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Congenital hypopituitarism due to novel compound heterozygous *POU1F1* gene mutation: A case report and review of the literature

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ABSTRACT

Failure to thrive is one of the most common complaints in the endocrinology and genetics clinic. An 8-month-old girl with presentation of motor developmental delay, failure to thrive, and midline facial defects, with history of hypoglycemia at birth and central congenital hypothyroidism (CCH), was brought to our genetic clinic. Hormone test demonstrated combined pituitary hormone deficiency with growth hormone deficiency (GHD), central hypothyroidism, and hypoprolactinemia. Brain magnetic resonance imaging (MRI) showed anterior pituitary hypoplasia (APH), abnormal pituitary stalk, and preserved posterior pituitary lobe. Whole exome sequence (WES) identified a compound heterozygous mutation of the *POU1F1* gene: c.649C>T (p.Arg217Ter) and c.662T>C (p.Ile221Thr), which are *de novo* mutation and inherited from mother, respectively. The patient's phenotype was consistent clinically with congenital hypopituitarism due to the *POU1F1* gene mutation. Based on our literature review, this is the first report of the c.662T>C mutation, to the best of our knowledge. Our study demonstrates the power of WES for early diagnosis of congenital hypopituitarism with its relative phenotype for improving prognosis and preventing irreversible deficit.

1. Introduction

Failure to thrive, sometimes combined with short stature and growth retardation, is one of the most common complaints in pediatric endocrinology and genetics clinics. It is influenced by multiple factors including genetic, metabolic, and environmental factors, with pure nutritional deficiency bearing the greatest responsibility for the cause of the disease [1]. Among these typical factors, congenital hypopituitarism has an incidence of approximately 1:3000 to 1:4000 in endocrine disease [2]. There are many genes that are considered as transcription factors to participate in signaling pathway of pituitary development accounting for 5–20% of congenital hypopituitarism. *POU1F1* mutation accounts for 0.4–20% in these mutations [3–10]. Here, we report an 8-month-old patient of novel compound heterozygous *POU1F1* gene mutation leading to congenital hypopituitarism, with the presentation of hypoglycemia, failure to thrive, and developmental delay. The patient showed catch-up growth after hormone replacement.

2. Materials and methods

We collected the girl's medical records, family history, and clinical presentation, with blood sample for hemogram, biochemistry profile, and hormone testing. Bone age study and brain MRI were performed. DNA collected from her and her parents was processed with shotgun library preparation using the KAPA HyperPrep kit, and short-read sequencing using the Illumina NovaSeq 6000 instrument, then CLC Genomic Workbench 12.0 software (Qiagen) was used for variant calling. Low-quality bases ($Q < 30$) were trimmed and aligned to the human reference genome (GRCh37/hg19) before mapping. Mapping parameters were set to default values, except for mapping length for the read, with similarity set to 0.9. Only one read was set to map to the reference genome. We filtered the variants by comparing them with common variant databases (dbSNP version 150 and Taiwan Biobank). The human phenotype ontology database was used to identify candidate genes based on patient phenotypes, including universal developmental delay (HP:0001263), failure to thrive (HP:0001508, HP:0001531), and

Abbreviations: CCH, Central congenital hypothyroidism; GHD, Growth hormone deficiency; MRI, Magnetic resonance imaging; APH, Anterior pituitary hypoplasia; WES, Whole exome sequence; TVGH, Taipei Veterans General Hospital.

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hypopituitarism (HP:0040075). In addition, variants of candidate genes were screened for functions involving the CDS, 5′-UTR, 3′-UTR and splicing sites; variants in the CDS region were analyzed for changes in protein structure with SIFT and PROVEAN software. Variants previously reported in the ClinVar database as benign or likely benign were filtered out. We also performed Sanger sequencing analyses for her and her parents with further trio analysis. The report of variant data was submitted to ClinVar database by us (SCV001759936 and SCV001759937).

All data collected were de-identified in the study. The corresponding author has full access to all data and bears final responsibility for the decision to submit the data for publication. There is no conflict of interest. The study was supported by the Ministry of Science and Technology, Taiwan [Grant Number: 110-2628-B-075-010], and Taipei Veterans General Hospital [Grant Number: V110B-007]. The research protocol was approved by the Taipei Veterans General Hospital (TVGH) Institutional Review Board (TVGH-2018-09-006A). A full explanation of the study aims and procedures was provided, and informed consent was obtained from the patient's parents.

3. Results

This is an 8-month-old girl, with maternal obstetric history of G1P1, born after 39 weeks with natural spontaneous delivery and vertex position. Her birth length was 47 cm (10th-50th percentile), her birth weight was 2505 g (3rd-10th percentile), and her head circumference was 30 cm (<3rd percentile). There was no hereditary disease or consanguineous marriage known in her family. Array comparative genomic hybridization of amniotic fluid reported no abnormal finding. There was no significant abnormality during physical examination at birth. However, drowsy consciousness with convulsion showed up at 4 days old. Hypothermia and hypoglycemia were found at the hospital where she was born. Central hypothyroidism, motor developmental delay, and gastroesophageal reflux were observed at the second and third hospital. Symptoms improved after levothyroxine and domperidone supplementation. However, poor body weight and body length gain were noticed in following months.

She came to our hospital, the fourth hospital, TVGH at 8 months old. At our hospital, she was in good spirit, and had stable vital signs with no specific symptoms. She had a body length of 56 cm (<3rd percentile) and a body weight of 4.3 kg (<3rd percentile). She was unable to sit without support and failed to reach for objects. Frontal bossing, saddle nose, upturned nose, maxillary hypoplasia, and deep philtrum were found (Fig. 1a, b). Hemogram and biochemistry profile displayed only hypoglycemia (serum glucose: 2 mmol/L, normal range: 3.6–5.6 mmol/L), with normal hemogram, electrolytes concentration, liver function, and renal function. Results of hormone testing showed central hypothyroidism with sufficient supplementation (thyroid stimulating hormone: <0.005 mU/L, normal range: 0.5–5.5 mU/L; free thyroxine: 14.7 pmol/L, normal range: 12–33 pmol/L), hypoprolactinemia (prolactin: 0.36 μg/L, normal range in female: 4.79–23.3 μg/L), and low serum insulin-like growth factor-1 (<2 nmol/L, normal range in 7–9 months old female: 10.5–30.5 nmol/L), with normal serum level of insulin (2.9 pmol/L, normal range: 18.1–172.9 pmol/L), and C-peptide (33.1 pmol/L, normal range: 364.2–1456.8 pmol/L). Random adrenocorticotropic hormone (9.8 pmol/L, normal range: <10.1 pmol/L) and cortisol (482.8 nmol/L, normal range: 166.1–507.6 nmol/L) tested at 08:00 in the morning also presented with partial adrenal insufficiency pattern. Insulin test and clonidine test both revealed a complete lack of growth hormone elevation. The growth hormone levels were all <0.05 μg/L (normal range: >10 μg/L) during insulin test, and the peak growth hormone level was 0.508 μg/L (normal range: >10 μg/L) during the clonidine test. Bone age study presented 3 months old (Fig. 1c). Small size of the pituitary gland and pituitary stalk, less distinct pituitary stalk enhancement, and preserved normal bright signal intensity of posterior pituitary lobe were found on precontrast T1 weighted image of brain MRI. Normal myelination and optic chiasma were also observed (Fig. 1d).

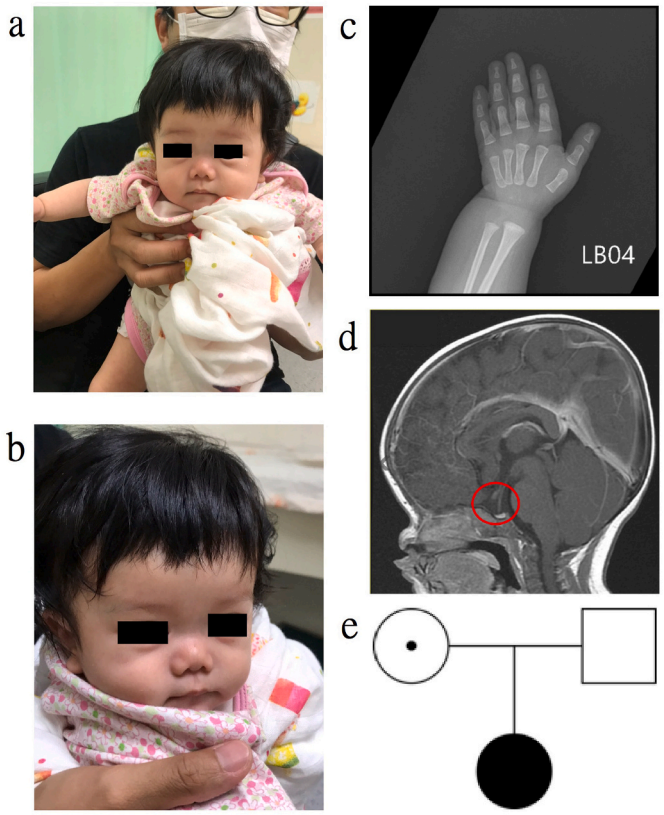

Fig. 1. The photograph of the patient, the image findings, and the pedigree. a. Front view at her age of 8 months old. b. Side view at her age of 8 months old. c. Bone age study. d. Precontrast T1 weighted image of Brain MRI. e. The pedigree of patient's family.

Notably, WES illustrated two significant mutations as compound heterozygous affecting the *POU1F1* gene, NM_000306.4:c.649C>T (located at ch3: 87261289), NP_000297.1:p.Arg217Ter, and NM_000306.4:c.662T>C (located at ch3: 87261276), NP_000297.1:p.Ile221Thr. The former one has been reported as likely pathogenic to combined pituitary hormone deficiency on ClinVar database (VCV000998004.2), with a global allele frequency of 0.0009% (GnomAD_exome/dbSNP ID: rs761275346). The latter is a new mutation without any available frequency data on the gnomAD database. UniProt has classified this mutation site as "Homeobox", the DNA binding domain. It is calculated that the pathogenicity is 85.7%, which exceeds the threshold of 50.0%, and meets the PM2 standard of ACMG Guide 2015. In addition, 38 of 41 non-VUS missense variants of the *POU1F1* gene are pathogenic, indicating that the PP2 criteria are met. In the end, both PROVEAN and SIFT predicted this mutation as "Damaging". In summary, according to ACMG Guidelines 2015, this mutation can be classified as "Likely pathogenic". Sanger sequencing of *POU1F1* gene from the patient and her parents and paternity testing confirmed the former mutation as a *de novo* mutation, with the latter inherited from mother. The pedigree is shown in Fig. 1e.

We started growth hormone supplementation (1 IU/kg/week) after diagnosis, with levothyroxine supplementation (4.4 μg/kg/day) remained. We educated the family when the stress dose of a glucosteroid would be needed. In addition, when she gets ill, we suggested treating her with cortisone supplementation (12 mg/m^2/dose) and coming back to our hospital as soon as possible. Upon follow-up assessment at 1 year and 7 months old, her body length was 72.2 cm, and her body weight was 6.6 kg, increased by 16.2 cm and 2.3 kg in 11 months. Her growth chart is shown in Fig. 2. She could run with wide base gait, climb up stair

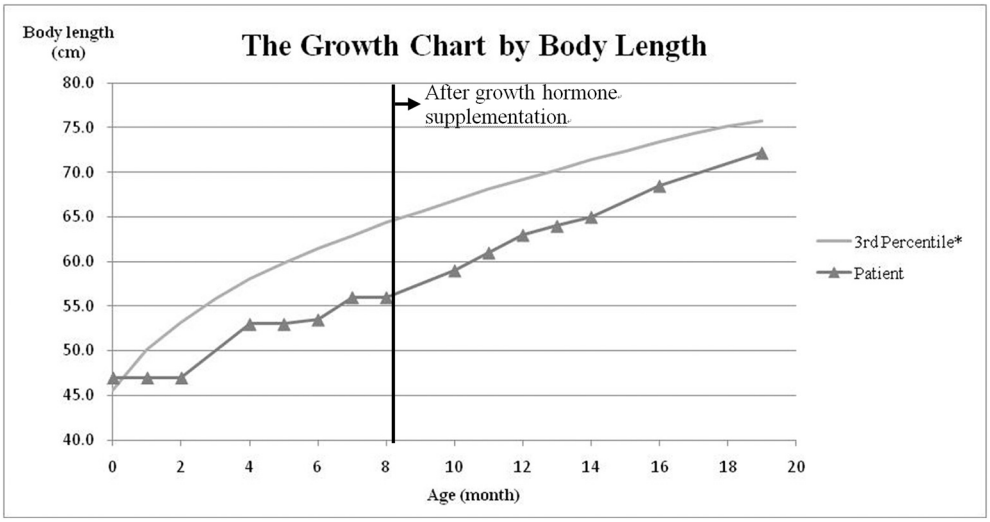

Fig. 2. The growth chart by body length of the patient.
*The reference of the 3rd percentile of the body length is obtained from Chen and Chang 2010 [11].

with help, and wave goodbye. She was also able to doodle, cooperate with parents to change clothes, and say around 10 words. No more developmental delay was present.

4. Review and discussion

To date, there are only few reports on congenital hypopituitarism with *POU1F1* gene mutation (Fig. 3, Table 1) [3,4,6–10,12–29]. In the earlier reports, the R271W mutation was firstly recognized within numerous patients, suspicious as a hot spot [8,12–16]. E230K mutation was reported to be common in Maltese patients [8]. There was only one patient reported in Taiwan with homozygous F233S mutation in 2011 [17]. To our best knowledge, the mutation of I221T identified in our patient was a novel mutation. We use WES as an available and powerful tool to identify the mutation, which is now widely used for the diagnosis of patient with congenital anomaly. The two mutations identified in our patient are located in the DNA binding domain with autosomal recessive inheritance pattern, and acted as compound heterozygosity. The *POU1F1* gene functioned as a pituitary-specific transcription factor which expressed late in pituitary development and influenced the differentiation of thyrotrophs, somatotrophs, and lactotrophs [2,30–32].

The phenotype of hormone deficiency mostly, but not always presented with CCH, GHD, and hypoprolactinemia as combined pituitary hormone deficiency, and the onset time and time at diagnosis of these hormone deficiencies varies. The onset time and severity of CCH varies from at birth to never showed up, although if presented, CCH was usually diagnosed at first soon after birth. The onset time of GHD was usually at birth, but the time at diagnosis might range from the neonatal period to the adult age. Hypoprolactinemia was usually presented, but sometimes untested due to its less clinical significance. The age at diagnosis of congenital hypopituitarism with the *POU1F1* mutation ranged from 6 months old to 18 years old, with symptoms depending on the age at diagnosis and the hormone affected. In the literature, the patient was born with appropriate for gestational age, and presented sometimes the phenotypes traits of midline facial defects such as frontal bossing, saddle nose, upturned nose, maxillary hypoplasia, cleft palate, prominent philtrum, and single central incisor. The early symptoms included prolonged jaundice, poor appetite, low muscle tone, and

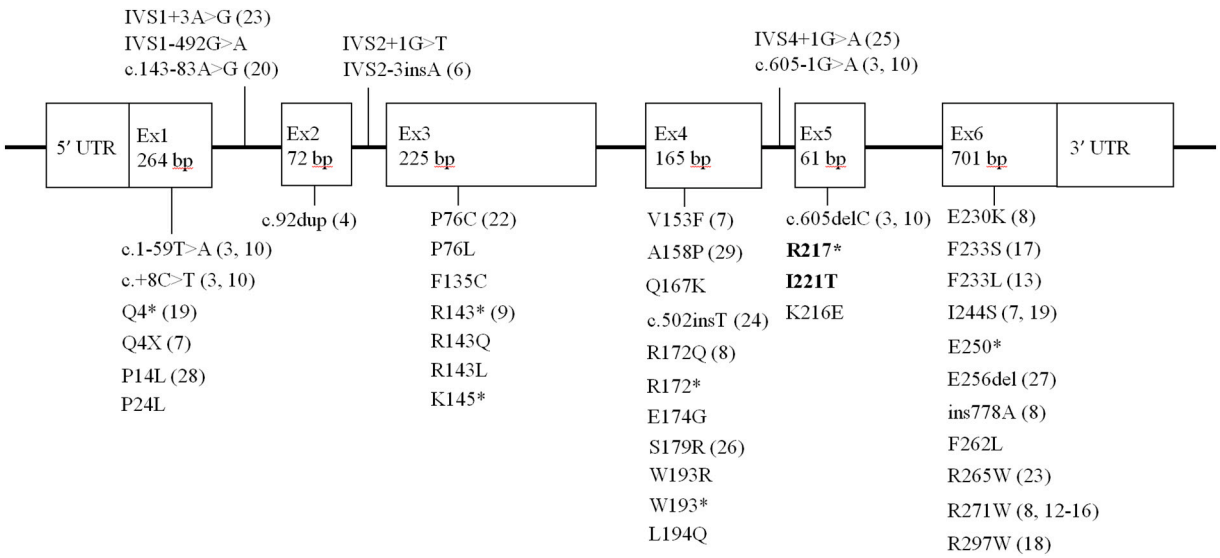

Fig. 3. The diagram of *POU1F1* gene with the identified mutation. The mutations discovered in our patient are marked in Bold. Numbers in parentheses indicate reference citations. The other mutations without citations are obtained from the Human Gene Mutation Database.

Table 1
Congenital hypopituitarism with *POU1F1* gene mutation.

Writer, publish date	Study type and case	Gene mutation of *POU1F1*	Sex	Age at diagnosis (year)	Presentation	Influenced hormone	MRI	Follow up
Jullien et al., 2021	Cohort study	Homozygous c.92dup (p.Ala32Cysfs42)	–	–	–	GH, TSH, PRL	–	–
Li et al., 2020	Case report	Heterozygous c.767-769del (p.Glu256del)	M	0.8	Failure to thrive, hypoglycemia, poor appetite, constipation	GH, TSH, PRL	–	–
Chen, Zhang, Wu, & Li, 2019	Case report	Heterozygous c.889C > T (p.R297W)	F	2.3	Failure to thrive, midline facial defects	GH, TSH	APH	Catch-up growth
Birla et al., 2019	Cohort study	C.605-1G > A	–	–	–	–	–	–
		C.605delC	–	–	Failure to thrive	GH, TSH	–	–
		C.1–59 T > A	–	–	–	–	–	–
		C. + 8C > T	–	–	–	–	–	–
Blum et al., 2018	Cohort study							
	Sibling 1	Homozygous c.427C > T (p.Arg143Ter)	F	3.0	Failure to thrive, hypoglycemia, prominent forehead, late dentition	GH, TSH	–	–
	Sibling 2	Homozygous c.427C > T (p.Arg143Ter)	F	2.0	Failure to thrive	GH, TSH	–	–
Bas et al., 2018	Case series							
	1 sporadic patient	Homozygous c.731 T > G (p.I244S)	M	1.7	Failure to thrive, precocious puberty at 7-year-9-month-old	GH, TSH, PRL	APH	Catch-up growth
	1 sporadic patient	Homozygous c.10C > T (p.Q4*)	M	0.5	Failure to thrive, precocious puberty at 10-year-old	GH, TSH, PRL	APH	Catch-up growth
Takagi et al., 2017	Case report							
	Sibling 1	Heterozygous c.143-83A > G	F	0.3	Failure to thrive	GH, TSH, PRL	APH	Catch-up growth
	Sibling 2	Heterozygous c.143-83A > G	F	0.3	Failure to thrive	GH, TSH	Normal	Catch-up growth
Bertko et al., 2017	Cohort study	Homozygous c.-1387_214 + 455del	M	11.5	Failure to thrive	GH, TSH, PRL	APH	–
Sobrier et al., 2016	Case series of 9 patients	Heterozygous c.227C > T (p.Pro76Leu)	–	–	Failure to thrive	GH	APH or normal	–
Birla et al., 2016	Case control study							
	3 familys, 5 patients	Homozygous/ heterozygous c.605-1G- > A	5 M	1.6–9	Failure to thrive	GH, TSH	APH	–
	1 family, 1 patient	Homozygous c.605delc	M	5.0	Failure to thrive	GH, TSH	APH	–
	2 familys, 2 patients	Heterozygous c.1-59 T > A	2 M	15–18	Failure to thrive	GH, TSH, FSH, LH	Normal	–
	1 family, 1 patient	Heterozygous c. + 8C- > T	M	8.0	Failure to thrive	GH, TSH	EPP	–
De Rienzo et al., 2015	Cohort study: 1 patient	Homozygous IVS2-3insa	F	0.5	Failure to thrive	GH, TSH, PRL	APH	–
Bas et al., 2015	Cohort study							
	1 family, 2 patients	Homozygous p.V153F	1 F, 1 M	0.9–4.1	Failure to thrive	GH, TSH, PRL	APH	–
	1 sporadic patient	Homozygous p.I244S	M	2.0	Failure to thrive	GH, TSH, PRL, FSH, LH	APH	–
	1 sporadic patient	Homozygous p.Q4X	M	0.5	Failure to thrive	GH, TSH	APH	–
	1 sporadic patient	Homozygus Ex1-2 deletion	M	0.6	Failure to thrive	GH, TSH, PRL	APH	–
Turton, Strom, Langham, Dattani, & Le Tissier, 2012	Case report	Compound heterozygosity: IVS1 + 3 nt(A > G)/c.793C > T (p.R265W)	M	8.0	Failure to thrive, global developmental delay, midline facial defect, micropenis	GH, TSH, PRL	APH	Catch-up growth, improved neurodevelopment
Tenenbaum-Rakover, Sobrier, & Amselem, 2011	Case report	Homozygous c.502inst (p.Thr168IlefsX7)	M	0.8	Failure to thrive, prolonged jaundice, constipation, hypoglycemia, seizure, midline facial defect, micropenis, delay puberty	GH, TSH, PRL	APH	Short stature
Lee et al., 2011	Case report	Homozygous c.698 T > C (p.F233S)	F	2.2		GH, TSH, PRL		

(*continued on next page*)

Table 1 (*continued*)

Writer, publish date	Study type and case	Gene mutation of *POU1F1*	Sex	Age at diagnosis (year)	Presentation	Influenced hormone	MRI	Follow up
					Failure to thrive, developmental delay, hypotonia, poor oral intake		Sunken diaphragma sella	Poor compliance, Kocher-Debre-Semelaigne syndrome
De Graaff et al., 2010	Cohort study: 1 patient	P.R271W	M	–	–	GH, TSH, PRL	–	–
Snabboon et al., 2008	Case report	Homozygous IVS4 + 1G > A	M	18.0	Failure to thrive, midline facial defect, cretinism	GH, TSH, PRL	APH	Poor compliance, delayed psychomotor development, severe short stature
Miyata et al., 2006	Case report	Homozygous p.S179R	M	4.0	Failure to thrive, poor feeding	GH, TSH, PRL	APH	Short stature
Turton et al., 2005	Cohort study							
	1 family, 2 patients	Compound heterozygosity: c.688G > A (p.E230K)/c.515G > A (p.R172Q)	2 M	0.1–0.3	Failure to thrive	GH, TSH, PRL	APH	–
	2 familys, 2 patients	Homozygous c.688G > A (p.E230K)	1 F, 1 M	1.4–2.3	Failure to thrive	GH, TSH, PRL	APH	Catch-up growth
	3 familys, 5 patients	Heterozygous c.811C > T (p.R271W)	2 F, 3 M	0.2–6	Failure to thrive	GH, TSH, PRL	APH or normal	Short stature
	1 sporadic patient	Compound heterozygosity: c.688G > A (p.E230K)/ins778a	F	2.4	Failure to thrive	GH, TSH, PRL	APH	–
Rainbow et al., 2005	Cohort study							
	1 family, 2 patients	Heterozygous p.R271W	2 F	0.9–1.3	Failure to thrive, optic nerve hypoplasia	GH, TSH, PRL	APH	–
	1 couple of twins patients	Homozygous p.F233L	2 F	At birth	Intrauterine growth retardation, midline facial defect, short upper limbs, poor feeding	GH, TSH	–	Expired at 3-week-old and 2-month-old
Ward et al., 1998	Case report	Heterozygous c.811C > T (p.R271W)	M	1.7	Failure to thrive, prolonged jaundice, constipation, hypoglycemia, developmental delay, midline facial defect	GH, TSH, PRL	Normal	–
Rodrigues Martineli, Braga, De Lacerda, Raskin, & Graf, 1998	Case report	Heterozygous c.811C > T (p.R271W)	F	13.0	Failure to thrive, midline facial defect, normal psychomotor development	GH, TSH, PRL	APH	Poor compliance, short stature, hypothyroidism
Fofanova et al., 1998	Cohort study	Heterozygous p.P14L	F	3.8	Failure to thrive	GH, TSH, PRL	–	Catch-up growth
Arnhold et al., 1998	Case report	Heterozygous p.R271W	F	14.0	Failure to thrive, normal psychomotor development, delay pubarche	GH, TSH, PRL	Reduce size of pituitary	Short stature
Pfaffle et al., 1992	Cohort study: 2 patients	Homozygous c.527C > G (p.A158P)	1 F, 1 M	–	–	GH, TSH, PRL	Normal	–

M: male; F: female; GH: growth hormone; TSH: thyroid stimulating hormone; PRL: prolactin; FSH: follicle-stimulating hormone; LH: luteinizing hormone; APH: Anterior pituitary hypoplasia.

constipation, which are the features of CCH. If left undiagnosed or untreated, failure to thrive and psychomotor developmental problems would gradually develop into cretinism. If GHD was present, hypoglycemia with seizure might be noticed at neonatal period, or the patient might came to clinic due to failure to thrive. There were few reports exhibiting that the hypothalamic–pituitary–gonadal axis was somehow affected. A Brazilian patient was reported with delay pubarche [16], and another patient was reported with delay puberty [24]. On the contrary, another two patients demonstrated central precocious puberty pattern [19]. The possible mechanism of this presentation needs further study. In MRI, *POU1F1* mutation usually causes pituitary dysplasia, with APH but normal pituitary stalk and posterior lobe, without septo-optic dysplasia or other brain anomaly [30]. Normal structure of pituitary gland may also be observed. Considering the fact that some patient presented with normal pituitary gland at young age but turned into APH when getting older, and the *POU1F1* gene was responsible for pituitary cell survival, it might suggest that APH was developed progressively.

Our patient has typical presentation of congenital hypopituitarism with *POU1F1* mutation including hypoglycemia, motor developmental delay, and failure to thrive. GHD, CCH, and hypoprolactinemia were all diagnosed during infancy, with brain MRI showing APH. We would closely monitor her secondary sex characteristics development and do the gonadotropin releasing hormone stimulation test at an appropriate timing. Our patient had good response to hormone supplementation, as both growth curve and developmental milestone showed catching up pattern with symptoms all resolved. We diagnosed her by recognizing the specific midline facial defects, the history of CCH, and WES, at a relatively young age compared to other patient reported. This report has

presented a patient of congenital hypopituitarism with *POU1F1* mutation diagnosed by WES, and has reviewed all the reported inherited congenital hypopituitarism patients. With WES, we could confirm the phenotype and treat the patient as soon as possible, hoping to avoid the possible irreversible deficit.

5. Conclusion

Congenital hypopituitarism is a rare cause of failure to thrive at young age. This study shows that the technique of WES facilitates early diagnosis and early treatment in our patient to avoid irreversible deficit. As the approach of genetic analysis becomes more and more effective, our study might support that WES could be an efficient diagnostic tool for indistinct congenital abnormalities.

Research data sharing statement

In order to protect patient's personal privacy, research data would remain confidential and would not be shared.

Authors' contributions

Wei-Yu Chen's contribution includes collecting the data, performing the revision and the interpretation of all the clinical data, and writting the manuscript. Dau-Ming Niu collected the data and helped interpretation. Li-Zhen Chen collected the data and performed the revision. Chia-Feng Yang conceived the study, participated in its design and coordination, and helped drafting the manuscript and revision. All authors have read and approved the final manuscript.

Declaration of Competing Interest

None.

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References

[1] M. Daniel, L. Kleis, A.P. Cemeroglu, Etiology of failure to thrive in infants and toddlers referred to a pediatric endocrinology outpatient clinic, Clin. Pediatr. (Phila) 47 (8) (2008) 762–765.
[2] F. Castinetti, R. Reynaud, A. Saveanu, M.H. Quentien, F. Albarel, A. Barlier, et al., Clinical and genetic aspects of combined pituitary hormone deficiencies, Ann. Endocrinol. (Paris) 69 (1) (2008) 7–17.
[3] S. Birla, P. Vijayakumar, S. Sehgal, S. Bhatnagar, K. Pallavi, A. Sharma, Characterization of a novel *POU1F1* mutation identified on screening 160 growth hormone deficiency patients, Horm. Metab. Res. 51 (4) (2019) 248–255.
[4] N. Jullien, A. Saveanu, J. Vergier, E. Marquant, M.H. Quentien, F. Castinetti, et al., Clinical lessons learned in constitutional hypopituitarism from two decades of experience in a large international cohort, Clin. Endocrinol. 94 (2) (2021) 277–289.
[5] T. Brue, A. Saveanu, N. Jullien, T. Fauquier, F. Castinetti, A. Enjalbert, et al., Lessons from monogenic causes of growth hormone deficiency, Ann. Endocrinol. (Paris) 78 (2) (2017) 77–79.
[6] F. De Rienzo, S. Mellone, S. Bellone, D. Babu, I. Fusco, F. Prodam, et al., Frequency of genetic defects in combined pituitary hormone deficiency: a systematic review and analysis of a multicentre Italian cohort, Clin. Endocrinol. 83 (6) (2015) 849–860.
[7] F. Bas, Z.O. Uyguner, F. Darendeliler, Z. Aycan, E. Cetinkaya, M. Berberoglu, et al., Molecular analysis of *PROP1, POU1F1, LHX3*, and *HESX1* in Turkish patients with combined pituitary hormone deficiency: a multicenter study, Endocrine 49 (2) (2015) 479–491.
[8] J.P. Turton, R. Reynaud, A. Mehta, J. Torpiano, A. Saveanu, K.S. Woods, et al., Novel mutations within the *POU1F1* gene associated with variable combined pituitary hormone deficiency, J. Clin. Endocrinol. Metab. 90 (8) (2005) 4762–4770.
[9] W.F. Blum, J. Klammt, S. Amselem, H.M. Pfaffle, M. Legendre, M.L. Sobrier, et al., Screening a large pediatric cohort with GH deficiency for mutations in genes regulating pituitary development and GH secretion: Frequencies, phenotypes and growth outcomes, EBioMedicine 36 (2018) 390–400.
[10] S. Birla, R. Khadgawat, V.P. Jyotsna, V. Jain, M.K. Garg, A.S. Bhalla, et al., Identification of novel *PROP1* and *POU1F1* mutations in patients with combined pituitary hormone deficiency, Horm. Metab. Res. 48 (12) (2016) 822–827.
[11] W. Chen, M.H. Chang, New growth charts for Taiwanese children and adolescents based on World Health Organization standards and health-related physical fitness, Pediatr. Neonatol. 51 (2) (2010) 69–79.
[12] L.C. de Graaff, J. Argente, D.C. Veenma, M.L. Drent, A.G. Uitterlinden, A. C. Hokken-Koelega, *PROP1, HESX1, POU1F1, LHX3* and *LHX4* mutation and deletion screening and *GH1* P89L and IVS3+1/+2 mutation screening in a Dutch nationwide cohort of patients with combined pituitary hormone deficiency, Horm. Res. Paediatr. 73 (5) (2010) 363–371.
[13] L.A. Rainbow, S.A. Rees, M.G. Shaikh, N.J. Shaw, T. Cole, T.G. Barrett, et al., Mutation analysis of *POUF-1, PROP-1* and *HESX-1* show low frequency of mutations in children with sporadic forms of combined pituitary hormone deficiency and septo-optic dysplasia, Clin. Endocrinol. 62 (2) (2005) 163–168.
[14] L. Ward, M. Chavez, C. Huot, P. Lecocq, R. Collu, J.C. Decarie, et al., Severe congenital hypopituitarism with low prolactin levels and age-dependent anterior pituitary hypoplasia: a clue to a PIT-1 mutation, J. Pediatr. 132 (6) (1998) 1036–1038.
[15] A.M. Rodrigues Martineli, M. Braga, L. De Lacerda, S. Raskin, H. Graf, Description of a Brazilian patient bearing the R271W Pit-1 gene mutation, Thyroid 8 (4) (1998) 299–304.
[16] I.J. Arnhold, M. Nery, M.R. Brown, T.C. Voss, T.C. VanderHeyden, M.E. Adess, et al., Clinical and molecular characterization of a Brazilian patient with Pit-1 deficiency, J. Pediatr. Endocrinol. Metab. 11 (5) (1998) 623–630.
[17] N.C. Lee, W.Y. Tsai, S.F. Peng, Y.C. Tung, Y.H. Chien, W.L. Hwu, Congenital hypopituitarism due to *POU1F1* gene mutation, J. Formos. Med. Assoc. 110 (1) (2011) 58–61.
[18] J. Chen, X.X. Zhang, X.C. Wu, J. Li, Clinical and genetic characteristics of a young child with combined pituitary hormone deficiency type I caused by *POU1F1* gene variation, Zhongguo Dang Dai Er Ke Za Zhi 21 (7) (2019) 685–689.
[19] F. Bas, Z.Y. Abali, G. Toksoy, S. Poyrazoglu, R. Bundak, C. Gulec, et al., Precocious or early puberty in patients with combined pituitary hormone deficiency due to *POU1F1* gene mutation: case report and review of possible mechanisms, Hormones (Athens) 17 (4) (2018) 581–588.
[20] M. Takagi, H. Kamasaki, H. Yagi, R. Fukuzawa, S. Narumi, T. Hasegawa, A novel heterozygous intronic mutation in *POU1F1* is associated with combined pituitary hormone deficiency, Endocr. J. 64 (2) (2017) 229–234.
[21] E. Bertko, J. Klammt, P. Dusatkova, M. Bahceci, N. Gonc, L. Ten Have, et al., Combined pituitary hormone deficiency due to gross deletions in the *POU1F1* (*PIT-1*) and *PROP1* genes, J. Hum. Genet. 62 (8) (2017) 755–762.
[22] M.L. Sobrier, Y.C. Tsai, C. Perez, B. Leheup, T. Bouceba, P. Duquesnoy, et al., Functional characterization of a human *POU1F1* mutation associated with isolated growth hormone deficiency: a novel etiology for IGHD, Hum. Mol. Genet. 25 (3) (2016) 472–483.
[23] J.P. Turton, M. Strom, S. Langham, M.T. Dattani, P. Le Tissier, Two novel mutations in the *POU1F1* gene generate null alleles through different mechanisms leading to combined pituitary hormone deficiency, Clin. Endocrinol. 76 (3) (2012) 387–393.
[24] Y. Tenenbaum-Rakover, M.L. Sobrier, S. Amselem, A novel *POU1F1* mutation (p. Thr168IlefsX7) associated with an early and severe form of combined pituitary hormone deficiency: functional analysis and follow-up from infancy to adulthood, Clin. Endocrinol. (Oxf.) 75 (2) (2011) 214–219.
[25] T. Snabboon, W. Plengpanich, P. Buranasupkajorn, R. Khwanjaipanich, P. Vasinanukorn, S. Suwanwalaikorn, et al., A novel germline mutation, IVS4+ 1G>A, of the *POU1F1* gene underlying combined pituitary hormone deficiency, Horm. Res. 69 (1) (2008) 60–64.
[26] I. Miyata, S. Vallette-Kasic, A. Saveanu, M. Takeuchi, H. Yoshikawa, A. Tajima, et al., Identification and functional analysis of the novel S179R *POU1F1* mutation associated with combined pituitary hormone deficiency, J. Clin. Endocrinol. Metab. 91 (12) (2006) 4981–4987.
[27] Q. Li, J. Li, G. Chang, Y. Ding, Y. Wang, Y. Shen, et al., Clinical and genetic analysis of an infant with combined pituitary hormone deficiency due to *POU1F1* gene variants, Zhonghua Yi Xue Yi Chuan Xue Za Zhi 37 (9) (2020) 1018–1020.
[28] O.V. Fofanova, N. Takamura, E. Kinoshita, M. Yoshimoto, Y. Tsuji, V.A. Peterkova, et al., Rarity of PIT1 involvement in children from Russia with combined pituitary hormone deficiency, Am. J. Med. Genet. 77 (5) (1998) 360–365.
[29] R.W. Pfaffle, G.E. DiMattia, J.S. Parks, M.R. Brown, J.M. Wit, M. Jansen, et al., Mutation of the POU-specific domain of Pit-1 and hypopituitarism without pituitary hypoplasia, Science 257 (5073) (1992) 1118–1121.
[30] F. Castinetti, R. Reynaud, A. Saveanu, N. Jullien, M.H. Quentien, C. Rochette, et al., Mechanisms in endocrinology: An update in the genetic aetiologies of combined pituitary hormone deficiency, Eur. J. Endocrinol. 174 (6) (2016) R239–R247.
[31] L.C. Gregory, M.T. Dattani, The molecular basis of congenital hypopituitarism and related disorders, J. Clin. Endocrinol. Metab. 105 (6) (2020).
[32] K.S. Alatzoglou, L.C. Gregory, M.T. Dattani, Development of the Pituitary Gland, Compr. Physiol. 10 (2) (2020) 389–413.