmune diseases, by performing a PubMed search with the string “(autoantibody圣诞老人) OR autoimmunity OR auto-reactive)” AND followed by the name of each protein and manually selecting relevant original papers [38–93]. As summarized in Table 4, of the 46 CNS proteins homologous to TSH-R, 5 (11%; LGR4, chondroadherin, alpha-1A adrenergic receptor, Mu opioid receptor, and melanin-concentrating hormone receptor 1) were reported to stimulate autoAb, and in the following conditions: CNS demyelinating disease, autoimmune hepatitis, refractory hypertension, psychiatric disorders, chronic fatigue syndrome and vitiligo [38–51]. Of the utmost interest are anti-LGR4 autoAbs, because they were detected also in patients with AIT [30]. Noteworthy is also information available on epitopes of melanin-concentrating hormone receptor 1 [27], with aa 85–98 and 254–260 being major autoantibody epitopes, aa 51–80 and 154–158 being minor autoantibody epitopes, and aa 254–260 being the target of function-blocking antibodies. Thus, the segment 119–393 of melanin-concentrating hormone receptor 1, which we found to be homologous to the segment 424–1621 of Tg, contains epitopes (aa 154–158 and 254–260), as does the homologous TSH-R segment (epitope at aa 441–661).

As summarized in Table 5, of the 27 CNS proteins homologous to Tg, 2 (7%; nidogen-1/entactin and ephrin type-B receptor 2) receptor 2) were reported to generate autoAb, and in the following conditions: certain types of glomerulonephritis, autoimmune uveoretinitis, systemic lupus erythematosus and related disorders (systemic vasculitis, rheumatoid arthritis), pulmonary renal syndrome, the Aicardi-Goutiéres syndrome, acute necrotizing encephalopathy, and systemic sclerosis [52–62]. As mentioned above (see heading “Topographic position of the homologous proteins with respect to domains and epitopic regions of each thyroid autoantigen”) of the 6 Tg-homologous segments of nidogen-1/entactin (of which one matches the epitopic region of Tg at aa 20–190, and another overlaps with the two epitopic region of Tg 1116–1168 and 1168–1269), four entirely contain the epitope 867–887 (segments 849–917, 847–919, 859–922 and 867–925), while two partially overlap with it (segments 874–919 and 880–919). It is noteworthy that segments 849–917 and 867–925 of nidogen-1, which entirely include an epitope
## Table 3
Homologies between thyroid peroxidase (TPO) and proteins from brain or central nervous system.

| Protein [Entrez Protein GI accession number] | Protein segment | TPO segment | Identity | Overall homology* | E value | Coincidences with** |
|---------------------------------------------|-----------------|-------------|----------|-------------------|--------|---------------------|
| 1 Peroxidin homolog/Melanoma-associated antigen MG50/Vascular peroxidase 1 [109150416] | 604-1314 | 8-734 | 41% | 58% | 1.89 × 10^{-15} | Eno A D |
| 2 Peroxidin-like protein [633365073] | 516-1201 | 40-734 | 38% | 55% | 5.01 × 10^{-150} | Eno A D |
| 3 Prostaglandin G/H synthase 2/Cyclooxygenase-2 [4506265] | 208-340 | 318-459 | 28% | 43% | 1.50 × 10^{-8} | A |
| 4 Prostaglandin G/H synthase 1/Cyclooxygenase-1 [18104967] | 227-518 | 324-650 | 22% | 40% | 1.35 × 10^{-9} | Eno A D |
| 5 Fibrillin-1/Asprosin/Epididymis secretory sperm binding protein [311033452] | 515-572 | 768-840 | 32% | 47% | 0.011 | |
| | 570-613 | 794-840 | 36% | 55% | 0.129 | |
| | 611-655 | 794-841 | 43% | 56% | 3.33 × 10^{-4} | |
| | 723-765 | 796-840 | 37% | 55% | 0.015 | |
| | 908-952 | 794-840 | 36% | 51% | 0.063 | |
| | 1024-1070 | 794-840 | 38% | 48% | 0.005 | |
| | 1068-1104 | 794-832 | 38% | 51% | 1.620 | |
| | 1174-1238 | 774-840 | 29% | 46% | 1.196 | |
| | 1216-1280 | 775-840 | 33% | 52% | 9.48 × 10^{-4} | |
| | 1344-1404 | 776-840 | 38% | 55% | 4.31 × 10^{-5} | |
| | 1392-1455 | 784-847 | 27% | 50% | 0.635 | |
| | 1645-1692 | 793-843 | 35% | 45% | 0.166 | |
| | 1888-1930 | 793-840 | 37% | 50% | 2.828 | |
| | 1928-1973 | 794-840 | 53% | 63% | 8.86 × 10^{-7} | |
| | 1973-2055 | 752-840 | 31% | 47% | 2.29 × 10^{-5} | |
| | 2129-2199 | 740-832 | 30% | 45% | 0.005 | |
| | 2244-2291 | 793-840 | 37% | 52% | 2.02 × 10^{-4} | |
| | 2289-2334 | 794-841 | 33% | 47% | 0.546 | |
| | 2413-2507 | 768-862 | 34% | 46% | 3.61 × 10^{-5} | |
| | 2522-2567 | 794-840 | 36% | 46% | 0.340 | |
| | 2657-2648 | 766-840 | 30% | 47% | 5.324 | |
| | 2646-2678 | 794-829 | 47% | 58% | 0.198 | |
| | 2701-2794 | 794-840 | 44% | 59% | 0.064 | |
| | 872-920 | 790-840 | 43% | 50% | 0.023 | |
| | 1047-1091 | 794-840 | 51% | 61% | 5.63 × 10^{-4} | |
| | 6 Adhesion G protein-coupled receptor E2/EGF-like module receptor 2/CD312 [23397611] | 65-101 | 794-830 | 40% | 59% | 0.030 | |
| | 158-191 | 791-825 | 54% | 62% | 1.82 × 10^{-4} | |
| | 209-240 | 793-825 | 45% | 63% | 0.155 | |
| | 3799-3897 | 746-838 | 34% | 41% | 3.33 × 10^{-4} | |
| | 7 Protopodulin Fat 4 [165932370] | 359-433 | 747-838 | 33% | 46% | 4.08 × 10^{-4} | |
| | 8 Low-density lipoprotein receptor-related protein 4 (LRP-4) [157384998] | 355-397 | 794-839 | 36% | 54% | 0.431 | |
| | 585-636 | 794-847 | 38% | 50% | 0.506 | |
| | 627-671 | 794-840 | 42% | 51% | 1.506 | |
| | 750-794 | 794-840 | 44% | 59% | 0.064 | |
| | 872-920 | 790-840 | 43% | 50% | 0.023 | |
| | 1047-1091 | 794-840 | 51% | 61% | 5.63 × 10^{-4} | |
| | 9 Latent-transforming growth factor beta-binding protein 4 (LTBP4) [110347431] | 1539-1604 | 764-825 | 37% | 55% | 1.419 | |
| | 487-557 | 794-866 | 36% | 46% | 0.004 | |
| | 570-614 | 794-841 | 39% | 54% | 0.174 | |
| | 681-724 | 795-840 | 39% | 56% | 0.323 | |
| | 763-816 | 793-852 | 35% | 46% | 5.987 | |
| | 867-911 | 794-840 | 44% | 53% | 0.396 | |
| | 982-1028 | 792-840 | 42% | 44% | 0.874 | |
| | 1153-1196 | 794-840 | 38% | 48% | 1.322 | |
| | 1169-1238 | 770-840 | 35% | 47% | 0.074 | |
| | 1443-1487 | 794-841 | 41% | 52% | 0.992 | |
| | 1884-1930 | 794-841 | 43% | 52% | 0.041 | |
| | 1959-2012 | 795-841 | 35% | 51% | 0.217 | |
| | 2083-2148 | 795-862 | 35% | 45% | 0.196 | |
| | 2204-2236 | 793-825 | 50% | 64% | 1.605 | |
| | 2368-2468 | 762-862 | 31% | 42% | 0.001 | |
| | 2483-2528 | 794-840 | 41% | 50% | 5.275 | |
| | 2536-2601 | 766-831 | 39% | 52% | 0.078 | |
| | 2598-2640 | 786-829 | 47% | 56% | 4.494 | |
| | 10 Fibrillin-3 [56237021] | 902-979 | 785-862 | 28% | 42% | 0.034 | |
| | 1074-1286 | 626-840 | 24% | 36% | 0.013 | |
| | 1200-1244 | 794-840 | 43% | 56% | 0.001 | |

(continued on next page)
of this protein, are homologous to two segments of Tg which correspond entirely to the Tg epitope 1473–1526.

As summarized in Table 6, of the 47 CNS proteins homologous to TPO, 7 (15%; fibrillin-1/aspriosin, fibrillin-3, LR2-3, LR2-4, P-selectin/C6D2P/granule membrane protein 140/leukocyte-endothelial cell adhesion molecule 3, and the aforesaid nodogen-1/entactin) were homologous to the entire TPO epitope 1473–1526.

Concerning ephrin-type-B receptor 2, the only Tg-homologous segment (aa 269–312) marginally overlaps with a known epitope (aa 309–318) of the protein, while its Tg counterpart (aa 1473–1531)
reported to generate autoAb, and in the following conditions: recurrent pregnancy loss, pregnancy-induced hypertension, systemic sclerosis, localized scleroderma, CREST (calcinosis, Raynaud's esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, mixed connective tissue disease, type 1 diabetes mellitus, primary pulmonary hypertension syndrome, myasthenia gravis, autoimmune polyglandular syndrome type 3, amyotrophic lateral sclerosis, ABBA disease (a renal disease characterized by kidney antibrush border antibodies and renal failure), rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Behçet's disease, and idiopathic thrombocytopenic purpura [52–60,63–73,84–93].

Of interest, it was found that the random peptide TNRRGRSPGAL, which Dolcino et al. found to be recognized by nearly all sera of patients with psoriatic arthritis, shows amino acid sequence homology and cross-reacts with some skin autoantigens, including fibrillin-3 [86]. Of the 22 TPO-homologous segments of fibrillin-1, seven contained, or had some overlap with, an epitope of the protein. In the majority of cases, the autoantigenic peptide reported in literature had some modifications (citrullinated, methylated or cysteinylated). In detail, segment 723–765 contained the epitopes 733–748 (citrullinated in R11) and 737–752 (citrullinated in R7), segment 917–932 (citrullinated in R14), 921–936 (citrullinated in R10), 925–940 (citrullinated in R6) and almost all of the epitope 947–955 (cysteinylated in C4), segment 1186–1194 and the epitope 1203–1211 (which is reported in literature in two versions, without or with methylation in C6), segment 1256–1264 (methylated in C8), segment 2301–2316 (citrullinated in R6 and R11), 2305–2320 (citrullinated in R2 and R7) and 2309–2324 (citrullinated in R3); segments 1645–1692 and 2413–2507 had rather limited overlap with epitopes 1689–1697 (methylated in C7) and 2502–2510 (methylated in C8), respectively. All parts of TPO homologous to fibrosin-1 had insignificant (5 aa or less) or no overlap with known TPO epitopes, with one exception (segment 740–832, matching aa 2129–2199 of fibrosin-1, contains the entire TPO epitope 766–775 and part of epitope 842–861).

The 17 TPO-homologous segments of fibrillin-3 contained an epitope in four cases, while their TPO counterparts had four complete and one partial overlap with an epitope. The only match between two epitope-
containing segments was that between aa 2368–2468 of fibrillin-3 (which include the epitope 2425–2440, citrullinated in R9, and 2429–2444, citrullinated in R5 and R14) and aa 762–782 of TPO (which include the epitope 766–775). The segment 763–816 of fibrillin-3 (which contains the epitope 773–786) matched segment 793–852 of TPO, which has an 11-residue overlap with the autoepitope 842–861 of the protein. The epitope-containing segments without an epitope-containing homolog were localized at positions 570–614 (containing epitope 594–602) and 867–911 (containing epitope 878–886) of fibrillin-3, and positions 794–866, 795–862 (both containing epitope 842–861) and 766–831 (containing epitope 766–775) of TPO. All other homologous segments of both proteins had insignificant or no overlap with known epitopes.

Concerning LRP-2, three TPO-homologous segments were found, of
which only one (aa 1388–1428) contained autoepitopes (aa 1397–1428, citrullinated in R12 and R16, and aa 1401–1416, citrullinated in R8 and R12); their TPO counterparts had insignificant or no overlap with known epitopes. Upon describing one patient with AIT and membranous nephropathy, the authors report that low-density lipoprotein receptor-related protein 2 (megalin) is expressed on thyroid cells in a TSH-dependent manner and could be the link between the two diseases [91].

The single local homology found between LRP-4 and TPO involved aa 359–433 of LRP-4, which contain the epitopes 361–376 (citrullinated in R13) and 365–380 (citrullinated in R9), and aa 747–838 of TPO, which contain the epitope 766–775.

A single local homology was found also between P-selectin and TPO, but in this case neither segment (aa 531–621 and 759–843, respectively) contained epitopes (there was only an overlap of few residues in the case of the TPO segment).

Discussion

Expanding our previous data [25], we have provided some evidence for molecular mimicry between thyroid autoantigens and CNS-expressed proteins being a reasonable mechanism for HE/SREAT. First, a limited number of CNS-expressed proteins match relatively short to relatively long sequences of the thyroid autoantigens. Second, the homologous sequences of the three thyroid autoantigens almost always contain at least one epitope. Third, the CNS areas where the thyroid-autoantigen homologous proteins are expressed match CNS areas where abnormalities were detected at biopsy/necropsy and/or by neuroimaging in patients with HE/SREAT. Fourth, the literature associated a number of the homologous CNS-expressed proteins with a number of autoimmune disorders (not necessarily CNS-restricted), in which corresponding serum autoAb were detected.
TSH-R belongs to the superfamily of the rhodopsin-like G protein-coupled receptors (GPCR), whose ectodomain belongs, in turn, to the family of proteins with leucine-rich repeats (LRR) \[94\]. Thus, many of the homologies found (Table 1, Fig. 2) were not unexpected. Interestingly, the TSH-R regions of homology involve its nine LRR repeats, the serpentine domain (aa 414–682, with seven transmembrane helices) and most of the cytoplasmic tail (aa 683–764). Further to the last 20 residues (aa 745–764), two other TSH-R regions are spared by

![Homologies between CNS-expressed proteins and TPO](image-url)

Fig. 4. Homologies between CNS-expressed proteins and TPO. Segments in black represent single homologous sequences, segments in gray represent the cumulative span of multiple, overlapping homologous sequences of the same protein.

Peroxidase homolog
Peroxidase-like protein
Prostaglandin G/H synthase 2
Prostaglandin G/H synthase 1
Dual oxidase 2 precursor variant, partial
Fibrillin-1
Adhesion G protein-coupled receptor E2
Protocadherin Fat 4
LDL receptor-related protein 4 (LRP-4)
Latent-TGF beta-binding protein 4 (LTBP4)
Fibrillin-3
Latent TGF beta-binding protein 1 (LTBP1)
Seizure-related 6-like protein 2
CUB and sushi domain-containing protein 1
EGF receptor 5 (EGFR-5)
Fibrillin 1 variant, partial
Multiple EGF-like domains protein 6
Seizure 6-like protein
Catherin family member 10
LDL receptor-related protein 2 (LRP-2)
EGF-containing fibrillin-like ECM protein 2
Nephronecin
Complement component C1q receptor
Fibrillin 5
Toll-like protein 1
EGF-containing fibrillin-like ECM protein 1
SCUBE1
Latent-TGF beta-binding protein 1 (LTBP1)
KIAA1237 protein, partial
Vitamin K-dependent protein S
Protein HEK homolog 1
LDL receptor-related protein 1B (LRP-1B)
P-selectin (CD62P)
Fibrillin-1 (FBL-1)
Fibrillin 1
Protein kinase C-binding protein NELL2
NOTCH4 protein
Complement receptor type 2
Nidogen-1
CSMD2 protein
CRELD2 beta
Endosialin
EGF-like protein 7
Pro-LDL receptor-related protein 1
CUB and sushi domain-containing protein 3
Thrombospondin 3
EGF-like protein 6
Mutant p53 binding protein 1 variant, partial

[SIGNAL peptide, CCP=domain abundant in complement control proteins, EGF=epidermal growth factor-like domain, TM=transmembrane region, C=cytoplasmic region]
Involvement in autoimmune disorders, as resulting from a PubMed search, of the proteins that we found share local homology with thyrotropin receptor (TSH-R).

Table 4

| Protein                                      | No. of articles | Citations                  | Results                                                                 |
|----------------------------------------------|-----------------|----------------------------|-------------------------------------------------------------------------|
| Leucine-rich repeat-containing G-protein coupled receptor 4 (LGR4) | 1               | Greer JM et al. 2017 [38]  | Patients with both CNS disease andAITD have elevated levels of T cells and antibodies to LGR4, which is expressed in brainstem and spinal cord |
| Chondroadherin                               | 1               | Mazzara S et al. 2015 [39] | Autoantibodies to chondroadherin are present in autoimmune hepatitis patients and could be used as diagnostic/prognostic markers |
| Alpha-1A adrenergic receptor                 | 2               | Wenzel K et al. 2008 [40]  | Agonistic autoantibodies to alpha-1A adrenergic receptor are present in patients with hypertension and are a possible cause of hypertension. |
| Mu opioid receptor                           | 5               | Tanaka S et al. 2003 [42]  | Autoantibodies to mu opioid receptor were found in 13.1% of 122 psychiatric patients. |
| Macé G et al. 2002 [44]                     | Autoantibodies to mu opioid receptor are commonly expressed in healthy humans and may promote Fas-mediated apoptosis |
| Macé G et al. 1999 [45]                     | Autoantibodies that bind the first and third extracellular loops of the mu opioid receptor mimic morphine-induced receptor activation |
| Macé G et al. 1999 [46]                     | Some IgG autoantibodies to mu opioid receptor have a morphine-like activity |
| Melanin-concentrating hormone receptor 1    | 5               | Kroon MW et al. 2013 [47]  | Autoantibodies to melanin-concentrating hormone receptor 1 are common in the sera of patients with vitiligo |
| Li Q et al. 2011 [48]                       | Melanin-concentrating hormone receptor 1 is a well-known autoantigen in vitiligo |
| Gavalias NG et al. 2009 [49]                | In vitiligo patients, peptides 85-96 and 254-260 are major autoantibody epitopes of melanin-concentrating hormone receptor 1, peptides 51-80 and 154-158 are minor autoantibody epitopes, peptide 254-260 is the target of function-blocking antibodies. Several domains of melanin-concentrating hormone receptor 1 are recognized by autoantibodies from vitiligo patients. |

Of the 46 TSH-R homologous proteins, 41 do not appear in the Table, because we retrieved no literature about their involvement in autoimmune disorders. These proteins are: Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5), Relaxin receptor 2/Leucine-rich repeat-containing G-protein coupled receptor 8 (LGR8), Relaxin receptor 1/Leucine-rich repeat-containing G-protein coupled receptor 7 (LGR7), Leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 2 (LINGO2), Somatostatin receptor type 2, Neuropeptide Y receptor type 1, Apelin receptor, Neuregulin-1 receptor/Neurokinin B receptor/Tachykinin receptor 3, Free fatty acid receptor 3, Melanopsin/Opsin-4, G-protein coupled estrogen receptor 1/Membrane estrogen receptor, Vasopressin V1a receptor, Probable G-protein coupled receptor 34, G-protein coupled receptor 26, Orexin 2 receptor, Oxytocin receptor, Orexin receptor type 1, Galanin receptor type 2, GPER protein, N/OFQ opioid receptor, Type 2 angiotensin II receptor, Alpha-1B adrenergic receptor, Bombesin receptor subtype-3, Neuropeptide Y receptor type 5, C3a anaphylatoxin chemotactic receptor, Substance-P receptor/Tachykinin receptor 1, Proteinase-activated receptor 2, Trace amine-associated receptor 6 (TaR-6), Urotensin-2 receptor/G-protein coupled receptor 14, Nociceptin receptor, G-protein coupled receptor 24, C-C chemokine receptor type 7/Epsine-Barr virus-induced G-protein coupled receptor 1/MIP-3 beta receptor, Olfactory receptor 2A14, Vasopressin V2 receptor, Neuropeptide S receptor, Trace amine-associated receptor 8 (TaR-8), Neuropeptides B/W receptor type 2, Olfactory receptor 2 J3, G protein-coupled receptor, Oxoglutamate (alpha-ketoglutarate) receptor 1, 5-hydroxytryptamine receptor 7 (5-HT7).

Homologies: the signal peptide (first 20 residues) and, upon ignoring LGR4, LGR5, LGR7 and LGR8, the region 255–369. This last region encompasses the LRR9 repeat at 250–317 with its TSH-R specific sequence at aa 317–366. This segment 317–366 (also called the 50-residue long C-peptide of TSH-R), that is deleted following an intramolecular cleavage, is TSH-R specific because it is absent in the cognate gonadotropin receptors (FSH-R, LH-R) [95].

Assuming that the CNS-expressed TSH-R undergoes the same intramolecular cleavage as the thyrocyte-expressed TSH-R, then the CNS cell will continue to have a cell-attached TSH-R, so called B subunit, with a few extracellular residues distal to the cleaved 317–366 segment, the whole serpentine domain and the intracellular C-terminus. This approximately 400-residue long portion of TSH-R will retain zones of homology with alpha-eno lace, AKR1A and several CNS-expressed proteins, as well as a number of epitopes. Most of these epitopes bind TSH-R Ab that inhibit the TSH-R signaling. Thus, it is possible that, whatever the function(s) of TSH-R may be in the CNS, binding to these Ab might inhibit such function(s).

Also not surprising is the presence of esterases in the list of proteins homologous to the C-terminal part of Tg, because the segment starting at aa 2188 is the acetylcholinesterase domain of this thyroid autoantigen.

As reported by Veneziani et al. [96] “type I repeats of Tg share varying degrees of homology with a six-residue cysteine motif found in a variety of proteins. These include: … the cell-adhesion protein nidogen/entactin, the insulin-like growth factor binding protein (IGFBP), … the proteolytic tecom…” Moreover, “The cysteine-rich units of Tg share limited structural analogy with the epidermal growth factor (EGF)-homologous repeats found, in single or multiple copies, in a variety of proteins... The homology between
acetate deacetylase/ Monocyte/macrophage serine esterase/
Retinyl ester hydrolase/Carboxylesterase/Cocaine carboxylesterase/Egasyn/
Methylumbelliferyl-boxylesterase 4A, Carboxylesterase 8 (CES8), KIAA1366 protein.
drolyl hydrolyase, KIAA1480 protein, Carboxylesterase 1/Acyl-coenzyme A:cholesterol acyltransferase/Brain boxylesterase 5A, Neuroligin-2, Brain carboxylesterase hBr3, Liver carboxylesterase 1/Acyll-coenzyme A:cholesterol acyltransferase/Brain boxylesterase hBr1/Asparagine/Epithidymis secretary sperm binding protein.

Table 5
Involvement of the proteins that we found share local homology with thyroperoxidase in autoimmune disorders, as resulting from a PubMed search.

| Protein                       | No. of articles | Citations | Results                                                                 |
|-------------------------------|-----------------|-----------|-------------------------------------------------------------------------|
| Nidogen-1/Entactin            | 9               | Fukatsu A et al. 1987 [52] | Rats injected with mercuric chloride develop autoantibodies to various components of the glomerular basement membrane, including entactin. |
| Saxena R et al. 1990 [53]    | Anti-entactin antibodies were found in extracapillary glomerulonephritis. |
| Saxena R et al. 1991 [54]    | Circulating anti-entactin antibodies are present in specific types of glomerulonephritis, but not in others nor in healthy subjects. |
| Saxena R et al. 1994 [57]    | Patients with systemic lupus erythematosus often have anti-entactin antibodies, which are more common in case of severe disease. |
| Saxena R et al. 1995 [58]    | Two of 40 patients with pulmonary renal syndrome had anti-entactin autoantibodies. |
| Li QZ et al. 2005 [59]       | Autoantibodies to entactin are frequent in patients with lupus but not associated with disease activity. |
| Cuadrado E et al. 2015 [60]  | IgG antibodies to several autoantigens, including entactin, are present in patients with Aicardi-Goutieres syndrome, an autoimmune disorder with some similarities to systemic lupus erythematosus which particularly targets the cerebral white matter. |
| Azzouz DF et al. 2016 [62]   | Patients with systemic sclerosis or systemic lupus erythematosus show autoantibodies to entactin type B receptor 2. |

Table 6
Involvement of the proteins that we found share local homology with thyroperoxidase in autoimmune disorders, as resulting from a PubMed search.

| Protein                       | No. of articles | Citations | Results                                                                 |
|-------------------------------|-----------------|-----------|-------------------------------------------------------------------------|
| Fibrillin-1/Asparagine/Epithidymis secretary sperm binding protein. | 11 | Atanasova MA et al. 2011 [63] | Increased anti-fibrillin-1 IgM antibodies in patients with recurrent pregnancy loss may contribute to the pathogenesis of this condition. |
| Admou B et al. 2009 [64]      | Anti-fibrillin-1 autoantibodies may be present in systemic sclerosis patients. |
| Grassegger A et al. 2008 [65] | Anti-fibrillin-1 autoantibodies seem to have important roles in the pathogenesis of systemic sclerosis. |
| Zhou X et al. 2005 [66]       | Anti-fibrillin-1 autoantibodies are specifically present in systemic sclerosis patients and may induce activation of normal dermal fibroblasts into a profibrotic phenotype, which resembles that of systemic sclerosis. |
| Nicoloff G et al. 2005 [67]   | Anti-fibrillin-1 autoantibodies can be found in diabetic patients. |
| Pandey JP et al. 2001 [68]    | Anti-fibrillin-1 autoantibodies in systemic sclerosis patients are associated with specific KM and GM allotypes (genetic markers of immunoglobulin kappa and gamma chains, respectively). |
| Tan FK et al. 2000 [69]       | Anti-fibrillin-1 autoantibodies in systemic sclerosis patients correlate with specific ethnic groups but not HLA alleles. |
| Morse JH et al. 2000 [70]     | Anti-fibrillin-1 autoantibodies are present in primary pulmonary hypertension, other than in systemic sclerosis, CREST (calcinosis, Raynaud’s esophageal dystomyelitis, sclerodactyly, and telangiectasia) syndrome, mixed connective tissue disease. |
| Lundberg I et al. 2000 [71]   | Anti-fibrillin-1 autoantibodies are present in CREST (calcinosis, Raynaud’s esophageal dystomyelitis, sclerodactyly, and telangiectasia) syndrome and mixed connective tissue disease. |
| Arnett FC et al. 1999 [72]    | Anti-fibrillin-1 autoantibodies are present in patients with linear scleroderma or morphea. |
| Tan FK et al. 1999 [73]       | Anti-fibrillin-1 autoantibodies may be found in patients with systemic sclerosis, CREST (calcinosis, Raynaud’s esophageal dystomyelitis, sclerodactyly, and telangiectasia) syndrome, mixed connective tissue disease. |

Of the 27 Tg homologous proteins, 25 do not appear in the Table, because we retrieved no literature about their involvement in autoimmune disorders. These proteins are: Testican-1/Protein SPOCK, Testican-2/SPARC/osteonectin, CWCV, and Kazal-like domains proteoglycan 2 (SPOCK2), SPARC-related modular calcium-binding protein 1/Secreted modular calcium-binding protein 1 (SMOC-1), Testican-3, SPARC-related modular calcium-binding protein 2/Secreted modular calcium-binding protein 2 (SMOC-2), Insulin-like growth factor-binding protein 5, CUB and EGF-like domain-containing protein 1, Ephrin type-B receptor 6, Ephrin type-B receptor 7, Acetylcholinesterase (Yt blood group), Butyrylcholinesterase, Neurologin-3, Neurologin-4, X-linked, Neurologin-4, Y-linked, Neurologin-1, Carboxylesterase 3 (CES3), Cocalin esterase, Carboxylesterase 5A, Neurologin-2, Brain carboxylesterase hBr3, Liver carboxylesterase 1/Acyll-coenzyme A:cholesterol acyltransferase/Brain carboxylesterase hBr1/Asparagine/Epithidymis secretary sperm binding protein. [continued on next page]
| Protein | No. of articles | Citations | Results |
|---------|----------------|-----------|---------|
| Low-density lipoprotein receptor-related protein 4 (LRP-4) | 12 | Inoue H et al. 2020 [74] | Case report of a patient affected by myasthenia gravis and autoimmune polyendocrine syndrome type 3, with autoantibodies to both acetylcholine receptor and low-density lipoprotein receptor-related protein 4 antibody inhibition. |
| | | Park KH et al. 2018 [75] | Analysis of multiple autoantibodies (including those to low-density lipoprotein receptor-related protein 4) in patients with myasthenia gravis. |
| | | Obhrai K et al. 2018 [76] | Report of a case of myasthenia gravis and amyotrophic lateral sclerosis, with autoantibodies to acetylcholine receptor and low-density lipoprotein receptor-related protein 4. |
| | | Ishikawa H et al. 2017 [78] | Report of two cases of myasthenia gravis and invasive thymoma, with autoantibodies to acetylcholine receptor and low-density lipoprotein receptor-related protein 4. |
| | | Li Y et al. 2017 [79] | Identification of autoantibodies to low-density lipoprotein receptor-related protein 4 in Chinese patients with myasthenia gravis. |
| | | Takahashi H et al. 2016 [80] | Report of two cases of amyotrophic lateral sclerosis with autoantibodies to low-density lipoprotein receptor-related protein 4, who showed myasthenic symptoms. |
| | | Marino M et al. 2015 [81] | Analysis of the presence of autoantibodies to low-density lipoprotein receptor-related protein 4 in an Italian cohort of 101 myasthenic patients, 45 healthy blood donors and 40 patients with other neurological diseases. |
| | | Zisimopoulou P et al. 2014 [82] | Autoantibodies to low-density lipoprotein receptor-related protein 4 were found in 18.7% of about 800 patients with myasthenia gravis from 10 countries. |
| | | Zouvelou V et al. 2013 [83] | Report of two cases of myasthenia gravis with autoantibodies to low-density lipoprotein receptor-related protein 4. |
| Fibrillin-3 | 1 | Dolcino M et al. 2014 [86] | The peptide TNRRGSPGAL, recognized by nearly all sera of patients with psoriatic arthritis, shows homology and cross-reacts with some skin autoantigens, including fibrillin-3. |
| fibrillin 1 variant, partial | 11 | Atanasova MA et al. 2011 [63] | Increased anti-fibrillin-1 IgM antibodies in patients with recurrent pregnancy loss may contribute to the pathogenesis of this condition. |
| | | Admou B et al. 2009 [64] | Autoantibodies may be present in systemic sclerosis patients. |
| | | Grasnegger A et al. 2008 [65] | Anti-fibrillin-1 autoantibodies seem to have important roles in the pathogenesis of systemic sclerosis. |
| | | Zhou X et al. 2005 [66] | Anti-fibrillin-1 autoantibodies are specifically present in systemic sclerosis patients and may induce activation of normal dermal fibroblasts into a profibrotic phenotype, which resembles that of systemic sclerosis. |
| | | Nicoll G et al. 2005 [67] | Anti-fibrillin-1 autoantibodies can be found in diabetic patients. |
| | | Pandey JP et al. 2001 [68] | Anti-fibrillin-1 autoantibodies in systemic sclerosis patients are associated with specific KM and GM allotypes (genetic markers of immunoglobulin kappa and gamma chains, respectively). |
| | | Tan FK et al. 2000 [69] | Anti-fibrillin-1 autoantibodies in systemic sclerosis patients correlate with specific ethnic groups but not HLA alleles. |
| | | Morse JH et al. 2000 [70] | Anti-fibrillin-1 autoantibodies are present in primary pulmonary (continued on next page). |
Table 6 (continued)

| Protein | No. of articles | Citations | Results |
|---------|-----------------|-----------|---------|
| P-selectin (CD62P)/Granule membrane protein 140/Leukocyte-endothelial cell | 2 | Jiang H et al. 1993 [92] | Autoantibodies to granule membrane protein 140 were found in 13/46 patients with severe hypertension, other than in systemic sclerosis, CREST (calcinosis, Raynaud’s esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, mixed connective tissue disease. |
| Nidogen-1/Entactin | 9 | Fukatsu A et al. 1987 [52] | Anti-fibrillin-1 autoantibodies are present in CREST (calcinosis, Raynaud’s esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome and mixed connective tissue disease. |
| Vascular peroxidase 1, Peroxidasin-like protein, Prostaglandin G/H synthase 2/ | 16 | | Autoantibodies to granule membrane protein 140 were found in 17/92 patients with idiopathic thrombocytopenic purpura.

Of the 47 TPO homologous proteins, 40 do not appear in the Table, because we retrieved no literature about their involvement in autoimmune disorders. These proteins are: Peroxidasin homolog/Melanoma-associated antigen MGS90/ Vascular peroxidase 1, Peroxidasin-like protein, Prostaglandin G/H synthase 2/...
Cyclooxygenase-2, Prostaglandin G/H synthase 1/Cyclooxygenase-1, Adhesion G protein-coupled receptor E2/EGF-like module receptor 2/CD312, Proctokinase Fat 4, Latent-transforming growth factor beta-binding protein 4 (LTBP4), Latent-transforming growth factor beta-binding protein 1 (LTBP1), Seizure related 6-like protein 2, CUB and sushi domain-containing protein 1, C-type lectin domain family 14 member A/Epidermal growth factor receptor 5 (EGFR-5), Multiple epidermal growth factor-like domains protein 6, Seizure 6-like protein/KAIA0927 protein, Cadherin EGF LAG seven-pass G-type receptor 2/Cadherin family member 10/Filamin homolog 3, EGF-containing fibulin-like extracellular matrix protein 2, Neuroneptin/Preosteoblast EGF-like repeat protein with mammal domain/EGFL6-like, Complement component Clq receptor/CD93, Fibulin 5, Tolloid-like protein 1, EGF-containing fibulin-like extracellular matrix protein 1, Signal peptide, CUB and EGF-like domain-containing protein 1, Latent-transforming growth factor beta-binding protein 1 (LTBP1), KIAA1237 protein, partial, Vitamin K-dependent protein S, Protein HEG homolog 1, Low-density lipoprotein receptor-related protein 1B (LRP-1B), Fibulin-1, Fibulin-1, Protein kinase C-binding protein NELL2, NOTCH4 protein, complement receptor type 2, dual oxidase 2 precursor variant, partial, CSM2D protein, Cysteine-rich with EGF-like Domains 2 (CRELD2) beta, Endosialin/CD248, Prolow-density lipoprotein receptor-related protein 1/Alpha-2-macroglobulin receptor/Apolipoprotein E receptor/CD91, CUB and sushi domain-containing protein 3, Thrombospondin-3, Epidermal growth factor-like protein 6, Mutant p53 binding protein 1 variant, partial.

**EGF-like modules is based primarily on the position of six cysteins (numbered Cys1 through CysVI). Type I repeats of Tg differ from typical EGF-like modules for the spacings between some of the cysteines, and the presence of unrelated inserts of variable length at conserved positions**.

Finally, because TPO belongs to the Haem peroxidase superfamily, namely haem-containing enzymes that use hydrogen peroxide as the electron acceptor to catalyse oxidative reactions (http://www.ebi.ac.uk/interpro/entry/IPR019791), homologies with peroxidasins, prosta glandin G/H synthases/cyclooxygenases, dual oxidase 2 were expected. In addition, the stretch 742–795 of TPO contains SUSHI repeats that have been identified in several proteins of the complement system, while aa 796–838 is the calcium-binding EGF domain (https://www.ncbi.nlm.nih.gov/protein/AAA61217.2). Accordingly, also not unexpected were the homologies with complement component Clq receptor, CUB and sushi domain-containing proteins (including Tolloid-like protein 1), endosialin/CD248 (a protein with one EGF-like domain and one sushi domain), P-selectin (CD62P)/granule membrane protein 140/leukocyte-endothelial cell adhesion molecule 3/platelet activation dependent granule-external membrane protein (a protein with one EGF-like domain and multiple sushi domains), cysteine-rich with EGF-like domains 2 beta, adhesion G protein-coupled receptor E2/EGF-like module receptor 2, EGF-containing fibulin-like extracellular matrix proteins, nepronecin/preosteoblast EGF-like repeat protein with mammal domain/EGFL6-like, multiple EGF-like domains protein 6, C-type lectin domain family 14 member A/EGF receptor 5 (EGFR-5), and other proteins with multiple EGF-like domains (fibrillins, proctokinase fat 4, low-density lipoprotein receptor-related proteins, latent-transforming growth factor beta-binding proteins, fibulins, protein HEG homolog 1, protein kinase C-binding protein NELL2, NOTCH4, thrombospondin-3, and nidenogen-1/entactin). Of note, aa 846–919 of nidenogen 1/entactin correspond to the Tg type 1 repeat domain of this sulfated glycoprotein widely distributed in basement membranes and tightly associated with laminin (https://www.uniprot.org/uniprot/PIF14543).

Among CNS proteins homologous to TPO, low-density lipoprotein receptor-related protein 4 (LRP4) deserves particular attention. LRP4 has a central role in synaptic development and maintenance, and acts as the muscle receptor for neural agrin, propagating the signal to muscular tyrosin kinase receptors (MuSK) for acetylcholine receptors (AChR) clustering at the neuromuscular junction (NMJ), a peripheral cholinergic synapse between motor neurons and skeletal muscle fibers [97]. LRP4 autoantibodies are detected in some patients with myasthenia gravis (MG), and the inhibition of the LRP4-agrin interaction appears to be responsible, at least in part, for their pathogenicity [98]. In a systematic review, autoimmune thyroid disease was the most frequent of 23 associated autoimmune disorders, occurring in 10% of MG patients [99]. LRP4 antibodies have also been detected in 10–23% of amyotrophic lateral sclerosis (ALS) patients [100–101].

As to the NMJ, neurotransmission in the CNS requires precise control of neurotransmitter release from presynaptic terminals and responsiveness of neurotransmitter receptors on postsynaptic membrane, and this process is regulated by glial cells; however, underlying mechanisms are not fully understood. Being expressed in the brain, LRP4 has been implicated in hippocampal synaptic plasticity [102–103]. It has been demonstrated that glutamate release in the hippocampal regions of the brain is impaired in LRP4-defective mice, revealing a critical role of the LRP4-agonin signalling in modulating astrocyte ATP release and synaptic glutamatergic transmission [103–104]. More recently, it has been demonstrated that LRP4 is reduced in the brain of patients with Alzheimer disease (AD), paralleling the reduced levels in an AD mouse model that are associated with exacerbation of cognitive impairment and increases in the amount of amyloid aggregates [105]. Impaired synaptogenesis and altered synaptic transmission at the temporal regions are commonly associated with cognitive disturbances, behavioral alterations, memory reduction. All the above-mentioned disturbances are likewise described in HE/SREAT. Hence, in the light of the homology between LRP4 and TPO, and considering that presence of LRP4 in temporal areas of the brain has been described, we could speculate on a possible cross-reactivity between anti-TPO antibodies and LRP4, explaining the cognitive and behavioural manifestations of HE/SREAT.

The multiformal clinical symptomatology of SREAT and its dramatic responsiveness to the corticosteroid therapy (as also supported by the disappearance of abnormalities detected at neuroimaging and electroencephalography, in parallel with a fall both in the serum and CSF levels of the pre-therapy markedly elevated thyroid Ab levels), is better explained by the following scenario. Prior to therapy, elevated levels of thyroid Ab (viz. any of TgAb, TPOAb and TSH-R-Ab) would gain access to the CSF through a damaged blood–brain-barrier. Not only, as we explained previously [25], any of these thyroid Ab can attack CNS cells that express the corresponding autoantigen (viz. any of Tg, TPO, TSH-R) but it/they may attack cells that express one or more of CNS-expressed proteins described here and previously [25]. A requisite for this last attack and associated Ab binding with at least one of these proteins is that the thyroid Ab has/have been elicited by one or more epitopes contained in regions of the thyroid autoantigen that share homology with such CNS protein(s). As shown in this paper, a given region of a given thyroid autoantigen can share homology with only one, a few or several CNS-expressed proteins. Hence, it would be hard to find two HE/SREAT patients with the same panel of symptoms. Once steroid therapy has knocked-down thyroid Ab levels and thyroid Ab passage into the CNS, then attacks to the above CNS cells would terminate and symptoms, neuroimaging and electroencephalography abnormalities disappear.

CNS proteins that share a series of homologies with antibodies associated to HE/SREAT have a prevalent distribution in areas correlated with the limbic system and temporal regions in general, as also supported by the literature data on neuroradiological alterations which are prevalent in these regions in HE/SREAT patients (Supplementary Tables 1–5). This could justify some symptoms, such as confusion, behavior and memory disorders, and epilepsy. In our study, homologies are also detectable among some proteins located in the blood–brain barrier (BBB) (i.e. proteins of the Notch families and HE/SREAT associated antibodies target, determining a BBB damage and suggesting a possible mechanism of brain aggression by autoantibodies and immunocompetent cells.

A similar mechanism could only be suggested also for cerebellar ataxia in HE/SREAT. In fact, the intimate pathological mechanism underlyng cerebellar ataxia development in HE/SREAT has already been investigated, however it remains obscure; an impaired presynaptic
short-term plasticity between parallel fiber-Purkinje cell transmissions and defective glutamate release have been postulated as potential pathological mechanisms in some patients with HE/SREAT [106–107].

The spatial position of the homologous segments in relation to cell compartments (extracellular, transmembrane, intracellular) and in the context of the three-dimensional structure of the respective proteins (conformation and chemical characteristics of protein surface, degree of solvent exposure) may be important in the pathogenesis of autoimmune diseases. As a general rule, autoantibodies against extracellular, solvent exposed parts of a molecule are more often directly pathogenic, while the role of autoimmunity against parts of the molecules that are normally “hidden” from the immune system is less straightforward.

Some authors compared autoimmune conditions characterized by intracellular and extracellular target autoantigens, pointing out differences and possible implications of this difference in clinical, monitoring, diagnostic and therapeutic terms [108]. By analogy, these considerations could be applied to autoimmunity against exposed and hidden parts of molecules, and this aspect, currently unexplored, could be an intriguing line of future research in the field of SREAT.

In conclusion, we support our idea of HE/SREAT being ignited by thyroid autoantigens that, after having gained access to CS, bind to Tg, TPO and TSH-R expressed in cells of the CNS [25] forming immune complexes. In addition to this mechanism, it is well possible that TgAb, TPOAb, TSH-R Ab may cross-react with CNS-expressed proteins that share local homology with the corresponding thyroid autoantigens. Depending on the prevalent thyroid Ab that forms the immune complex, the homologous protein(s) that cross-react(s), the CNS area(s) and cell (s) expressing such homologous protein(s) and the resulting impairment of its/their function(s), given symptoms will appear, thus explaining the notoriously multiform clinical presentation and neuroradiological abnormalities of HE/SREAT. If one admits that pathogenesis ensues from TgAb, TPOAb, TSH-R Ab that gain access to the CNS and the necessity of such Ab to be directed against epitopes that are shared with the corresponding CNS-expressed homologous protein(s), then the probability of occurrence of such epitope requisite would be relatively rare. This rarity fits with the knowledge of HE/SREAT being a rare event compared with the high frequency of HT, the most prevalent autoimmune disease.

At the very minimum, we believe that our data will prompt a number of investigations to directly prove the involvement in HE/SREAT of at least some of the CNS-proteins having homology with the thyroid autoantigens. For instance, one straightforward implication is to check serum thyroid Ab (any of TSH-RAb, TgAb, TPOAb) detected in patients with SREAT for cross-reactivity with the corresponding homogenous CNS-proteins (TSH-R-homologous, Tg-homologous, TPO-homologous). Another straightforward translational implication of our data is to characterize epitopically serum thyroid autoantibodies in patients with HT and GD (both TgAb and TPOAb in HT, and at least TSH-RAb in GD). If any of these serum Ab recognize epitopes of the corresponding thyroid autoantigen that fall in regions sharing homology with any of the known HT/SREAT autoantigens (alpha-enolase, AKRIA, DDAH) and/or of any of the CNS-expressed proteins we report here, once it/they have been proved as autoantigens associated with HT/SREAT, then HT or GD patients can be sorted out in terms of risk for HT/SREAT.

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CRediT authorship contribution statement

Salvatore Benvenga: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Supervision. Alessandro Antonelli: Validation, Writing – review & editing. Poupak Fallahi: Validation, Writing – review & editing. Carmen Bonanno: Validation, Data curation, Writing – original draft. Carmelo Rodolico: Validation, Data curation, Writing – original draft. Fabrizio Guarneri: Formal analysis, Investigation, Writing – original draft, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2021.100274.

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