

Table 2
Frequency of Autoimmune Markers in Study Children With Type 1 Diabetes

Marker	Early-Onset Group (Diagnosis Age <5 Years; %)	Late-Onset Group (Diagnosis Age >5 Years; %)	P Value
TpoA	6	9	1.00
TGA	9	11	1.00
IAA	50	65	.43
GAD	32	77	<.01
ICA	29	68	<.01

TpoA indicates thyroid peroxidase antibody; TGA, thyroglobulin antibody

Table 3
HLA Data in the 2 Major Ethnic Subgroups of Study Children With Onset of Type 1 Diabetes Before 5 Years of Age

HLA Allele(s)	Percentage of Whites With Allele(s) (%)	Percentage of Hispanics With Allele(s) (%)
DRB1*0401-DQA1*03-DQB1*0302	70.6	.0
DRB1*0402-DQA1*03-DQB1*0302	.0	92.9
DRB1 0401	35.3	.0
DRB1 0405	.0	21.4

Tables 1-3 are adapted from Hathout EH et al. *Pediatrics* 2003;111: 860-863.

of the disease among the younger patients may account for more frequent and more severe complications of the disease occurring earlier in life. However, the data in this paper are suggestive that there are autoimmune and genetic differences among type 1 diabetic patients according to age (early vs late onset), and these may account for the differences in the control and the outcome of the disease. Chromosomal abnormalities (parental isodisomy of chromosome 6) also have been described among patients with the transient form of

neonatal diabetes.¹ Studies like these suggest that EOD probably is not classic type 1 diabetes mellitus, and thus may require unique approaches for prevention and therapy.

Fima Lifshitz, MD

Reference

1. Metz C et al. *J Pediatr* 2002;141:483-489.

The Thyrotropin Receptor Autoantigen in Graves Disease is the Culprit as well as the Victim

The thyrotropin (TSH) receptor (TSHR) is the only 7-transmembrane G-protein coupled receptor (GPCR) for glycosylated hormones that undergoes cleavage after its primary formation; the amino terminal extracellular domain is cleaved at/near amino acid 289 (*subunit A*) leaving a short residual extracellular amino acid sequence, the 7 transmembrane domains and extracellular and intracellular connecting loops, and the intracellular carboxyl terminal domain (*subunit B*). Subunit A then circulates and can serve as an immunogen. The role of *subunit A* of the TSHR in the pathogenesis of autoimmune hyperthyroidism and the development of TSHR stimulating immunoglobulin (TSIg) was examined by the present investigators. They constructed within adenovirus cDNA transcripts of the

amino terminal 289 amino acid sequence (*subunit A*), the wild-type (wt) *TSHR* from which amino acids 317-366 had been removed rendering the truncated TSHR resistant to cleavage, and the intact wt *TSHR*.

Adenoviruses expressing different forms of the TSHR were then administered to female mice who subsequently developed abnormalities of thyroid function and antibodies of variable biologic activity in response to these proteins. In animals receiving TSHR 1-289, clinical, biochemical, and thyroid histologic evidence (thyromegaly, hyperthyroxinemia, and follicular hyperplasia) of thyrotoxicosis developed. These animals also developed TSig (assessed by increase in cyclic AMP formation in CHO cells expressing TSHR). In only a few mice receiving cleavage resistant TSHR or wt

TSHR were serum thyroxine levels increased and thyroid follicular hyperplasia present. In contrast, all mice, regardless of the form of TSHR received, developed high but approximately equal titers of immunoglobulins that bound to TSHR or inhibited radiolabeled TSH from binding to TSHR. TSIg did not develop in animals receiving cleavage resistant TSHR, but did appear in 30% of those injected with wt TSHR. Higher titers of thyroid blocking antibodies (assessed by their effect on TSH mediated increase in cyclic AMP generation in CHO cells expressing TSHR) were present in mice receiving the cleavage resistant form of the TSHR than in those receiving TSHR 1-289. The authors conclude that it is the extracellular segment of the TSH receptor that is ordinarily shed that serves as the immunogen for the development of TSIg in this experimental model of hyperthyroidism (and by analogy in patients with Graves disease).

Chen C-R, et al. *J Clin Invest* 2003;111:1897-1904.

First Editor's Comment: *This extremely interesting manuscript provides significant insight into the pathogenesis not only of thyrotoxicosis, but of autoimmune thyroid disease itself. Thus, when the ectodomain of the TSHR is cleaved, it provokes the production of TSHR stimulating immunoglobulins (as well as low titers blocking antibodies) in genetically susceptible individuals. In other at-risk patients, the intact TSHR (or perhaps other sequences or epitopes of the TSHR) or TSH itself, serves as the immunogen for development of TSHR function-blocking antibodies. Other components of the thyroid gland serve as immunogens for antibodies that are injurious to the thyroid cell. A human monoclonal antibody has been recently isolated from a patient with Graves disease, but the epitope of the TSHR to which it is directed has not been identified to date.^{1,2} It would be of interest if it were directed to the ectodomain of the human TSHR.*

While a number of tyrosine kinase receptors shed their extracellular domains (growth hormone binding protein, prolactin binding protein, many cytokines), it is apparently unusual for G-protein coupled receptors to do so. This is an area that merits further examination.

Allen W. Root, MD

Second Editor's Comment: *In Dr. Root's editorial comment, he refers to the recent identification of a monoclonal antibody that stimulates the TSH receptor in the thyroid cell to release thyroxin.^{1,2} This also was no small accomplishment in helping us understand Graves' disease more fully. As pointed out by Dayan, who states:*

"So, is the final proof of the existence of thyroid-

stimulating immunoglobulin after a journey of 47 years of anything more than academic interest? Almost certainly the answer is "yes." First, this finding might lead to a new generation of assays for thyroid-stimulating immunoglobulin in which competition for labeled TSH is replaced by competition for specific monoclonal antibodies. If a sensitive assay can be developed, it should have close to 100% specificity for Graves' disease and replace all other antibody tests, such as antithyroid peroxidase and antithyroglobulin, in this condition. Second, it should finally allow us to understand how such antibodies, even in the monomeric Fab form, can activate the TSH receptor. Such understanding of the biology of glycoprotein-hormone receptors may lead to new small-molecule agonists and antagonists not only for thyroid disease but also for hypogonadism and infertility (via the closely related receptors for luteinising and follicle-stimulating hormones). And it may prove possible to clone a potent human TSH-receptor-blocking antibody which might provide a rapid initial treatment for thyrotoxicosis. Third, the finding may lead to a better understanding of the pathogenesis of Graves' disease. How is it that the spontaneous development of such agonist antibodies, unique in autoimmune diseases, occurs so frequently (almost 1 in 100 of the population)? Does the agonist activity itself, once it appears, promote autoimmunity in a positive feedback loop? Most intriguingly, cloning of agonist TSH-receptor autoantibodies might reveal antibodies that contribute to thyroid eye-disease, the most mysterious manifestation of Graves' disease, and perhaps lead to inhibitors for these antibodies. And finally, agonist antibodies may prove a useful therapeutic agent in their own right, such as to enhance iodine-131 uptake in thyroid cancers. Many of the holy grails of biological science, from the structure of DNA to the nature of the T-cell antigen receptor, have been found. Thankfully, once in hand, they change into pointers to the many more waiting to be discovered."

The findings of Chen and those of Sanders et al are linked closely and the almost simultaneous reporting of these factors which are linked should permit a logarithmic advance in our understanding of how antibodies and receptor structure and function can relate and, consequently, provide better therapy of immunological diseases.

Robert M. Blizzard, MD

References

1. Sanders J, et al. *Lancet* 2003;362:126-128.
2. Dayan CM. *Lancet* 2003;362:92-93.