

ORIGINAL ARTICLE

Contribution of genetic factors to neonatal transient hypothyroidism

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Background: The causes of neonatal transient hypothyroidism (NTH) remain incompletely understood. Whether it is influenced by genetic background is rarely discussed and remains unproven. A defect in thyroid peroxidase is a common cause of dyshormonogenesis of the thyroid gland in Taiwanese, with a novel mutation (2268insT) present in nearly 90% of alleles studied.

Objective: To determine if the presence of this common mutation is associated with NTH in Taiwan.

Methods: A mismatched primer was designed and used for this specific 2268insT mutation to screen 1000 normal babies and 260 babies with confirmed NTH.

Results: The carrier rate for 2268insT in normal babies (1/200) was significantly lower than in babies with NTH (1/13; $p < 0.0001$).

Conclusions: The results strongly suggest that the presence of this thyroid peroxidase mutation contributes to the development of NTH. Likely pathogenetic explanations include the effect of the stress of extrauterine adaptation during labour on an immature pituitary-thyroid axis in genetically predisposed individuals, combined with environmental triggers such as iodine deficiency, perinatal iodine exposure, and/or goitrogen contamination.

The prevalence of permanent congenital hypothyroidism is reported to be 1 in 4000 live births in Europe and North America.^{1,2} Thyroid dysgenesis, including thyroid aplasia (agenesis), hypoplasia, ectopy, or hemiagenesis, is responsible for 80–85% of congenital hypothyroidism. The remaining 15–20% is caused by inborn errors in thyroid hormone synthesis, also known as dyshormonogenesis of the thyroid gland.^{3,4} Hereditary defects at virtually all levels of thyroid hormone synthesis, secretion, and action have been identified.³ The major steps involved in thyroid hormone synthesis are (a) active transport of iodide into the thyroid follicular cells by the sodium iodide symporter, (b) covalent binding of iodide to tyrosine residues (iodide organification) within the thyroglobulin molecule, and (c) coupling of iodotyrosine residues to thyroglobulin to produce thyroxine (T4) and triiodothyronine (T3). Thyroid peroxidase (TPO) catalyses both the iodide organification and the coupling of iodotyrosine.³ Mutation of the TPO gene, the cause of a total iodine organification defect, is the most severe and common condition leading to dyshormonogenesis of the thyroid gland in white people.⁵

In Taiwan, the prevalence of permanent congenital hypothyroidism is 1 in 5788 live births.⁶ About 20% of cases of congenital hypothyroidism are caused by dyshormonogenesis,⁶ of which about 50% are caused by the total iodine organification defect.⁷ A novel mutation (2268insT) of the TPO gene was identified in nearly 90% of alleles studied in these patients presenting with total iodine organification defect.⁷

Besides the permanent form of congenital hypothyroidism, neonatal transient hypothyroidism (NTH) has often been detected by confirmatory specialist centres since the introduction of systematic screening of newborns. The causes remain incompletely understood. Environmental factors (including iodine deficiency^{8,9} and postnatal iodine exposure^{10,11}), maternal factors (such as intrauterine exposure to antithyroid drugs,¹² iodine, or maternal antithyroid antibodies¹³), and neonatal factors (prematurity¹⁴) have all been associated with NTH. However, these factors alone do not

explain why some newborns present with NTH, whereas others in similar environments with similar exposures do not. Whether NTH is also influenced by genetic background is rarely discussed and remains unproven.

The daily dietary intake of iodine in Taiwan is higher than the recommended amount.¹⁵ The prevalence of NTH requiring the administration of T4 replacement between the neonatal period and 2–3 years of age is estimated to be 1 in 2500,¹⁶ higher than in most other iodine sufficient regions (1:50 000 in North America).¹⁷ However, this high prevalence remains unexplained. Heterozygous carriers of metabolic disorders may develop an abnormal metabolite profile during stress. For example, carriers of phenylketonuria have higher serum phenylalanine concentrations than normal subjects during protein loading tests.¹⁸ Furthermore, a transient impairment of thyroidal iodine organification has been related to NTH in some patients.¹⁹ Therefore we hypothesised that carriers of TPO gene defects may be susceptible to the development of NTH during the stress of labour and extrauterine adaptation. In this study, we sought to determine if the presence of a common TPO mutation (2268insT) in Chinese is associated with NTH in Taiwan.

PATIENTS AND METHODS

Local recruitment of patients with NTH

Newborns (3–5 days old) with thyroid stimulating hormone (TSH) concentrations >40 $\mu\text{U/ml}$, or between 10 and 40 $\mu\text{U/ml}$ at two consecutive heel pricks, detected by screening in a region of northern Taiwan, were referred for confirmatory studies of congenital hypothyroidism to our hospital, a national referral and consultation centre. All referred newborns had technetium-99m scans, thyroid ultrasound scans, bone age studies, thyroid function tests (TSH, T3, T4, free T4, and thyroglobulin), and thyroid antibody examinations (antibodies to TSH receptor, thyroglobulin, and TPO).

Abbreviations: NTH, neonatal transient hypothyroidism; PCR, polymerase chain reaction; T3, triiodothyronine; T4, thyroxine; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone

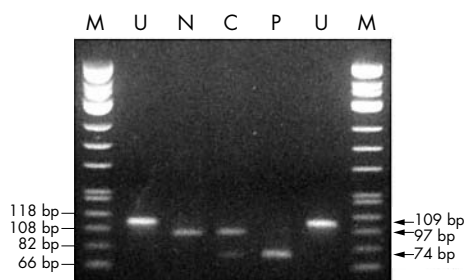


Figure 1 Representative results of polymerase chain reaction (PCR) of amplification created restriction site primers for screening of the 2268insT mutant of the TPO gene, after *HincII* digestion. The arrows point to the products of PCR (109 bp), normal allele after *HincII* digestion (97 bp), and mutant allele after *HincII* digestion (74 bp). M, Marker; U, product of PCR without *HincII* digestion; N, PCR product from a normal subject (without 2268insT mutant) after *HincII* digestion; C, PCR product from a 2268insT mutant carrier after *HincII* digestion; P, PCR product from a patient with homozygous 2268insT mutant.

Babies whose screening TSH concentrations were >40 $\mu\text{U/ml}$ received thyroid hormone replacement pending confirmatory thyroid function test results. In the presence of eutopic glands and normal thyroid function (TSH <10 $\mu\text{U/ml}$) at the time of confirmatory diagnostic studies, treatment was discontinued, and the infant was excluded from our study. Babies with eutopic glands and high TSH concentrations (>40 $\mu\text{U/ml}$) were placed, or continued, on T4 replacement, and included in the follow up study population. Babies with eutopic glands, TSH concentrations of 10–40 $\mu\text{U/ml}$, and T4 concentrations >103 nmol/l (>80 $\mu\text{g/l}$) were also taken off T4 replacement and followed until TSH had normalised. They were considered to have developed transient hyperthyrotropinaemia, and were excluded from our study, because collection of their data was incomplete. Conversely, if TSH rose further during follow up, the baby was immediately placed back on thyroid hormone treatment and included in our follow up study. Babies with eutopic glands and confirmed hypothyroidism received T4 replacement and were regularly followed for about three years. At that time, unless dysmorphogenetic-type congenital hypothyroidism was confirmed during follow up, T4 replacement was withdrawn for three weeks and the thyroid function tests were repeated. Patients with serum TSH concentrations >20 $\mu\text{U/ml}$, or persistent TSH concentrations of 10–20 $\mu\text{U/ml}$ in the presence of T4 concentrations <103 nmol/l (<80 $\mu\text{g/l}$) after withdrawal of T4 replacement, were considered to have dysmorphogenetic-type congenital hypothyroidism; they were therefore placed back on T4 treatment and excluded from the study population. Otherwise, a diagnosis of NTH was made, and the patient was included in the study. Between 1992 and 1997, 92 patients were diagnosed as having NTH, and were enrolled as group A.

Guthrie cards of NTH from newborn screening centre

A total of 168 filter paper cards of babies who were born between 1995 and 1997, had an initial screening TSH concentration >40 $\mu\text{U/ml}$, and, after two to three years of follow up, were confirmed to have NTH were collected from a newborn screening centre that cares for babies born in southern Taiwan (group B). All babies placed on T4 replacement for two to three years were registered in a national newborn screening follow up centre.

Guthrie cards of normal controls

A total of 1000 Guthrie cards of babies who were born in 1997 and had a screening TSH concentration <10 $\mu\text{U/ml}$ were randomly selected from the same newborn screening centre.

Screening of the carriers of the 2268insT mutation

Genomic DNA was extracted by standard methods from a 3 mm diameter blood spot obtained from the Guthrie card. Amplification created restriction site methodology was used for this specific 2268insT mutation. A pair of mismatched primers was designed with sequences as follows: forward primer, 5'-TGACTACATGTCAACCTGTCCAC-3'; reverse primer, 5'-AGGACGCGCCTCCCAGACTCGTC-3'. This pair of amplification created restriction site primers can create a new cut off point for the restriction enzyme, *HincII*, after polymerase chain reaction (PCR), carried out in a Perkin-Elmer 9600 thermocycler with an overall 25 μl reaction volume. Initial denaturation for five minutes at 94°C was followed by 40 cycles (each for 15 seconds at 94°C, 20 seconds at 60°C, 30 seconds at 72°C), and ended with a 10 minute extension at 72°C. After amplification, aliquots of the 109 bp products were digested with *HincII* at 37°C over two to three hours. The normal allele had a 97 bp fragment and the mutant allele a 74 bp fragment. Both fragments were identified by electrophoresis on 3% agarose gels (fig 1).

Analysis of babies with NTH who had the 2268insT mutant

Ten of 92 babies diagnosed as having NTH and followed in our hospital were found to carry one 2268insT mutant. To determine whether they had an impairment of iodide organification, or another TPO mutant that causes a mild defect of TPO, the patients underwent analysis of the TPO mutation and an iodine perchlorate discharge test. Our methods for TPO mutation screening and the iodine perchlorate discharge test have been described in detail in previous reports.⁷ All procedures were approved by the Institutional Review Board of Taipei Veterans General Hospital. The parents were informed of the details of the study and gave their written consent to participate.

Comparison of babies with and without the 2268insT mutation

The sex distribution, gestational age, family history, serum TSH and T4 concentration, and thyroid antibodies at confirmation of diagnosis, and serum TSH and T4 concentration after T4 withdrawal in babies with NTH with and without the 2268insT mutation were compared, to determine if clinical or biochemical differences exist between the two types of patient.

Statistical analysis

Fisher's exact test was used to compare sex distribution, gestational age, family history, serum TSH and T4 concentration, and thyroid antibodies at confirmation of diagnosis between babies with and babies without the 2268insT mutation. The Mann-Whitney U test was used to compare between-group serum TSH and T4 concentrations after T4 withdrawal, and the Kruskal-Wallis test was used to compare among-group TSH and T4 concentrations. Values are presented as mean (SD). $p < 0.05$ was considered significant.

RESULTS

A 2268insT mutant was present in five out of 1000 normal controls, 10 out of 92 babies in group A, and 10 out of 168 babies in group B. The carrier rates of 2268insT in groups A and B were similar ($p = 0.31$). The sum of carrier rates in group A and B babies was 1 in 13, significantly different from the 1 in 200 babies with normal screening results ($p < 0.0001$). This result confirms that carriers of this TPO mutation are at higher risk of developing NTH during the neonatal period.

Table 1 Results of thyroid function and iodine perchlorate discharge tests at initial confirmatory study or after three weeks of withdrawal of treatment at 3 years of age in patients with neonatal transient hypothyroidism

Patient	Sex	TSH* ($\mu\text{U/ml}$)	T4* (nmol/l)	RAIU at 2 h (%)	Dis (%)	TSH ($\mu\text{U/ml}$)	T4 (nmol/l)
1	M	>100	<25.8	15.0	36.0	4.3	101.7
2	M	41.8	70.8	14.0	21.4	4.6	83.2
3	M	>100	26.1	9.9	21.2	3.4	87.5
4	F	98.1	56.4	13.9	+7.9†	6.8	88.2
5	M	>100	26.6	12.9	+8.53†	3.2	132.7
6	M	>80	73.0	19.5	+16.4†	6.8	110.7
7	M	>100	<25.8	11.3	+0.7†	2.4	81.3
8	F	>100	<25.8	12.2	+15.6†	1.9	118.8
9	F	68.1	79.2	ND	ND	5.71	104.2
10	F	32.6	53.1	ND	ND	4.29	135.2
Normal range		<10	77–205	2–12	<15	0.25–4	58–161

*Measured at initial confirmatory diagnosis.

†Indicates increase in RAIU.

RAIU, Radioactive iodine uptake; Dis, % of discharge in iodine perchlorate discharge test; ND, not determined.

Babies with NTH with the 2268insT mutant

Ten of 92 babies followed in our hospital were carriers of the 2268insT mutant. Of eight babies who had the iodine perchlorate discharge test, three had a high release percentage, strongly suggesting that they also carried another mild form of TPO gene mutation. Individual exons of this gene were amplified and sequenced in these three patients, but no other mutation was found. The remaining seven patients also underwent TPO gene analysis, without detection of other mutations. Table 1 presents detailed information on these patients.

Comparison of babies with or without 2268insT mutation

There were no significant differences between babies with or without the 2268insT mutation in sex distribution, prematurity, family history, thyroid antibodies, serum TSH, or T4 concentrations at confirmatory examinations or after withdrawal of T4 replacement. Table 2 presents detailed comparisons between these two groups. It is noteworthy that mean TSH concentrations were high after T4 withdrawal in both groups. When we compared these two groups with a control group consisting of 20 age matched healthy euthyroid children with constitutional short stature followed in our ambulatory clinic (table 2), the mean TSH concentration was significantly different ($p < 0.0001$), but T4 was not ($p = 0.177$). Another noteworthy finding was the high prevalence of family history of thyroid disorders in both groups, particularly among babies with 2268insT mutations. Four out of 10 babies with 2268insT mutations had family histories of thyroid disorders. Among them, two mothers and one grandmother had diagnoses of hyperthyroidism. One baby's father also had hyperthyroidism, and her grandmother had thyroid cancer. Family histories were available in 62 of 82 babies with NTH without 2268insT mutations. Of these, four mothers had diagnoses of hyperthyroidism, and one mother had a goitre. In addition, 10 other babies had family

histories of thyroid disorders, including hypothyroidism, hyperthyroidism, goitre, and thyroid cancer, among more distant relatives.

DISCUSSION

Several thyroid disorders, such as non-endemic simple goitre or autoimmune thyroid diseases, have been shown to be strongly associated with genetic factors.^{20–21} However, a genetic influence in NTH has rarely been discussed and remains unproven. A mild, persistent increase in TSH concentrations during childhood in babies with NTH or transient neonatal hyperthyrotropinaemia has been observed in several studies.^{22–23} Some authors have even suggested that all infants with raised TSH at newborn screening are at risk of developing subclinical hypothyroidism in early childhood.²² In this study, we found that six of 10 babies with the 2268insT mutation, and 41 of 82 babies without this mutation, had serum TSH concentrations above the upper normal limit of 4 $\mu\text{U/ml}$ after T4 withdrawal. The mean TSH concentrations in both groups were significantly higher than in the control group. One baby with and two without the 2268insT mutation also had small thyroid nodules or very mild goitres on thyroid echograms during follow up after this study. The goitre and thyroid nodules disappeared rapidly after the patients were placed back on T4 treatment. These observations confirmed that, in some babies, NTH is not only caused by environmental factors, but is also of intrinsic origin. Furthermore, our molecular study strongly suggests that the presence of a TPO mutation contributes to the development of NTH. The sum of this evidence indicates that genetic factors play an important aetiological role.

Two babies with NTH were found to have a transient thyroid iodine organification impairment at an early post-natal iodide discharge test, as first described by Nose *et al.*¹⁹ Therefore, in some patients, NTH may be caused by "immaturity" of the organification enzyme within the thyroid gland. As TPO is the main enzyme responsible for

Table 2 Clinical and laboratory findings in babies with neonatal transient hypothyroidism with or without the 2268insT mutation, and in 20 control subjects

	No	M/F	GA <38 weeks	FH	TSH* $\geq 80 \mu\text{U/ml}$	T4* <25.8 nmol/l	AB	TSH† ($\mu\text{U/ml}$)	T4† (nmol/l)
2268insT(+)	10	6/4	1/10	4/10	7/10	3/10	0/8	4.29 (1.65)	105.3 (20.9)
2268insT(-)	82	42/40	9/82	15/62	32/82	26/82	3/75	4.36 (2.12)	110.3 (20.1)
p Value		0.74	0.9	0.26	0.9	1.0	0.12	0.95	0.47
Controls	20	11/9	–	–	–	–	–	2.04 (1.14)	103.7 (13.4)

Values of TSH and T4 are mean (SD); all other values are numbers of affected/non-affected. p Values are for comparisons between 2268insT(+) and 2268insT(-). Comparisons of differences among three groups, $p < 0.0001$ for TSH; $p = 0.409$ for T4.

*Measured at initial confirmatory diagnosis; †measured after T4 withdrawal.

M/F, Males/females; GA, gestational age; FH, positive family history; TSH, thyroid stimulating hormone; AB, antibody; T4, thyroxine.

iodine organification, we hypothesise that carrying this TPO gene defect may contribute to this immaturity. As three of eight patients with 2268insT mutations had a high release percentage in the iodine perchlorate discharge test, it is highly probable that these three babies were also carriers of another mild form of TPO gene mutation. Although we did not find it, an undetected mutation located in the regulatory or intron regions cannot be excluded, as the method we used does not examine these areas.

Because of the various clinical manifestations presented by the babies with the 2268insT mutation (table 1), we believe that it is not the only genetic factor contributing to NTH, and that a variety of intrinsic factors are necessary to explain these different clinical pictures. Furthermore, five carriers of 2268insT mutations who did not have high TSH concentrations at newborn screening were detected in this study. Although these NTH-free babies may have been exposed to fewer environmental triggers than those with NTH, it is also possible that their predisposing genetic factors were insufficient to reach the threshold for the development of NTH. On the other hand, we found 2268insT mutations in only 20 out of 260 babies with NTH. The causes of NTH in the other 240 babies remain unclear. In particular, 41 of 82 babies without 2268insT mutations had high baseline TSH concentrations. We believe that these patients have gene defects other than 2268insT mutations. Besides the TPO gene, other genes that interfere with the biosynthesis or regulation of thyroid hormone, such as a thyroglobulin, TSH receptor, and iodine transporter gene, are possible predisposing factors for NTH to be considered. Finally, we believe that the pathogenesis behind NTH is multifactorial and includes the effect of the stress of extrauterine adaptation on an immature pituitary-thyroid axis during labour in genetically predisposed individuals, combined with environmental triggers such as iodine deficiency, perinatal iodine exposure, and/or goitrogen contamination.

In this study, we also found a high prevalence of family history of thyroid disorders in both NTH groups. In Taiwanese adults, the prevalence of hyperthyroidism and hypothyroidism are estimated to be approximately 1.6% and 0.94% respectively.²⁴ The prevalence of hyperthyroidism in first relatives of the babies with 2268insT mutation is up to 15% (30% for families). Whether this represents a bias due to a small sample size or whether it actually reflects a TPO mutation with adult onset hyperthyroidism will be a focus of attention in our upcoming studies.

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