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LETTER TO THE EDITOR

Graves' disease precipitated by rickettsial infection

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To the Editor,

Graves' disease is an autoimmune thyroid disease associated with over activation of the thyrotropin receptor (TSHR) by elevated levels of TSHR-stimulating autoantibodies (TRAb) and triggered by the occurrence of environmental (exogenous) events in genetically predisposed individuals, particularly those possessing certain HLA haplotypes [1]. Infection is a trigger even when clinically inapparent—as shown by increased serum antibodies against Yersinia cross-reacting with TRAb because of molecular mimicry in some Graves' disease patients [2, 3].

We wish to report the first case of Graves' disease following, and likely precipitated by, rickettsial infection.

A 52-year-old male conservation worker presented with a 1-week history of low-grade fever, fatigue, and myalgias after returning from work on a remote off-shore island in Western Australia. He had been previously well and took no regular medication. Rickettsial infection was diagnosed (Rickettsia antibody titres rose from 1/128 to 1/512 dilution). He responded well to treatment with doxycycline. One month later, he presented to the emergency department of the local hospital with palpitations and was found to have atrial fibrillation—heart rate 96 per minute, blood pressure 116/80 mmHg. There were no cardiac murmurs or goiter. Investigations revealed thyrotoxicosis due to Graves' disease-free thyroxine 27 pmol/L (9–19), free triiodothyronine 18 pmol/L (3.0–5.5), TSH < 0.01 mU/L (0.4–4.0) TSH receptor Ab 7.4 IU/L (<1.2), and diffusely increased uptake on thyroid isotope scan. He was commenced on β-blockers and carbimazole with a satisfactory response.

We considered whether rickettsial infection might have triggered thyrotoxicosis by molecular mimicry and investigated further. We searched for homology between rickettsia proteins and TSHR and found that only one protein (ATPase) had such homology (Fig. 1). Examination of the patient's HLA haplotype revealed that the two homologous segments (amino acids 351–405 for TSHR and 75–133 of ATPase) contained HLA-binding motifs only for HLA DRB1*0301 (Fig. 1).

Graves' disease was likely triggered by a combination of two events: stress of infection and molecular mimicry. Infection by non-specific mechanisms is a cause in approximately 5 % of stress-related cases of Graves' disease. The molecular mimicry hypothesis states that during an infection, T-cells that recognize both a microbial antigen and a similar self-peptide become activated and cause autoimmunity. HLA class II molecules are critical, as they present pathogen-derived peptide antigens to the T-cells. Peptide specificity to a given HLA molecule is based on possession of an amino acid sequence motif (or motifs) [3].

We have shown that there was homology between rickettsia proteins and TSHR and that these homologous segments contained binding motifs for HLA DR1*0301 (Fig. 1)—an HLA molecule that is consistently richer in binding motifs for the pair of endogenous (thyroid autoantigens) and exogenous (microbiological) proteins [3]. We hypothesize that the combination of rickettsia infection and HLA DR3 was sufficient to initiate a T cell response resulting in TRAb and hyperthyroidism.

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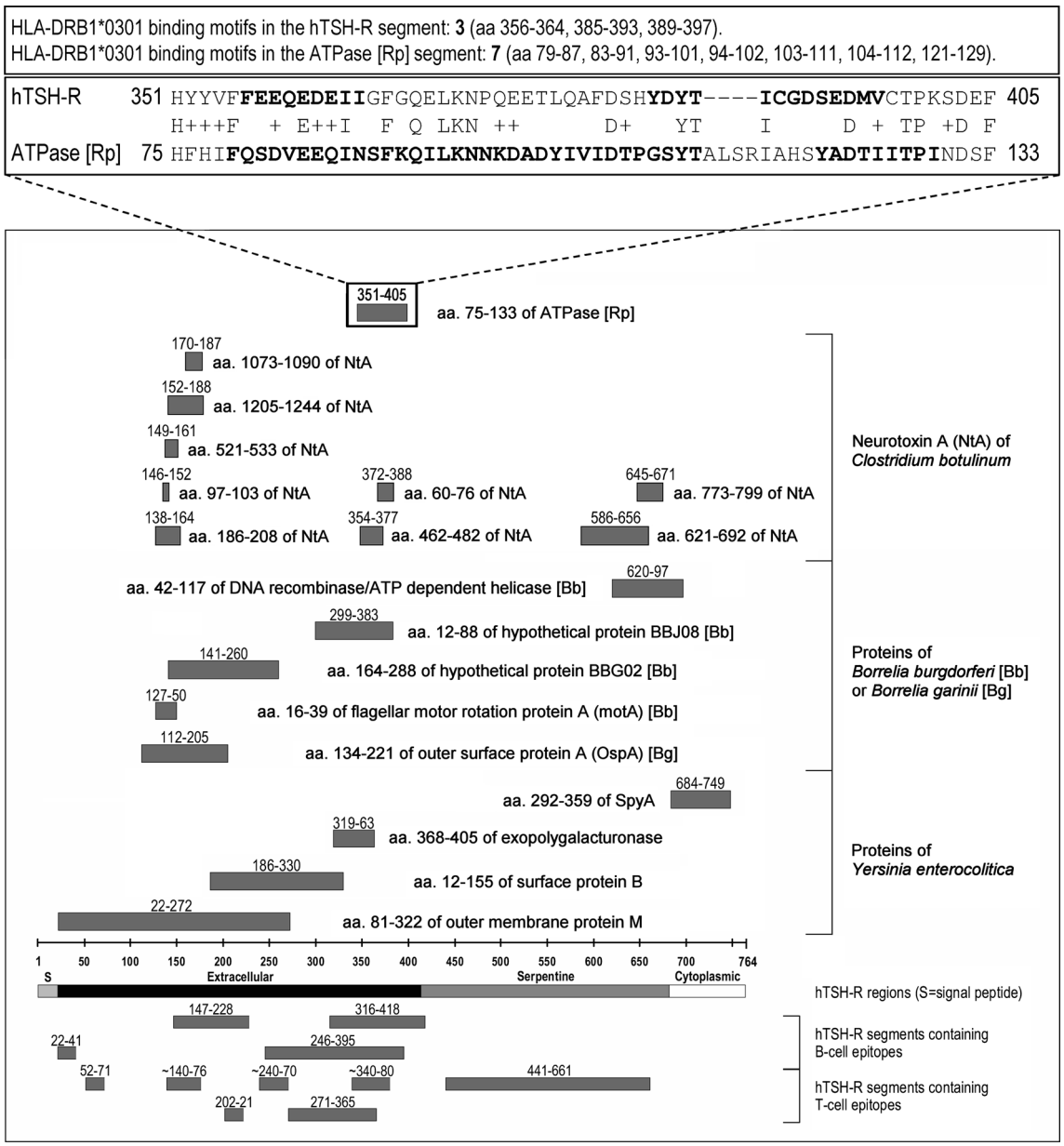

Fig. 1 Amino acid sequence homology between human thyrotropin receptor (hTSHR) and Rickettsia prowazekii ATPase, which was the sole protein of the 140,418 Rickettsia proteins deposited in the Entrez Protein database of National Center for Biotechnology Information, to display an homology with hTSHR. Amino acids are in the one *letter code*, and the *bold-faced* ones constitute the HLA-binding motif. The *plus* symbol indicates similarity between the two aligned amino acids. Note that the matched segment 351–405 of hTSHR shares homology with other microbial proteins [3] and belongs to a region containing both T- and B-cell epitopes. Not shown is the complete HLA genotype of this patient, namely A 01:01/32:01,C 07:01/12:02, B 08:01/52:01, DRB1 03:01/15:02, DQB1 02:01/06:01, DPB1 01:01/04:01

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

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