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Congenital Neonatal Hyperthyroidism Caused by Germline Mutations in the TSH Receptor Gene: Case Report and Review of the Literature

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Abstract

Neonatal hyperthyroidism, a rare and serious disorder occurs in two forms. An autoimmune form associated with maternal Graves' disease, resulting from transplacental passage of maternal thyroid-stimulating antibodies, and a nonautoimmune form, resulting from mutations in the stimulatory G protein or the thyrotropin receptor (TSHR) causing constitutive activation of intracellular signaling cascades. To date, 29 separate cases of thyrotoxicosis caused by germline mutations of the TSHR have been documented. These cases have expressed themselves in a range of clinical consequences. This report describes a new case of a newborn with nonautoimmune hyperthyroidism secondary to a constitutively active TSHR mutation (S281N) whose clinical course was complicated by severe respiratory compromise. Typical clinical findings in this disorder are discussed by a review of all previously published cases.

Keywords

thyrotropin receptor; TSHR; activating mutation; neonatal hyperthyroidism

Introduction

Neonatal hyperthyroidism is a rare and serious disorder of varying etiology. This condition has been linked to hyperkinesis, poor weight gain, ophthalmopathy, cardiac failure, systemic and pulmonary hypertension, hepatosplenomegaly, jaundice, and craniosynostosis (1), in

addition to tachycardia and thyroid enlargement (2). Congenital neonatal hyperthyroidism occurs either in an autoimmune form (Graves' disease) or in a non-autoimmune form.

The autoimmune form of neonatal hyperthyroidism is caused by the transplacental passage of thyroid stimulating antibodies (TSAb) from mothers with Graves' disease to the fetus. Autoimmune hyperthyroidism occurs in 1% of infants born to women with Graves' disease (1 out of 50,000 neonates) (3). This form of hyperthyroidism usually subsides in the first 4 months of life due to the clearance of maternal TSAb.

The nonautoimmune form results from constitutively active mutations either in the stimulatory G protein or in the thyrotropin (TSH) receptor (TSHR). These cause TSH-independent activation of the cyclic AMP pathway stimulating both thyroid hormone production and thyroid cell proliferation (4).

Here we report a new patient with sporadic congenital non-autoimmune thyrotoxicosis, due to a de-novo TSHR mutation. Our patient's clinical findings and a review of the clinical presentation of all published cases form the basis of this report.

Case Report

The propositus is a male, born preterm at 34 weeks gestation to a 39-year-old mother (gravida 4, para 4). Pregnancy was uncomplicated, although a sonogram showed thickened nuchal folds. Initial neonatal course was complicated by severe tachypnea, requiring intensive care monitoring. His birth weight was 2.35 kg (50th – 75th percentile) and his length was 46 cm (50th – 75th percentile). TSH, measured by the Pennsylvania Department of Health Screen, was 4.42 mU/l (normal range < 28.5 mU/l) and the supplemental newborn screen was reported as normal.

He had poor weight gain at 2 months of age. His anterior fontanel was closing and he was found to have fusing metopic sutures. Over the next two months, the patient failed to thrive despite supplemental tube feeding with breast milk. At his 4 month check, weighting 3.29 kg, his pediatrician obtained thyroid function tests revealing thyrotoxicosis with total T4 (TT4) of 38.7 µg/dl (normal range 4.6–10.4), free T4 (FT4) >12 ng/dl (normal range 0.8–1.4), a total T3 (TT3) of 916 ng/dl (normal range 83–183), a free T3 (FT3) >2000 pg/dl (normal range 225–370), and a TSH <0.019 mU/l (normal range 0.3–4.0). There was no family history of thyroid disease. He was tachypneic (respiratory rate of 32/min) and tachycardic (214 beats/min) at presentation to the emergency room and was admitted by Pediatric Endocrinology. He was 61.2 cm in length (3rd – 10th percentile), 4.2 kg (well below 3rd percentile), and head circumference was 38.9 cm. The anterior fontanel was closed. Significant findings on physical exam were prominent staring eyes, a diffusely enlarged thyroid gland (without palpable nodules), and craniosynostosis.

Skeletal survey at age 4.5 months showed markedly accelerated skeletal maturation with 37 radiopaque ossification centers (normal: 7.6 ± 1.9; method of Sontag, Snell, and Anderson). When compared to the standards of Greulich and Pyle the patient's hand and wrist corresponded to a skeletal age of 3 years.

Ultrasound of the thyroid gland revealed a diffusely enlarged gland with a thickened isthmus of 4 mm. The right lobe was $1.1 \times 1.3 \times 4.1$ cm. The left lobe was $1.1 \times 1.2 \times 3.5$ cm. Maternal thyroid hormone levels at the time of the propositus' presentation at the emergency room were normal, with a free T4 of 1.10 ng/dl, total T4 of 8.0 µg/dl, and total T3 of 132 ng/dl. At this time, the mother's thyroid peroxidase (TPO) antibodies test was negative (at the Mercy Hospital Clinical Laboratory, Pittsburgh, PA), and her thyroid-stimulating immunoglobulin (TSI) was 109%, which is below the reference range of <125% of basal activity. Also, at this time the propositus tested below the reference range for TSI (with a value of 104%) and he tested negative for TPO. It should be noted that when thyroid function tests were subsequently performed on the entire family (at the University of Chicago Medical Center Endocrinology Laboratory), the mother showed trace levels of TPO and TG antibodies (figure 2).

The patient was treated with potassium iodide (1 drop / 8 hours) for four days, and with ongoing propranolol (1.5 mg / 8 hours), propylthiouracil (7 mg / 8 hours), and levothyroxine (12.5 µg / day). The patient responded with clinical improvement. At the time thyroid function was obtained for the whole family (figure 2), the propositus had been on his therapeutic regimen for four weeks, and while he showed improvement from initial presentation (TT4 18.3 µg/dl, TT3 216 ng/dl), he was not yet euthyroid. After 2 months of this regimen, his TT4 was 14.7 µg/dl and FT4 was 1.5 ng/dl, although his TSH remained suppressed at 0.019 mU/l. With near normalization of thyroid function tests, the patient began to gain weight and improve his growth velocity. At 9 months of age, he was approximately at the 5th percentile for length but remained well below the 5th percentile for weight. While his tachycardia resolved, his tachypnea remained a significant problem necessitating continuous monitoring.

At the age of 8 months, he presented to pediatric pulmonology with severe respiratory symptoms consisting of stridor, snort, and nocturnal apneic episodes lasting up to 20 seconds and causing decreased peripheral oxygen saturation (< 80% by pulse oxymetry). He had mild gastroesophageal reflux and reactive airways. These were treated successfully with lansoprazole, ranitidine, and inhaled budesonide. The patient's family history was negative for asthma, obstructive sleep apnea/hypopnea, and gastroesophageal reflux. He demonstrated midface hypoplasia, dolichocephaly, with no adenopathy. He had persistent nasal drainage, enlarged tonsils, intact soft palate and posterior pharyngeal wall with large adenoids obstructing the nasopharynx. There was mild laryngomalacia on nasopharyngolaryngoscopy. The trachea was midline. With maximal inspiratory effort or when asleep, he had a stridorous low-pitched monophonic sound from his upper neck region. The snorts faded away with anterior jaw thrust and when awake. His chest had a normal AP diameter with pectus excavatum. Mild supra-sternal retractions noted with no cough. The percussion note was normal in the absence of fremitus. When awake his breathing was without stridor or wheeze. He had normal muscle mass with mild hypotonia. No hemangiomas or skin lesions were noted. Because of obstructive sleep apnea documented by a sleep study, adenoidectomy was performed, which produced temporary improvement.

Six months later, he had re-growth of adenoid tissue. He required a second surgical procedure, removing both tonsils and adenoids. Bronchoscopy was normal, with no lipid-laden macrophages in the bronchoalveolar lavage. Radiolabeled food scan was negative for aspiration or gastroesophageal reflux. His thyroid ultrasound revealed a goiter without evidence of airway obstruction.

At 14 months of age, he had 47 ossification centers (approximately 4 standard deviations above the mean; method of Snell, Sontag, and Anderson) and his skeletal age was 4 years 6 months (method of Greulich and Pyle). No further progression in his skeletal age was found on determinations at 26 months of age. A repeat thyroid ultrasound at age 23 months demonstrated a slight increase in gland size, but no thyroid nodules.

Materials and Methods

Informed consent was obtained from the parents for the clinical and laboratory evaluation of this patient. The protocol for genetic analysis was approved by the IRB and all family members tested gave a written consent. The proband and his immediate family (2 parents and 4 siblings) were studied for levels of thyroid hormone and for the presence of thyroid stimulating antibodies (TSAb).

Tests of Thyroid Function

Serum total 3,3',5,5'-tetraiodothyronine (thyroxine, TT4), 3,3',5,-triiodothyronine (TT3) and 3,3',5,-triiodothyronine (reverse T3, TrT3) concentrations were measured by immunoassays and TSH by a third generation chemiluminescence assay (Elecsys 2010, Roche, Indianapolis, IN). The serum free T4 index (FT4I) was calculated as the product of the serum TT4 and the T4-resin uptake value (5). The radioimmunoassay for serum thyroglobulin (TG) was an in house assay as reported (6). Thyroid peroxidase (TPO) and TG autoantibodies were measured by agglutination (Fujirebio Inc., Tokyo, Japan). In vitro bioassay (luciferase) to detect TSI was performed by Quest Diagnostics.

Sequencing of the *TSHR* Coding Regions

Venous blood samples from the patient and both parents were collected in EDTA and genomic DNA was isolated from leukocytes. All coding exons of the *TSHR* gene were amplified by polymerase chain reaction and subjected to bidirectional DNA sequencing as described (7).

Results and Discussion

The neonatal nonautoimmune hyperthyroidism in this patient could be attributed to a sporadic germline mutation of one allele of his *TSHR* gene. The point mutation results in the replacement of the normal serine at position 281 with asparagine (S281N) (figure 1). S281 is known to be crucial for preventing ligand-independent activation of *TSHR* and mutations at this site have been extensively studied in vitro (8, 9). The S281N mutation causes constitutive activation of the cyclic AMP signaling pathway stimulating both thyroid hormone production and thyroid cell proliferation. The mutation occurred de-novo, since

both parents did not harbor the TSHR mutation (not shown). In addition, both parents and all siblings had normal tests of thyroid function (figure 2).

Activating mutations of the TSHR gene present as either somatic or germline mutations. In the somatic form, an activating TSHR mutation can generate autonomously functioning thyroid nodules (adenomas), which are benign thyroid follicular neoplasms (10). Studies have shown that toxic thyroid adenomas are associated with TSHR gene mutations with a frequency ranging from 8–75% (11). Additionally, at least one case of a somatic TSHR gene mutation found in a malignant autonomously functioning thyroid nodule suggests the role of this mutation in the carcinogenic process (12). Germline activating TSHR gene mutations, on the other hand, result in congenital hyperthyroidism, as sporadic de-novo mutations or as familial autosomal dominantly inherited form.

Table 1 summarizes data of 29 previously reported cases of non-autoimmune hyperthyroidism resulting from *TSHR* germline mutations causing constitutive receptor activation, highlighting the variability of clinical consequences of this condition. While 10 of these cases were sporadic, de-novo mutations, 19 cases involved multiple family members. For symptom comparisons, we included only the index case from these 19 familial cases, as well as the 10 sporadic cases.

Our patient was born preterm, a relatively common finding in nonautoimmune hyperthyroidism. Of the 19 published cases for which gestational age at birth was noted, 6 patients were born earlier than 36 weeks gestational age. At the time of our patient's birth, the state screen utilized only TSH for identification of hypothyroidism. Both T4 and TSH are now included in the Pennsylvania State Screen, however the T4 screen is designed to detect hypothyroidism. While full-range T4 and TSH assays at birth may facilitate the early identification of non-autoimmune thyrotoxicosis, this is true only in 27% of instances, as in the majority of cases, frank thyrotoxicosis with suppressed serum TSH levels has been observed from months to years after birth (table 1). TSH in our patient was detectable at birth, and therefore the diagnosis of thyrotoxicosis could not be made until symptoms lead to repeat testing.

This patient was noted for craniosynostosis and failure to thrive, which, at identification, prompted the measurement of thyroid hormone levels. Of the published cases, 6 of 11 patients examined for craniosynostosis presented with this defect. While there are many reasons for early closure of the anterior fontanel, a thyroid cause should be always considered. Failure to thrive beyond the neonatal period is associated with both hypothyroidism and thyrotoxicosis.

Of 20 patients with germline activating *TSHR* mutations for which the weight percentile at presentation was reported, 14 were in the 50th percentile or lower, and 5 patients were in the 10th percentile or lower. Thus, severe underweight should also direct clinicians to the measurement of T4 and TSH. The advanced bone age in our patient is a common consequence of neonatal hyperthyroidism. In fact, of the 15 published cases with reported data on skeletal age, all had accelerated bone maturation.

Naturally, goiter is also a typical feature in patients at diagnosis (24 out of 29), and sometimes accompanied by proptosis (7 of 25 patients with reported data), as in the patient reported here. Of the previously described patients with nonautoimmune thyrotoxicosis, only one displayed respiratory symptoms, in the form of asphyxia at birth, from which the patient survived and experienced no further respiratory compromise (13). Thus, our propositus is the only patient with a constitutively activating germline *TSHR* mutation to exhibit severe and prolonged respiratory difficulty. Study of additional cases is required to understand if there is a causal association between non-autoimmune thyrotoxicosis and respiratory distress.

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References

1. Zimmerman D. Fetal and neonatal hyperthyroidism. *Thyroid*. 1999; 9(7):727–33. [PubMed: 10447021]
2. Krude H, Biebermann H, Krohn HP, Dralle H, Gruters A. Congenital hyperthyroidism. *Exp Clin Endocrinol Diabetes*. 1997; 105(Suppl 4):6–11. [PubMed: 9439907]
3. Polak M. Hyperthyroidism in early infancy: pathogenesis, clinical features and diagnosis with a focus on neonatal hyperthyroidism. *Thyroid*. 1998; 8(12):1171–7. [PubMed: 9920374]
4. Fuhrer D, Warner J, Sequeira M, Paschke R, Gregory J, Ludgate M. Novel TSHR germline mutation (Met463Val) masquerading as Graves' disease in a large Welsh kindred with hyperthyroidism. *Thyroid*. 2000; 10(12):1035–41. [PubMed: 11201847]
5. Refetoff S, Hagen SR, Selenkow HA. Estimation of the T4 binding capacity of serum TBG and TBPA by a single T4 load ion exchange resin method. *J Nucl Med*. 1972; 13(1):2–12. [PubMed: 4621446]
6. Lever EG, Refetoff S, Scherberg NH, Carr K. The influence of percutaneous fine needle aspiration on serum thyroglobulin. *J Clin Endocrinol Metab*. 1983; 56(1):26–9. [PubMed: 6847872]
7. Ringakanont U, Van Durme J, Montanelli L, Ugrasbul F, Yu YM, Weiss RE, et al. Repulsive separation of the cytoplasmic ends of transmembrane helices 3 and 6 is linked to receptor activation in a novel thyrotropin receptor mutant (M626I). *Mol Endocrinol*. 2006; 20(4):893–903. [PubMed: 16339276]
8. Corvilain B, Van Sande J, Dumont JE, Vassart G. Somatic and germline mutations of the TSH receptor and thyroid diseases. *Clin Endocrinol (Oxf)*. 2001; 55(2):143–58. [PubMed: 11531919]
9. Jaeschke H, Neumann S, Kleinau G, Mueller S, Claus M, Krause G, et al. An aromatic environment in the vicinity of serine 281 is a structural requirement for thyrotropin receptor function. *Endocrinology*. 2006; 147(4):1753–60. [PubMed: 16410307]
10. Russo D, Wong MG, Costante G, Chiefari E, Treseler PA, Arturi F, et al. A Val 677 activating mutation of the thyrotropin receptor in a Hurthle cell thyroid carcinoma associated with thyrotoxicosis. *Thyroid*. 1999; 9(1):13–7. [PubMed: 10037070]
11. Fuhrer D, Holzapfel HP, Wonerow P, Scherbaum WA, Paschke R. Somatic mutations in the thyrotropin receptor gene and not in the Gs alpha protein gene in 31 toxic thyroid nodules. *J Clin Endocrinol Metab*. 1997; 82(11):3885–91. [PubMed: 9360556]
12. Russo D, Tumino S, Arturi F, Vigneri P, Grasso G, Pontecorvi A, et al. Detection of an activating mutation of the thyrotropin receptor in a case of an autonomously hyperfunctioning thyroid insular carcinoma. *J Clin Endocrinol Metab*. 1997; 82(3):735–8. [PubMed: 9062474]
13. Lavard L, Sehested A, Brock Jacobsen B, Muller J, Perrild H, Feldt-Rasmussen U, et al. Long-term follow-Up of an infant with thyrotoxicosis due to germline mutation of the TSH receptor gene (Met453Thr). *Horm Res*. 1999; 51(1):43–6. [PubMed: 10095169]

14. Gruters A, Schoneberg T, Biebermann H, Krude H, Krohn HP, Dralle H, et al. Severe congenital hyperthyroidism caused by a germ-line neo mutation in the extracellular portion of the thyrotropin receptor. *J Clin Endocrinol Metab.* 1998; 83(5):1431–6. [PubMed: 9589634]
15. Guemas I, Guorguleva I, Rothenbuler A, Stuckens C, Weill J, Cartigny M. Hyperthyroidism due to an activating mutation of the thyrotropin receptor. *Hormone Research.* 2003; 60(2):98.
16. Biebermann H, Schoneberg T, Hess C, Germak J, Gudermann T, Gruters A. The first activating TSH receptor mutation in transmembrane domain 1 identified in a family with nonautoimmune hyperthyroidism. *J Clin Endocrinol Metab.* 2001; 86(9):4429–33. [PubMed: 11549687]
17. de Roux N, Polak M, Couet J, Leger J, Czernichow P, Milgrom E, et al. A neomutation of the thyroid-stimulating hormone receptor in a severe neonatal hyperthyroidism. *J Clin Endocrinol Metab.* 1996; 81(6):2023–6. [PubMed: 8964822]
18. Lee YS, Poh L, Loke KY. An activating mutation of the thyrotropin receptor gene in hereditary non-autoimmune hyperthyroidism. *J Pediatr Endocrinol Metab.* 2002; 15(2):211–5. [PubMed: 11874187]
19. Tonacchera M, Van Sande J, Cetani F, Swillens S, Schvartz C, Winiszewski P, et al. Functional characteristics of three new germline mutations of the thyrotropin receptor gene causing autosomal dominant toxic thyroid hyperplasia. *J Clin Endocrinol Metab.* 1996; 81(2):547–54. [PubMed: 8636266]
20. Schwab KO, Sohlmann P, Gerlich M, Broecker M, Petrykowski W, Holzapfel HP, et al. Mutations of the TSH receptor as cause of congenital hyperthyroidism. *Exp Clin Endocrinol Diabetes.* 1996; 104(Suppl 4):124–8. [PubMed: 8981019]
21. Holzapfel HP, Wonerow P, von Petrykowski W, Henschen M, Scherbaum WA, Paschke R. Sporadic congenital hyperthyroidism due to a spontaneous germline mutation in the thyrotropin receptor gene. *J Clin Endocrinol Metab.* 1997; 82(11):3879–84. [PubMed: 9360555]
22. Fuhrer D, Mix M, Wonerow P, Richter I, Willgerodt H, Paschke R. Variable phenotype associated with Ser505Asn-activating thyrotropin-receptor germline mutation. *Thyroid.* 1999; 9(8):757–61. [PubMed: 10482366]
23. Vaidya B, Campbell V, Tripp JH, Spyer G, Hat tersley AT, Ellard S. Premature birth and low birth weight associated with nonautoimmune hyperthyroidism due to an activating thyrotropin receptor gene mutation. *Clin Endocrinol (Oxf).* 2004; 60(6):711–8. [PubMed: 15163335]
24. Duprez L, Parma J, Van Sande J, Allgeier A, Leclere J, Schvartz C, et al. Germline mutations in the thyrotropin receptor gene cause non-autoimmune autosomal dominant hyperthyroidism. *Nat Genet.* 1994; 7(3):396–401. [PubMed: 7920658]
25. Thomas JS, Leclere J, Hartemann P, Duheille J, Orgiazzi J, Petersen M, et al. Familial hyperthyroidism without evidence of autoimmunity. *Acta Endocrinol (Copenh).* 1982; 100(4):512–8. [PubMed: 7124278]
26. Karges B, Krause G, Homoki J, Debatin KM, de Roux N, Karges W. TSH receptor mutation V509A causes familial hyperthyroidism by release of interhelical constraints between transmembrane helices TMH3 and TMH5. *J Endocrinol.* 2005; 186(2):377–85. [PubMed: 16079263]
27. Biebermann H, Krude H, Kohler B, Huhne K, Dralle H, Kohn H, et al. A novel germline mutation of the thyrotropin receptor gene leading to familial hyperthyroidism with different penetrance. *J Endocrinol Invest.* 1996; 19(Suppl 6):143.
28. Tonacchera M, Agretti P, Rosellini V, Ceccarini G, Perri A, Zampolli M, et al. Sporadic nonautoimmune congenital hyperthyroidism due to a strong activating mutation of the thyrotropin receptor gene. *Thyroid.* 2000; 10(10):859–63. [PubMed: 11081252]
29. Claus M, Maier J, Paschke R, Kujat C, Stumvoll M, Fuhrer D. Novel thyrotropin receptor germline mutation (Ile568Val) in a Saxonian family with hereditary nonautoimmune hyperthyroidism. *Thyroid.* 2005; 15(9):1089–94. [PubMed: 16187920]
30. Esapa CT, Duprez L, Ludgate M, Mustafa MS, Kendall-Taylor P, Vassart G, et al. A novel thyrotropin receptor mutation in an infant with severe thyrotoxicosis. *Thyroid.* 1999; 9(10):1005–10. [PubMed: 10560955]

31. Alberti L, Proverbio MC, Costagliola S, Weber G, Beck-Peccoz P, Chiumello G, et al. A novel germline mutation in the TSH receptor gene causes non-autoimmune autosomal dominant hyperthyroidism. *Eur J Endocrinol*. 2001; 145(3):249–54. [PubMed: 11517004]
32. Schwab KO, Gerlich M, Broecker M, Sohlmann P, Derwahl M, Lohse MJ. Constitutively active germline mutation of the thyrotropin receptor gene as a cause of congenital hyperthyroidism. *J Pediatr*. 1997; 131(6):899–904. [PubMed: 9427897]
33. Fuhrer D, Wonerow P, Willgerodt H, Paschke R. Identification of a new thyrotropin receptor germline mutation (Leu629Phe) in a family with neonatal onset of autosomal dominant nonautoimmune hyperthyroidism. *J Clin Endocrinol Metab*. 1997; 82(12):4234–8. [PubMed: 9398746]
34. Kopp P, van Sande J, Parma J, Duprez L, Gerber H, Joss E, et al. Brief report: congenital hyperthyroidism caused by a mutation in the thyrotropin-receptor gene. *N Engl J Med*. 1995; 332(3):150–4. [PubMed: 7800007]
35. Nwosu BU, Gourgoutis L, Gershengorn MC, Neumann S. A novel activating mutation in transmembrane helix 6 of the thyrotropin receptor as cause of hereditary nonautoimmune hyperthyroidism. *Thyroid*. 2006; 16(5):505–12. [PubMed: 16756474]
36. Kopp P, Jameson JL, Roe TF. Congenital nonautoimmune hyperthyroidism in a nonidentical twin caused by a sporadic germline mutation in the thyrotropin receptor gene. *Thyroid*. 1997; 7(5):765–70. [PubMed: 9349581]
37. Khoo DH, Parma J, Rajasoorya C, Ho SC, Vassart G. A germline mutation of the thyrotropin receptor gene associated with thyrotoxicosis and mitral valve prolapse in a Chinese family. *J Clin Endocrinol Metab*. 1999; 84(4):1459–62. [PubMed: 10199795]
38. Leclere J, Bene MC, Aubert V, Klein M, Pascal-Vigneron V, Weryha G, et al. Clinical consequences of activating germline mutations of TSH receptor, the concept of toxic hyperplasia. *Horm Res*. 1997; 47(4–6):158–62. [PubMed: 9167947]

Figure 1.

Results of TSHR gene sequencing. The electropherogram on the left is from a normal family member with both alleles of the wild-type (wt/wt). On the right is the electropherogram of the proband showing a G to A transition leading to a substitution of asparagine for serine at codon 281 (S281N).

Figure 2.

Pedigree of the family and results of thyroid function tests. Results of thyroid function tests are aligned with each individual symbol. Test results above or below the reference range are highlighted in red or blue color, respectively. These results were obtained 4 weeks after the patient's initial presentation, and the patient had begun his therapeutic regimen. Maternal thyroid autoantibodies were weakly positive in this assay, but they were negative when the mother was tested at initial presentation of the propositus at Mercy Hospital of Pittsburgh.

TABLE 1

Summary of clinical, laboratory and genetic information from 29 previously reported cases with activating TSHR *germline* mutations

Mutation	Reference	Fm or Sp (cases)	Age at Presentation	Premature? (<36 weeks)	T4 and T3	Cranio synostosis	Advanced Bone Age	Proptosis	Failure to Grow/Thrive	Enlarged Thyroid gland	Length at Presentation	Weight at Presentation	Treatment
Ser281Asn	Gruters et al 1998 [14]	Sp	4 mo	no, 36 wks	FT4=96.8 pmol/L, FT3=40.9 pmol/L	yes	n/a	no	n/a	no	49 cm (75th%)	2.52kg (50th%)	Antithyroid Drugs, Subtotal Thyroidectomy
Ala428Val	Guemas et al 2003 [15]	Fm	4 yr	no, 40 wks	FT4 elevated	n/a	yes	no	yes	yes	121 cm (>95th%)	18.9 kg (80th%)	n/a
Gly431Ser	Biebermann et al 2001 [16]	Fm (3)	3 yr	no, 36 wks	FT4=56.6 pmol/L	n/a	n/a	no	yes	yes	n/a	2.5 kg (50th%)	Antithyroid Drugs, Total Thyroidectomy
Met453Thr	DeRoux et al 1996 [17]	Sp	neonate	yes, 32 wks	FT4=100 pmol/L, FT3>35 pmol/L	no	n/a	yes	n/a	yes	41 cm (25th%)	1.69 kg (50th%)	Antithyroid Drugs
Met453Thr	Lavard et al 1999 [13]	Sp	7 mo	no, 36 wks	T4=404 nmol/L, T3=8.5 nmol/L	no	yes	yes	yes	yes	52 cm (100th%)	3.04 kg (80th%)	Antithyroid Drugs, Subtotal Thyroidectomy, Radioiodine Rx
Met463Val	Fuhrer et al 2000 [4]	Fm (8)	4.9 yr	no, 39 wks	FT4=61.9 pmol/L, FT3=14.3 pmol/L	n/a	yes	no	n/a	yes	n/a	3.69 kg (75th%)	Antithyroid Drugs
Met463Val	Lee et al 2002 [18]	Fm (9)	2.75 yr	no, 37 wks	FT4=35.4 pmol/L	n/a	n/a	no	n/a	no	n/a	2.7 kg (40th%)	Antithyroid Drugs
Ser505Arg	Tonachera et al 1996 [19]	Fm (5)	child	n/a	FT4>23 pmol/L	n/a	yes	no	n/a	yes	n/a	n/a	Antithyroid Drugs, Subtotal Thyroidectomy, Radioiodine Rx
Ser505Asn	Schwab et al 1996 [20]	Sp	neonate	no, 38 wks	FT4=78.5 pmol/L, FT3=31.5 pmol/L	yes	yes	yes	yes	yes	50 cm (50th%)	2.6 kg (10th%)	Antithyroid Drugs, Thyroidectomy
Ser505Asn	Holzapfel et al 1997 [21]	Sp	5 mo	no, 38 wks	FT4=78.5 pmol/L, FT3=31.5 pmol/L	yes	yes	yes	yes	yes	50 cm (50th%)	2.6 kg (20th%)	Antithyroid Drugs, Near-total Thyroidectomy
Ser505Asn	Fuhrer et al 1999 [22]	Sp	11 mo	no, 40 wks	T4=345 nmol/L, T3=9.3 nmol/L	n/a	yes	no	n/a	yes	47 cm (<5th%)	2.54 kg (<5th%)	Antithyroid Drugs
Ser505Asn	Vadva et al 2004 [23]	Fm (3)	19 mo	yes, 33 wks	T4=300 nmol/L, FT3=18.7 pmol/L	no	yes	no	n/a	yes	43 cm at 2 wks (5th%)	1.75 kg at birth (40th%)	Antithyroid Drugs, Total Thyroidectomy
Val509Ala	Duprez et al 1994 [24] Thomas et al 1982 [25]	Fm (9)	10 yr	n/a	FT4=21 pmol/L	n/a	n/a	no	n/a	yes	n/a	n/a	Antithyroid Drugs, Partial Thyroidectomy, Total Thyroidectomy
Val509Ala	Karges et al 2005 [26]	Fm (3)	4 yr	n/a	T4=182.75 nmol/L, T3=3.6 nmol/L	n/a	yes	no	n/a	yes	121.8 cm (97th%)	22.5 kg (90th%)	Antithyroid Drugs
Arg528His	Biebermann et al 1996 [27]	Fm (4)	2 mo	no, 38 wks	n/a	yes	n/a	no	n/a	yes	n/a	n/a	Total Thyroidectomy, Antithyroid drugs
Ile568Thr	Tonachera et al 2000 [28]	Sp	neonate	yes, 35 wks	FT4=160.9 pmol/L, FT3=2.62 pmol/L	no	yes	no	yes	yes	46 cm (50th%)	2.05 kg (25th%)	Antithyroid Drugs

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Mutation	Reference	Fm or Sp (cases)	Age at Presentation	Premature? (<36 weeks)	T4 and T3	Cranio synostosis	Advanced Bone Age	Proptosis	Failure to Grow/Thrive	Enlarged Thyroid gland	Length at Presentation	Weight at Presentation	Treatment
Ile568Val	Claus et al 2005 [29]	Fm (3)	16 yr	n/a	FT4=33.8 pmol/L, FT3=13.98 pmol/L	n/a	n/a	n/a	n/a	yes	n/a	n/a	Antithyroid Drugs
Val597Leu	Esapa et al 1999 [30]	Sp	9 mo	no, 37 wks	FT4=121 pmol/L, FT3=40 pmol/L	n/a	yes	no	yes	no	70.5 cm (50th%)	5.6 kg (<5th%)	Antithyroid Drugs, Total Thyroidectomy
Val597Phe	Alberti et al 2001 [31]	Fm (4)	5 yr	no	FT4=45.6 pmol/L, FT3=15.6 pmol/L	n/a	yes	no	no	yes	129 cm (>100th%)	34 kg (>100th%)	Antithyroid Drugs
Ala623Val	Schwab et al 1997 [32]	Fm (3)	neonate	no, 39 wks	FT4=48.8 pmol/L, FT3=19.3 pmol/L	n/a	yes	no	yes	no	49 cm (30th%)	2.7 kg (10th%)	Antithyroid Drugs
Met626Ile	Ringkananont et al 2006 [7]	Fm (5)	10 mo	no, 39 wks	n/a	n/a	n/a	n/a	n/a	no	95th%	n/a	Antithyroid Drugs
Phe631Leu	Kopp et al 1995 [34]	Sp	neonate	yes, 32 wks	T4=283.1 nmol/L, T3=4.62 nmol/L	no	yes	no	n/a	yes	44 cm (75th%)	1.66 kg (50th%)	Antithyroid Drugs, Subtotal Thyroidectomy, Radioiodine Treatment
Phe631Ser	Nwosu et al 2006 [35]	Fm (4)	42 yr	n/a	n/a	n/a	n/a	yes	n/a	yes	n/a	n/a	Antithyroid Drugs, Radioiodine Rx
Thr632Ile	Kopp et al 1997 [36]	Sp	neonate	yes, 33 wks	T4=347.5 nmol/L	yes	n/a	no	n/a	yes	n/a	1.45 kg (5th%)	Antithyroid Drugs, Subtotal Thyroidectomy, Radioiodine Rx
Pro639Ser	Khoo et al 1999 [37]	Fm (4)	10 yr	no	T4=205.9 nmol/L	n/a	n/a	yes	n/a	yes	131 cm at 7 yr (95th %)	20 kg at 7 yr (10th %)	Antithyroid Drugs, Subtotal Thyroidectomy
Asn650Tyr	Tonachera et al 1996 [19]	Fm (5)	14 yr	n/a	FT4>23 pmol/L	n/a	n/a	n/a	n/a	yes	n/a	n/a	n/a
Asn670Ser	Tonachera et al 1996 [19]	Fm (5)	17 yr	n/a	FT4>23 pmol/L	n/a	n/a	n/a	n/a	yes	n/a	n/a	Antithyroid Drugs, Radioiodine Rx
Cys672Tyr	Duprez et al 1994 [24] Leclere et al 1995 [38]	Fm (17)	18 mo	n/a	FT4>23 pmol/L	n/a	n/a	no	n/a	yes	n/a	n/a	Antithyroid Drugs