Case Report

R233H mutation in patients with tyrosine hydroxylase deficiency and corresponding phenotypes: a study of four cases and literature review

Chun-Mei Yao[1,*], Ya-Xian Deng[1], Ya-Jie Wang[1], Bao-Qin Gao[1], Cheng-Song Zhao[2]

[1]*Department of Pediatrics, Beijing Tiantan Hospital, Capital Medical University, 100070 Beijing, China*

[2]*Outpatient Department, Beijing Children's Hospital, Capital Medical University, 100045 Beijing, China*

*Correspondence: yaonvshihao1@163.com (Chun-Mei Yao)

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Owing to the small number of patients with tyrosine hydroxylase (TH) deficiency, no genotype-phenotype correlations have yet been identified. To investigate the genotype-phenotype correlation of R233H mutation in TH deficiency, we analyzed the clinical manifestations and treatment responses of four patients with the R233H homozygous mutation. Thirty-eight additional patients, available from the literature, known to be homozygous or heterozygous for the R233H mutation, were combined with the four cases from our hospital. Data for a total of 42 patients were retrieved. Our four patients showed clinical presentation consistent with Type A TH deficiency, and responded well to levodopa therapy, with an improvement in clinical symptoms within 1–2 weeks. In the 42 patients, 20 of 42 patients (48%) were homozygous and 22 (52%) were heterozygous for the R233H mutation. Of the 20 patients who were homozygous for the R233H mutation, a majority (80%) suffered from Type A TH deficiency. Of the 8 patients that were heterozygous for the R233H/the mutation located downstream of exon 11, 7 patients (86%) suffered from Type B TH deficiency. Of the 7 patients who were heterozygous for the R233H/nonsense mutation, 6 (86%) suffered from Type B TH deficiency. Genotype-phenotype correlation of R233H mutation was observed in TH deficiency. The homozygous R233H mutation frequently manifests as Type A TH deficiency, whereas R233H/nonsense mutation or any mutation located downstream of exon 11 manifests as Type B TH deficiency.

Keywords

Tyrosine Hydroxylase Deficiency; R233H; Mutation; Genotype-phenotype

1. Introduction

Tyrosine hydroxylase (TH) belongs to the aromatic amino acid hydroxylase family. It acts as a rate-limiting enzyme in catecholamine biosynthesis and is expressed in norepinephrine and dopaminergic neurons, sympathetic neurons, and chromaffin cells of the adrenal medulla. TH deficiency is a very rare progressive dystonia that is inherited in an autosomal recessive manner. Based on the presenting neurological features, TH deficiency can be divided in two phenotypes: an infantile onset, progressive, hypokinetic-rigid syndrome with dystonia (mild phenotype, Type A), and a complex encephalopathy with neonatal onset (severe phenotype, Type B) [1]. In recent years, TH deficiency has been diagnosed with increasing frequency. Direct mutation analysis has been performed in more than 100 TH deficiency patients, and R233H is the most frequent mutation, with 21 patients of 53 from China and 21 patients from the remaining other countries carrying this mutation [1–18]. This mutation is a G to A transversion at amino-acid position 698, resulting in histidine instead of arginine within the highly conserved domain of the TH protein, that is thought to interfere with the normal functioning of the TH protein.

Though more than 100 patients have been included in published literature, the majority of which are single-case reports, or included in a small number of cases, which makes the genotype-phenotype correlation being difficult to obtain. Although a large clinical trial was performed by Willemsen *et al.* [1], they didn't find that genotype-phenotype correlations existed in the R233H due to fact that the number of patients with R233H mutation was too small. Although these reports have assisted in our understanding of the clinical characteristics and prognosis of TH deficiency, no final conclusion with respect to a possible genotype-phenotype correlation for the R233H mutation could be drawn. The number of patients has increased, so to investigate whether the genotype-phenotype correlation really exists, we performed a study devoted to the R233H genotype-phenotype. A total of 42 patients with a mutation in R233H could be analyzed, including 21 patients from China (Table 1, Ref. [1–18]). Meanwhile, in this study, we reviewed the clinical features, treatment, and prognosis of four patients with homozygous mutation of R233H in TH at our hospital. These results should help to deepen clinicians' understanding of the clinical phenotype-genotype relationship of TH deficiency.

2. Method

We analyzed the clinical manifestations, diagnosis, and treatment of the 4 patients diagnosed with TH deficiency at Beijing Tiantan Hospital (Table 1, Ref. [1–18]), Patients 13–16). To obtain data on all patients with R233H mutation in TH deficiency reported to date, we searched Medline, PubMed, China National Knowledge Infrastructure (ht

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Table 1. Clinical phenotype, demographic data and results of mutation analysis of 42 patients with TH deficiency.

Ref.	Patients (family)	Origin	Gender	Age at onset (months)	Phenotype	Allele 1	Exon/Intron	Allele 2
[4, 17, 18]	1 (1)	Dutch	F	5	A	c.698G>A, R233H	6	c.698G>A, R233H
[4, 17, 18]	2 (2)	Dutch	M	3	A	c.698G>A, R233H	6	c.698G>A, R233H
[4, 17, 18]	3 (3)	Dutch	F	3	A	c.698G>A, R233H	6	c.698G>A, R233H
[5]	4 (4)	Lebanese	F	2	A	c.698G>A, R233H	6	c.698G>A, R233H
[7]	5 (5)	Spanish	F	4	A	c.698G>A, R233H	6	c.698G>A, R233H
[7]	6 (6)	Turkish	M	3 years	A	c.698G>A, R233H	6	c.698G>A, R233H
[7]	7 (7)	Turkish	M	2.5 years	A	c.698G>A, R233H	6	c.698G>A, R233H
[1]	8 (8)	Lebanese	NA	8	A	c.698G>A, R233H	6	c.698G>A, R233H
[1]	9 (8)	Lebanese	NA	4	A	c.698G>A, R233H	6	c.698G>A, R233H
[8, 9]	10 (9)	Chinese	F	7 years	A	R233H	6	R233H
[8, 9]	11 (9)	Chinese	M	7 years	A	R233H	6	R233H
[13]	12 (10)	Chinese	F	16	A	c.698G>A, R233H	6	c.698G>A, R233H
	13 (11)	Chinese	M	14	A	c.698G>A, R233H	6	c.698G>A, R233H
	14 (11)	Chinese	M	19	A	c.698G>A, R233H	6	c.698G>A, R233H
	15 (12)	Chinese	M	23	A	c.698G>A, R233H	6	c.698G>A, R233H
	16 (12)	Chinese	F	9	A	c.698G>A, R233H	6	c.698G>A, R233H
[1]	17 (13)	Dutch	NA	3	B	c.698G>A, R233H	6	c.698G>A, R233H
[1]	18 (14)	Dutch	NA	2	B	c.698G>A, R233H	6	c.698G>A, R233H
[1]	19 (15)	Belgian	NA	neonatal	B	c.698G>A, R233H	6	c.698G>A, R233H
[3]	20 (16)	Chinese	F	3	B	c.698G>A, R233H	6	c.698G>A, R233H
[12]	21 (17)	Chinese	M	3	A	c.698G>A, R233H	6	c.457C>T, R153X
[8, 9]	22 (18)	Chinese	F	6	B	R233H	4	R153X
[8, 9]	23 (19)	Chinese	F	4	B	R233H	4	R169X
[8, 9]	24 (19)	Chinese	M	4	B	R233H	4	R169X
[8, 9]	25 (20)	Chinese	M	3	B	R233H	4	R153X
[3]	26 (21)	Chinese	M	3	B	c.698G>A, R233H	4	c.457C>T, R153X
[3]	27 (22)	Chinese	M	3	B	c.698G>A, R233H	6	c.694C>T, Q232X
[10]	28 (23)	Chinese	M	3	NA	c.698G>A, R233H	14	c.1451G>T,R484L
[3]	29 (24)	Chinese	F	3	B	c.698G>A, R233H	11	c.1145T>C, I382T
[2]	30 (25)	German	M	5	B	R233H	Intron 11	c.1198-24T>A
[2]	31 (25)	German	F	4	B	R233H	Intron 11	c.1198-24T>A
[6]	32 (26)	Indian	M	10	B	c.698G>A, R233H	12	c.1282G>A,G428R
[6]	33 (26)	Indian	F	3	B	c.698G>A, R233H	12	c.1282G>A,G428R
[11]	34 (27)	Chinese	M	4	B	c.698G>A, R233H	Intron 12	c.1293+5G>C
[15]	35 (28)	Chinese	M	4	B	c.698G>A, R233H	12	c.1269-1273delGCTGT
[10]	36 (29)	Chinese	M	3	NA	c.698G>A, R233H	Intron 4	c.581-1 (IVS4)G > A
[4, 16, 18]	37 (30)	Dutch	M	4	A	c.698G>A, R233H	3	c.295delCL99fs
[1]	38 (31)	German	NA	9	A	c.698G>A, R233H	6	c.680A>G, D227G
[1]	39 (32)	Irish	NA	6	A	c.698G>A, R233H	5	c.620G>A, C207T
[1]	40 (33)	Brazilian	NA	3	A	c.698G>A, R233H	6	c.721G>A, A241T
[1]	41 (33)	Brazilian	NA	3	B	c.698G>A, R233H	6	c.721G>A, A241T
[14]	42 (34)	Chinese	F	1	A	c.698G>A, R233H	5	c.580+2T>C

NOTE: Ref, reference; M, male; F, female; NA, not available.

tp://www.cnki.net), and Wanfang Data (http://www.wanfangdata.com.cn) databases for papers published in English or Chinese up to August 2020. We used appropriate Medical Subject Headings (MeSH) terms obtained by expanding the search terms for "tyrosine hydroxylase deficiency" in English, and the Chinese equivalents, as search terms. We also tried to identify cases by cross-referencing papers. We included case reports in which an explicit diagnosis, including a gene diagnosis, of TH deficiency had been made. We compiled data for origin, gender, age of onset, phenotype, and mutation location. Written informed consent, including details of the study and its eventual publication, was obtained from the parents of the 4 patients in this study. Approval was obtained from the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University.

3. Results

3.1 Clinical manifestations, genotype, and treatment response of 4 patients diagnosed with TH deficiency in our hospital

Patient 13, a 7.5-year-old boy, was admitted to our hospital due to regression in motor development for six years. He was the first child born full-term to a non-consanguineous

Chinese couple. His birth weight was 3.0 kg with no history of asphyxia. He developed relatively normally during the first year after birth. Nevertheless, he was only able to walk on his toes with the help of others when he was 14 months old. Thereafter, he began to snore when awake, which disappeared with sleep. His intelligence and language comprehension were normal, but he had dysarthria and could not eat without aid. He was initially diagnosed with cerebral palsy at 18 months old, and showed no significant improvement after rehabilitation training since then. His parents claimed that their relatives had no similar medical history.

On physical examination at 7.5 years old, he weighed 28 kg. Both hands exhibited tetany when awake that disappeared when he slept. He had truncal hypotonia and could not sit without support. Hypokinesia and dystonic limbs were noted with hyperreflexia. There were no other remarkable symptoms such as abnormal eye movements, convulsion, hidrosis, ptyalism, etc., that were common in Type B TH deficiency. Genetic analysis revealed homozygosity for the missense mutant allele c.698 G to A of the *TH* gene, which resulted in an R233H substitution. His parents were both healthy carriers of the mutation. The clinical manifestations before treatment are shown in **Supplementary Video 1**. After admission, the patient was given levodopa orally, with an initial dose of 31.25 mg, q.d. (1.12 mg/kg/day). After three days, the child's symptoms improved dramatically, and his snoring disappeared (**Supplementary Video 2**). One week later, the dose was increased to 31.25 mg, b.i.d. (2.23 mg/kg/day). When the dose was increased to 50 mg, b.i.d (3.57 mg/kg/day) one week later, the patient developed dyskinesia (**Supplementary Video 3**), and therefore the dose was reduced to 25 mg q8H (2.68 mg/kg/day). The dyskinesia decreased, and gradually disappeared. The clinical manifestations were followed for one year, at which time his motor function was basically the same as that of normal children of the same age.

Patient 14, seen at 21 months, is the younger brother of Patient 13. He was admitted to our hospital due to walking on the left tiptoe for 2 months. He was born full-term, with a birth weight of 4.15 kg and no history of asphyxia. He developed relatively normally until two months prior to being admitted to our hospital. Nevertheless, he walked on his toes at 19 months old. On physical examination he weighed 14 kg, the left dorsal ankle flexion angle was 95°, and the right was normal. Other nervous system examinations showed no abnormality. There were no other remarkable symptoms such as abnormal eye movements, convulsion, hidrosis, or ptyalism. Genetic analysis revealed the same mutation as that of his older brother.

After admission, the patient was given oral levodopa at an initial dose of 15.625 mg, q.d., (1.12 mg/kg/day). After one week, the left tiptoe gait was improved, and the dose was increased to 2.23 mg/kg/day. Thereafter, the dose was not adjusted, and at present, the child's motor development is normal.

Patient 15, a 2.5-year-old boy, was the second child born full-term to a non-consanguineous Chinese couple. His birth weight was 2.8 kg with no history of asphyxia. He developed relatively normally until 23 months old. He could walk unaided at 1.5 years old. Nevertheless, he had lower limb weakness at 23 months old and showed abnormal gait and posture. His intelligence and language comprehension were normal, and he had no symptoms of abnormal eye movements, convulsion, hidrosis, or ptyalism. His parents claimed that their relatives had no similar medical history. Genetic analysis revealed homozygosity of R233H substitution. His parents were both healthy carriers of the mutation. The patient was also given levodopa orally, the initial dose was the same as Patients 13 and 14. After one day, the improved gait and posture could be seen in the patient, and after about 20 days, he had normal gait and posture. Now the patient takes levodopa (3.6 mg/kg/day) and his motor function was basically the same as that of normal children of the same age.

Patient 16, an 11-year-old girl, was the older sister of Patient 15. She was born full-term, with a birth weight of 3.4 kg and had a history of mild asphyxia. She developed relatively normally until 9 months, at which time her motor development worsened and at 11 months she couldn't sit alone. Thereafter she was wheelchair bound and completely dependent for the activities of daily life, and no diurnal fluctuation was observed. Her intelligence and language comprehension were normal. She was diagnosed as "spastic paraplegia" at 3 years of age, and she underwent surgery to lengthen the Achilles tendon. At 7 years of age, however, no significant improvement in motor function was observed. Her younger brother was found to harbor the R233H mutation, and subsequently the same mutation was detected in the patient. After a definitive diagnosis was made, this patient also received levodopa therapy, whereby a dramatic improvement in clinical symptoms was observed. The initial dose was the same as the previous three patients and then gradually increased to 3.6 mg/kg/day. This patient was able to stand without support after approximately 2 weeks of drug therapy, and was able to walk independently after 1 month of drug therapy. The gait of the patient was still slightly abnormal and no adverse reactions such as dyskinesia occurred.

3.2 Clinical data of patients with TH deficiency from our hospital and the ones from literature

Data from 38 additional patients, homozygous or heterozygous for the R233H mutation, were available from the published data. Among all 42 patients, there were 19 males and 14 females, and 9 for which gender was unknown (Table 1, Ref. [1–18]). There were 22 patients with Type A TH deficiency, 17 patients with severe Type B TH deficiency, and the phenotype of remaining 2 patients was not clear.

Among all 42 patients, 16 were from eight families, and the remaining 26 were sporadic cases. The reported cases were mainly from Asia and Europe (26 from Asia including 21 from China, 12 from Europe, 2 from Turkey), 2 from South America and none from North America, Africa or Oceania.

3.3 Genotype-phenotype relationships

In total, 20 of 42 patients (48%) were homozygous and the remainder were heterozygous for the R233H mutation. Of the heterozygous R233H mutation patients, 8 had the R233H/the mutation located downstream of exon 11, and 7 had the R233H/nonsense mutation and R233H/disruption of RNA splicing or missense mutation (the mutation located upstream of exon 11). Of the 20 patients who were homozygous for the R233H mutation, a majority (80%) suffered from Type A TH deficiency. Only 4 patients (20%) exhibited Type B TH deficiency. Of the 8 patients who were heterozygous for the R233H/the mutation located downstream of exon 11, 7 (86%) suffered from Type B TH deficiency, and the phenotype of the remaining patient is unknown. Of the 7 patients who were heterozygous for the R233H/nonsense mutation, 6 (86%) suffered from Type B TH deficiency and only 1 patient (14%) exhibited Type A TH deficiency. Of the remaining, 7 patients were heterozygous for the R233H/disruption of RNA splicing or missense mutation (the mutation located upstream of exon 11), 5 suffered from Type A TH deficiency, 1 (14%) exhibited Type B TH deficiency, and the phenotype of the remaining one patient is unknown.

4. Discussion

The TH deficiency, often started in the first year of life, has been reported with two phenotypes: (a) hypokinesia, rigidity, dystonia with diurnal fluctuation during infancy or childhood (Type A TH deficiency), which showed good tolerance to levodopa and an excellent response of motor function; and (b) complex encephalopathy, hypotonia, hypokinesia, dystonia, tremor, myoclonus and oculogyric crises, dystonic crises and dysautonomia in the neonatal period or early infancy (Type B TH deficiency), which showed poor tolerance to L-dopa and worse motor outcome [1, 8, 9]. Levodopa is the preferred treatment for TH deficiency, with most patients responding in a dramatic and long-lasting manner, especially in the patients with Type A TH deficiency, whereas other treatments such as rehabilitation have little effect [1, 19]. The levodopa dosages commonly used in TH deficiency range from 3 to 10 mg/kg/day, generally starting a with low dose; the dosage is gradually increased according to the patient's tolerance [1]. In patients with Type B TH deficiency, the initial dose is lower (below 0.5 mg/kg/day). Most patients with Type A TH deficiency responded well to the drug, and most of them showed an effect within one week. However, the effect of levodopa in Type B TH deficiency was not as significant as that of Type A, and the latency to respond was not as short as that of Type A TH deficiency [1]. In our study, 4 patients were improved within one week, in line with the characteristics of typical Type A TH deficiency, as shown in the **Supplementary Videos 1 and 2**. Before levodopa treatment, the older brother was unable to sit up on his own when lying in bed, but could easily sit up after only three days of treatment. No obvious side effects of levodopa were found during the one-year follow-up. For patients with Type A TH deficiency, even after years of missed diagnoses, levodopa induces a prolonged response without significant side effects, which is an important indicator for the clinical diagnosis of this disease [1, 19]. On the other hand, in the patients with Type B TH deficiency, response to levodopa therapy is null or limited by intolerable side effects such as hyperkinesia and irritability [1].

Diagnostic and therapeutic approaches for TH deficiency and guidance on prognosis can be offered to patients by elucidating the genotype-phenotype correlation of associated mutations. However, a cohort of adequate sample size is needed to effectively study this correlation, as previous studies on this disease involved a limited number of cases. Although the number of reported cases is gradually increasing, only patients with R233H mutations can be used in a genotype-phenotype evaluation as reports of patients harboring other TH deficiency mutations are insufficient. Upon analysis of the clinical characteristics of Chinese patients with TH deficiency, we found that patients with homozygous R233H mutation exhibited either Type A or Type B TH deficiency, with the majority constituting Type A patients [3, 8–10]. Due to the limited number of patients, we were not able to draw a precise conclusion on the correlation between genotype-phenotype.

We performed a literature search to clarify whether patients from different geographical regions carrying the R233H mutation and those harboring a heterozygous R233H mutation also displayed similar genotype-phenotype correlations. Therefore, we analyzed reports of 42 eligible patients, which was a sufficient number of cases to support this analysis [1–18]. Our analysis revealed that the homozygous R233H mutation frequently manifests as Type A TH deficiency, whereas R233H/nonsense mutation frequently manifests as Type B TH deficiency. Furthermore, R233H/any mutation type located downstream of exon 11 commonly manifests as Type B TH deficiency. It is noteworthy to mention that the number of patients with heterozygous R233H mutation were few, and our findings can only predict the trend of the genotype-phenotype relationship and cannot support a definitive conclusion. Nevertheless, the same R233H mutation, whether it is homozygous or heterozygous, does not always lead predictable phenotypes. These differences in phenotypes are reflected in patients with a family history of the disease as well as in sporadic cases in the population [1]. Analysis of clinical manifestations suggests that the variations in the observed phenotypes may be influenced by factors such as gender. Several studies have found that the clinical manifestations in female TH deficiency patients are more severe than those in males; this observation may be attributable to other variables such as genetic factors [1, 8, 20]. The severity of clinical symptoms seems to be correlated with residual enzyme activity of TH and levels of metabolic markers such as 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA). Unfortunately, as most patients did not undergo testing for enzyme activity or metabolic markers, we were not able to analyze the relationship between phenotype and enzyme activity, or between phenotype and metabolic markers.

TH deficiency is relatively rare, and patients with mutations other than R233H are also comparatively few, therefore it is difficult to analyze the genotype-phenotype relationship of other TH mutations. However, the genotype-phenotype relationship of the R233H mutation prompts us to pay attention to subsequent reports on such cases, so as to pool the clinical and biochemical data of all cases of R233H mutations and other TH mutations for comprehensive analysis, thereby providing better guidance to physicians and patients on therapeutic approaches and prediction of prognosis.

Abbreviations

b.i.d., bis in die; q.d., quaque die; TH, tyrosine hydroxylase; HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid.

Author contributions

All authors have made a substantial contribution to the study conception and design and critical reviewing of the manuscript. CY, YD and YW performed the literature search and quality assessment; CY, YD and YW have drafted the manuscript; YD performed the statistical analysis and analyzed the data; YD, BG and CZ interpreted the data, and made critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent, including details of the study and its eventual publication, was obtained from the parents of the 4 patients in this study. Approval was obtained from the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University, code (HY 2020-145-02).

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/JIN/21/1/10.31083/j.jin2101035.

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