

## ATTENTION DEFICIT–HYPERACTIVITY DISORDER IN PEOPLE WITH GENERALIZED RESISTANCE TO THYROID HORMONE

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**Abstract Background.** Attention deficit–hyperactivity disorder is a well-recognized psychiatric disorder of childhood. Its cause is unknown, but there is evidence of a familial predisposition. Symptoms suggestive of this disorder have been reported in subjects with generalized resistance to thyroid hormone, a disease caused by mutations in the thyroid receptor- $\beta$  gene and characterized by reduced responsiveness of peripheral and pituitary tissues to the actions of thyroid hormone. We systematically evaluated the presence and severity of attention deficit–hyperactivity disorder in 18 families with a history of generalized resistance to thyroid hormone.

**Methods.** We studied 49 affected and 55 unaffected family members; 52 were adults, and 52 were children. All subjects were evaluated with structured psychiatric questionnaires by interviewers who were unaware of the medical diagnosis. The number of symptoms of attention deficit–hyperactivity disorder was calculated for each subject.

**Results.** Among the adults, 11 of 22 subjects with generalized resistance to thyroid hormone (50 percent) and 2 of 30 unaffected subjects (7 percent) had met the criteria for attention deficit–hyperactivity disorder as children ( $P < 0.001$ ). Among the children, 19 of 27 subjects resistant to thyroid hormone (70 percent) and 5 of 25 unaffected subjects (20 percent) met the criteria for the disorder ( $P < 0.001$ ). The odds of having attention deficit–hyperactivity disorder were 3.2 times higher for affected male subjects than for affected female subjects and 2.7 times higher for unaffected male subjects than for unaffected female subjects. The mean symptom score was 2.5 times higher in the affected group than in the unaffected group (7.0 vs. 2.8,  $P < 0.001$ ). The frequency of other psychiatric diagnoses was similar in the two groups.

**Conclusions.** In our study sample, attention deficit–hyperactivity disorder is strongly associated with generalized resistance to thyroid hormone. (*N Engl J Med* 1993; 328:997-1001.)

ATTENTION deficit–hyperactivity disorder is one of a group of disruptive behavior disorders that also includes conduct and oppositional disorders.<sup>1</sup> The major symptoms are motor restlessness, impulsiveness, inattention, and distractibility. Persons with this disorder have little evidence of neuroanatomical abnormalities or abnormalities of neurotransmitter function,<sup>2</sup> and the few studies of neuroendocrine function have largely been confined to the effects of treatment with sympathomimetic medications.<sup>3</sup> Studies of families suggest that relatives of children with attention deficit–hyperactivity disorder have a much higher risk of this disorder as well as of antisocial personality disorder and depression than do relatives of children without the disorder.<sup>4</sup> However, the mechanism of genetic transmission of attention deficit–hyperactivity disorder remains undetermined.

Symptoms of hyperactivity are among the more commonly reported somatic and neuropsychiatric manifestations of generalized resistance to thyroid hormone,<sup>5,6</sup> but there has been no systematic study of attention deficit–hyperactivity disorder in persons with generalized resistance to thyroid hormone. Generalized resistance to thyroid hormone is characterized by elevated serum thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) concentrations that are accompanied by inappropriately normal or elevated thyrotropin concentrations and by reduced responsiveness of the pituitary gland and peripheral tissues to the actions of

thyroid hormone. More than two decades ago, the underlying pathophysiologic mechanism of generalized resistance was postulated to be an abnormality of the thyroid hormone receptor.<sup>7</sup> It was not until the thyroid hormone receptor was identified, however, that the association of thyroid resistance to a defective receptor could be directly studied on a molecular genetic level.<sup>8,9</sup> Initial studies demonstrated that the phenotype for generalized resistance to thyroid hormone was linked to the human thyroid receptor- $\beta$  ( $hTR\beta$ ) gene on chromosome 3.<sup>10-13</sup> In subsequent studies of familial and sporadic cases of generalized resistance to thyroid hormone, more than 30 mutations in exons 9 and 10 of the  $hTR\beta$  gene, which code for the hormone-binding domain of the receptor, have been identified.<sup>14-17</sup> In all but one of these mutations, only one of the two thyroid receptor- $\beta$  alleles of affected subjects has been involved, confirming the finding of previous familial studies that generalized resistance to thyroid hormone is primarily inherited in an autosomal dominant fashion.<sup>5</sup>

Because symptoms of attention deficit–hyperactivity disorder have been reported in persons with generalized resistance to thyroid hormone, we postulated that this disorder would be the prevalent psychiatric diagnosis and would segregate with generalized resistance to thyroid hormone. In this study we used criterion-based, structured interviews to evaluate affected and unaffected members of 18 families with generalized resistance to thyroid hormone for behavioral abnormalities.

## METHODS

### Subjects

Clinical data on 104 subjects from 18 families with generalized resistance to thyroid hormone were collected during hospitalizations in the clinical center of the National Institutes of Health (NIH). Subjects or their parents, when appropriate, gave informed

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consent to participate in the study protocols, which were approved by the NIH institutional review board. Clinical and biochemical data on 13 of these families have been reported previously.<sup>5,12-16</sup>

Serum T<sub>3</sub>, T<sub>4</sub>, free T<sub>4</sub>, and thyrotropin concentrations; 24-hour urinary excretion of hydroxyproline; and pulse-wave arrival time were measured at the NIH or Hazelton Biotechnologies (Vienna, Va.). The basal metabolic rate was measured at the National Naval Medical Center (Bethesda, Md.). The subjects were considered to have generalized resistance to thyroid hormone if they had normal or elevated serum thyrotropin concentrations, elevated serum T<sub>3</sub> and T<sub>4</sub> concentrations, and resistance of peripheral tissues to the actions of thyroid hormone.

### Genetic Studies

The methods used to characterize the mutations in the 13 families have been described previously.<sup>13-16</sup> Mutations were identified by direct sequencing of genomic DNA amplified by the polymerase chain reaction and confirmed by one of several alternative methods, including allele-specific hybridization, restriction-enzyme analysis, and chemical cleavage of DNA heteroduplexes.

### Determination of Psychiatric Diagnoses

The adults were interviewed by a single psychologist, who was unaware of any subject's medical diagnosis, using the lifetime version of the Schedule for Affective Disorders and Schizophrenia.<sup>18</sup> The subjects also answered questions from a 56-item, criterion-based checklist for the symptoms of attention deficit-hyperactivity disorder. Two psychiatrists, one of whom did not know the age, sex, or medical diagnosis of the subjects, independently scored the Schedule for Affective Disorders and Schizophrenia and the symptom checklist for each subject. The adults were given a diagnosis of attention deficit-hyperactivity disorder if, as children, they had had 8 or more of the 14 symptoms of the disorder listed in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R).<sup>1</sup> Among the 52 adults studied, there was only one discrepancy in diagnosis between the two psychiatrists. This subject did not have generalized resistance to thyroid hormone and was given a diagnosis of attention deficit-hyperactivity disorder.

The children were evaluated by one of two child psychiatrists; both were unaware of any subject's medical diagnosis. The child psychiatrist interviewed the child and one parent using, respectively, the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents—Parents' Version.<sup>19</sup> The psychiatric diagnoses were based only on information obtained from these interviews, with the use of criteria for childhood disorders from the DSM-III-R. The reliability between raters was tested by having each child psychiatrist listen to 10 taped interviews and then determine which criteria in the subsection on disruptive behavior disorders in the DSM-III-R applied to each interviewee. There were no discrepancies in diagnosis between the two child psychiatrists.

## RESULTS

The demographic and clinical characteristics of the study subjects are summarized in Table 1. Fifty-two were adults, and 52 were children (<18 years of age) at the time of the interviews. Twenty-two adults and 27 children had generalized resistance to thyroid hormone. The mean serum T<sub>3</sub>, T<sub>4</sub>, free T<sub>4</sub>, and thyrotropin concentrations were higher in the subjects with generalized resistance to thyroid hormone than in those without it (P<0.001). However, there were no significant differences in 24-hour urinary excretion of hydroxyproline, basal metabolic rate, or pulse-wave arrival time between the two groups, despite the differences in serum T<sub>3</sub> and T<sub>4</sub> concentrations.

The mutations identified in 13 families were located in two regions of the hTR $\beta$  gene: seven were clustered in exon 9, and six in exon 10.<sup>13-16</sup> All but one of these

**Table 1. Demographic and Clinical Characteristics of Subjects with and Those without Generalized Resistance to Thyroid Hormone.\***

CHARACTERISTIC	RESISTANCE TO THYROID HORMONE (N = 49)	NO RESISTANCE TO THYROID HORMONE (N = 55)	NORMAL RANGE	P VALUE†
Sex (M/F)	21/28	28/27	—	—
No. of adults/no. of children	22/27	30/25	—	—
Mean age (yr)				
Adults	37.1±10.9†	34.1±8.9	—	NS
Children	9.4±4.7	10.4±4.3	—	NS
Serum concentration				
T <sub>3</sub> (ng/dl)	282±92	151±31	88–162	<0.001
T <sub>4</sub> (μg/dl)	18.3±3.5	8.3±1.7	4.5–12.5	<0.001
Free T <sub>4</sub> (ng/dl)	3.8±0.8	1.4±0.3	1.0–1.9	<0.001
Thyrotropin (μU/ml)	3.8±1.6	2.7±1.5	0.5–4.0	<0.001
Urinary excretion of hydroxyproline (mg/24 hr)	40.0±24.0	48.0±29.0	25–77	NS
Basal metabolic rate (% of expected)	101±20	99±15	—	NS
Pulse-wave arrival time (msec)	195±66	222±56	186–235	NS

\*Plus-minus values are means ±SD. To convert values for T<sub>3</sub> to nanomoles per liter, multiply by 0.0154; to convert values for T<sub>4</sub> to nanomoles per liter, multiply by 12.87; to convert values for free T<sub>4</sub> to picomoles per liter, multiply by 12.87; and to convert values for hydroxyproline excretion to micromoles per 24 hours, multiply by 0.0076.

†By the unpaired t-test. NS denotes not significant.

were single-base missense mutations that cause the substitution of an amino acid in the T<sub>3</sub>-binding domain of the hTR $\beta$  protein. The one exception was a nucleotide insertion or a frame-shift mutation. In the remaining five families, direct sequencing of exons 9 and 10 did not reveal a mutation.

Since the psychiatric interviews for the adults and the children were different, the results were analyzed separately. The lifetime diagnoses given to the adults are summarized in Table 2. Attention deficit-hyperactivity disorder was the predominant diagnosis in the subjects with generalized resistance to thyroid hormone. Fifty percent of the affected subjects had had this disorder during childhood, as compared with 7 percent of the unaffected subjects (P<0.001). The results for the 13 families with known mutations (18 affected and 25 unaffected adults) were similar (50 percent vs. 4 percent, P<0.001). There were no significant differences between groups in the numbers of subjects with other psychiatric diagnoses.

The psychiatric diagnoses given to the children are summarized in Table 3. As was true for the affected adults, the predominant diagnosis given to the children with generalized resistance to thyroid hormone was attention deficit-hyperactivity disorder. Seventy percent of the affected children were given this diagnosis, as compared with 20 percent of the unaffected children (P<0.001). The results for the 13 families with known mutations (23 affected and 18 unaffected children) were similar (74 percent vs. 17 percent, P<0.001).

The likelihood (estimated by the odds ratio) of having attention deficit-hyperactivity disorder was 15 times higher for adults with generalized resistance to thyroid hormone than for unaffected adults and 10

times higher for affected children than for unaffected children.

We compared the frequency of attention deficit-hyperactivity disorder in the seven families with mutations in exon 9 with that in the six families with mutations in exon 10. Thirteen of the 20 subjects with mutations in exon 9 had had attention deficit-hyperactivity disorder during childhood, as compared with 14 of the 21 subjects with mutations in exon 10 ( $P$  not significant).

Since attention deficit-hyperactivity disorder is more common in boys than girls,<sup>20</sup> we examined the effect of sex on diagnosis. Sixteen of the 21 affected male subjects (76 percent) and 14 of the 28 affected female subjects (50 percent) met the diagnostic criteria for the disorder ( $P$  not significant). Among unaffected family members, 5 of the 28 male members (18 percent) and 2 of the 27 female members (7 percent) had the disorder ( $P$  not significant). The odds of having attention deficit-hyperactivity disorder were 3.2 times higher for affected male subjects than for affected female subjects and 2.7 times higher for unaffected male subjects than for unaffected female subjects.

The number of symptoms of attention deficit-hyperactivity disorder was treated as a dependent variable in a two-way analysis of variance with respect to sex and illness (Fig. 1). There was a sex effect ( $F = 11.67$ ,  $P < 0.001$ ), with male subjects having more symptoms than female subjects, and an illness effect ( $F = 34.31$ ,  $P < 0.001$ ), with affected subjects having more symptoms than unaffected subjects, but no interaction between sex and illness ( $F = 2.33$ ,  $P < 0.13$ ). The mean number of symptoms in the subjects with generalized resistance to thyroid hormone was 2.5 times higher than in the unaffected subjects (7.0 vs. 2.8,  $P < 0.001$ ).

There was no correlation between the number of symptoms of attention deficit-hyperactivity disorder and serum  $T_3$ ,  $T_4$ , free  $T_4$ , or thyrotropin concentrations in either the subjects with generalized resistance to thyroid hormone or those without generalized resistance (data not shown).

## DISCUSSION

We studied 104 members of 18 families for behavioral abnormalities, using criterion-based, structured interviews. Forty-nine subjects had generalized resistance to thyroid hormone, and 55 did not. The unaffected family members, who served as a control group, had genetic and environmental backgrounds similar to those of the family members with generalized resistance to thyroid hormone, except that the latter group had a mutant thyroid receptor gene. Despite these very similar backgrounds, a significantly higher percentage of adults and children with generalized resistance to thyroid hormone had attention deficit-hyperactivity disorder. The likelihood of having the disorder was 15 times higher for adults with generalized resistance to thyroid hormone than for unaffected adult family members, and 10 times higher for children with generalized resistance to thyroid hormone than for unaffected children. Both affected and

**Table 2. Psychiatric Diagnoses Given to Adults with and Those without Generalized Resistance to Thyroid Hormone.**

DIAGNOSIS*	RESISTANCE TO THYROID HORMONE (N = 22)		NO RESISTANCE TO THYROID HORMONE (N = 30)	
	TOTAL NO. (%)	NO. WITH ADHD (%)†	TOTAL NO. (%)	NO. WITH ADHD (%)†
ADHD	11 (50)	11 (50)	2 (7)‡	2 (7)
Mood disorders	6 (27)	4 (18)	6 (20)	2 (7)
Anxiety disorders	3 (14)	3 (14)	1 (3)	0
Psychoactive substance use disorders	3 (14)	3 (14)	3 (10)	2 (7)
Antisocial personality disorder	2 (9)	2 (9)	1 (3)	1 (3)

\*The psychiatric diagnoses listed are lifetime diagnoses.

†The number of subjects with a particular psychiatric disorder who also had a diagnosis of attention deficit-hyperactivity disorder (ADHD).

‡ $P < 0.001$  for the comparison with adults with generalized resistance to thyroid hormone (by Fisher's exact test, two-tailed).

unaffected male subjects had a risk of attention deficit-hyperactivity disorder that was three times higher than that of their female counterparts, which is consistent with the generally accepted fact that this disorder is more prevalent among boys.<sup>20</sup>

In 13 of the 18 families, mutations were identified and correlated with the presence of generalized resistance to thyroid hormone in all affected subjects. Moreover, in vitro functional studies of these mutant hTR $\beta$  receptors have shown decreased or absent  $T_3$ -binding affinity and decreased transcriptional activation of positive  $T_3$ -response elements, as compared with the normal receptor.<sup>15,16,21</sup> These studies provide strong evidence that the identified mutations of the hTR $\beta$  gene cause the syndrome of generalized resistance to thyroid hormone. The mutations were clustered in two areas of the hTR $\beta$  gene: seven were in exon 9, and six in exon 10. The frequency of attention deficit-hyperactivity disorder was similar in the families with mutations in exon 9 and in those with mutations in exon 10. In contrast, in a previous study of these 13 families that included 48 of the 104 subjects in this study, speech abnormalities were significantly more common in families with mutations in

**Table 3. Psychiatric Diagnoses Given to Children with and Those without Generalized Resistance to Thyroid Hormone.**

DIAGNOSIS*	RESISTANCE TO THYROID HORMONE (N = 27)		NO RESISTANCE TO THYROID HORMONE (N = 25)	
	TOTAL NO. (%)	NO. WITH ADHD (%)†	TOTAL NO. (%)	NO. WITH ADHD (%)†
Disruptive behavior disorders	23 (85)	19 (70)	7 (28)‡	5 (20)
ADHD	19 (70)	19 (70)	5 (20)‡	5 (20)
Oppositional disorder	10 (37)	7 (26)	5 (20)	4 (16)
Conduct disorder	4 (15)	3 (11)	1 (4)	0
Mood disorders	5 (19)	4 (15)	4 (16)	3 (12)
Anxiety disorders	4 (15)	4 (15)	6 (24)	1 (4)
Avoidant personality	0	0	2 (8)	0
Enuresis	4 (15)	4 (15)	1 (4)	0

\*The psychiatric diagnoses listed are lifetime diagnoses. Some subjects had more than one disruptive behavior disorder.

†The number of subjects with a particular psychiatric disorder who also had a diagnosis of attention deficit-hyperactivity disorder (ADHD).

‡ $P < 0.001$  for the comparison with children with generalized resistance to thyroid hormone (by Fisher's exact test, two-tailed).

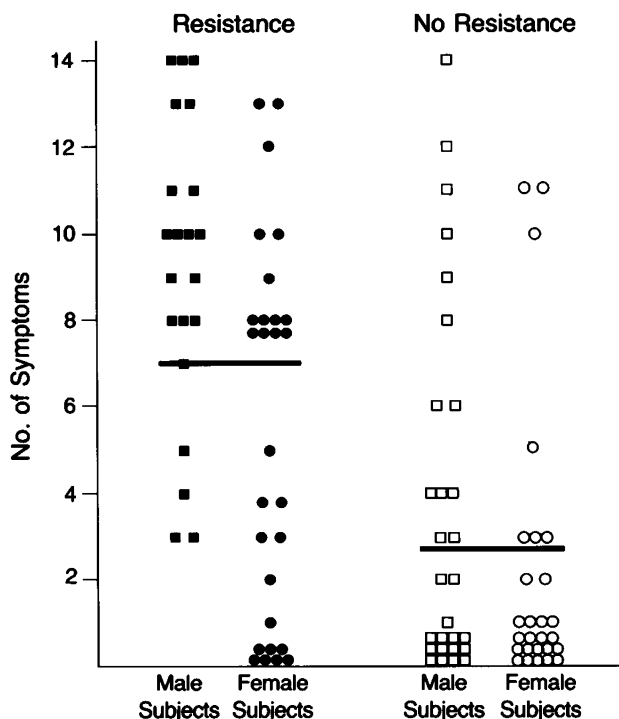


Figure 1. Distribution of Symptoms of Attention Deficit-Hyperactivity Disorder among Subjects with and Those without Generalized Resistance to Thyroid Hormone.

The horizontal lines indicate the mean number of symptoms. The group with generalized resistance to thyroid hormone had a mean of 7.0 symptoms, as compared with a mean of 2.8 for the group of unaffected family members ( $P < 0.001$ ).

exon 9 than in those with mutations in exon 10.<sup>16</sup>

In our adult subjects, mood, anxiety, psychoactive substance use, and antisocial personality disorders were often associated with attention deficit-hyperactivity disorder. Similarly, children with psychiatric diagnoses that included conduct and oppositional defiant, mood, and anxiety disorders also often had attention deficit-hyperactivity disorder. This pattern of coexisting conditions is similar to that found among persons with attention deficit-hyperactivity disorder in the general population.<sup>22</sup>

Serum  $T_4$  and  $T_3$  concentrations were elevated and serum thyrotropin concentrations inappropriately normal in the subjects with generalized resistance to thyroid hormone, reflecting the compensatory physiologic response of the pituitary-thyroid system to tissue resistance. Although the combination of increased thyroid secretion and decreased responsiveness to thyroid hormones would be expected to lead to a state of functional euthyroidism in most tissues, the tissue sensitivity to thyroid hormone varies in affected subjects.<sup>5</sup> For example, the pituitary gland was resistant in all our subjects, as indicated by the inappropriately normal or elevated serum thyrotropin concentrations, despite the presence of elevated serum  $T_4$  and  $T_3$  concentrations. Some patients have resting tachycardia, however, suggesting that cardiac tissue is relatively less resistant than the pituitary gland. We can only speculate on the functional responsiveness of the cen-

tral nervous system. However, even if the brain was relatively more responsive to thyroid hormone than other tissues, and hence relatively hyperthyroid, hyperthyroidism is unlikely to account for the increased frequency of attention deficit-hyperactivity disorder in our subjects. Although overactivity, restlessness, and a lack of concentration are symptoms of thyrotoxicosis, the most prevalent psychiatric diagnoses given to patients with thyrotoxicosis are those of anxiety and anxiety-related disorders, along with mood disorders, rather than attention deficit-hyperactivity disorder.<sup>23</sup> It is possible that the presence of attention deficit-hyperactivity disorder in these patients would be attributed to the thyrotoxic state and therefore not reported. However, anecdotal evidence suggests that the behavioral symptoms of subjects with generalized resistance to thyroid hormone and concomitant attention deficit-hyperactivity disorder improve during therapy with  $T_3$  (unpublished data).

Thyroid hormone is essential for normal brain development, and its absence causes mental retardation.<sup>24</sup> The mechanism of action of thyroid hormone is initiated by hormone binding to the  $T_3$  receptor. In the human fetus, the concentration of  $T_3$  receptors is low at 10 weeks of gestation, but it increases 10-fold by the 16th week, coincidentally with neuroblast proliferation.<sup>25</sup> In rat brain, the levels of thyroid receptor- $\beta$  messenger RNA (mRNA) increased 40-fold from 19 days of gestation to 10 days after birth, a period that coincides with  $T_3$ -regulated developmental changes in the brain.<sup>25</sup> The regulation of the expression of myelin basic protein mRNA in rat brain is mediated by the interaction of the activated thyroid receptor with a thyroid-response element in the promoter region of this gene.<sup>27</sup> In addition, expression of the NGFI-A gene, an immediate early-response gene implicated in the control of brain-cell proliferation and aspects of brain development, is directly regulated by  $T_3$  in the brains of neonatal, but not adult, rats.<sup>28</sup> Taken together, these studies suggest the importance of the thyroid receptor- $\beta$  protein in brain development. Theoretically, mutations of the hTR $\beta$  gene could result in behavioral abnormalities through several different mechanisms, including potentially irreversible effects on axonal routing, neuronal proliferation and migration, and the regulation of gene expression during critical periods of brain development.

In addition to its putative role in brain development, the thyroid receptor-thyroid hormone complex may influence catecholamine neurotransmitter systems thought to be involved in the pathophysiology of attention deficit-hyperactivity disorder. Sympathomimetic drugs, such as dextroamphetamine sulfate and methylphenidate, are commonly used to treat patients with this disorder.<sup>29</sup> Thyroid hormone has sympathomimetic properties that may be mediated by the interaction of the activated thyroid receptor with putative thyroid-response elements in the promoter region of genes involved in the homeostasis of the catecholamine neurotransmitter system.

Further evidence of a putative role of the hTR $\beta$  gene in attention deficit-hyperactivity disorder comes

from in vitro functional studies showing that the ability of the wild-type hTR $\beta$  to activate a positive thyroid-response element is inhibited by the mutant hTR $\beta$  and that this effect could be reversed by high concentrations of T<sub>3</sub>.<sup>21,30</sup> We speculate that in affected subjects with generalized resistance to thyroid hormone, the mutant hTR $\beta$  protein competes with the wild-type hTR $\beta$  protein in a dominant negative fashion and thus down-regulates the catecholamine-neurotransmitter function. This down-regulation, in conjunction with the previously postulated irreversible effects of a mutant hTR $\beta$  gene on brain development during fetal life, may cause the symptoms of attention deficit-hyperactivity disorder.

This study has several potential implications with respect to attention deficit-hyperactivity disorder in general. Although it is unlikely that a substantial percentage of patients with this disorder also have generalized resistance to thyroid hormone, prospective studies of thyroid function should be undertaken in these patients because they may have less overt thyroid-related causes of the disorder. Moreover, there could be a role for thyroid hormone in the treatment of the disorder, either as a primary pharmacotherapeutic agent or as a supplement that potentiates the effect of sympathomimetic medications.

We have identified linkage between a well-recognized psychiatric disorder and a specific, defined genetic abnormality. Specifically, we found that subjects with generalized resistance to thyroid hormone have a markedly increased frequency of attention deficit-hyperactivity disorder as compared with their unaffected family members. This study and future studies of the neurobiologic correlates of generalized resistance to thyroid hormone may provide new insights into the basic pathogenesis and treatment of attention deficit-hyperactivity disorder.

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