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),

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 weight 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: 3.6–5.5 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).

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 glucocorticoid would be needed. In addition, when she gets ill, we suggested treating her with cortisone supplementation (12 mg/m²/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.
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. 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].](image)

![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.](image)
| 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.Ala32CysfsX42) | – | – | – | 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 | Homozygous c.605-1G > A | – | – | – | – | – | – |
| 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 | – | – |
| 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 | – |
| Takagi et al., 2017 | Case report | Sibling 1 Homozygous c.143-83A > G | M | 0.5 | Failure to thrive, precocious puberty at 10-year-old | GH, TSH, PRL | APH | – |
| Bertko et al., 2017 | Cohort study | Heterozygous c.143-83A > G | F | 0.3 | Failure to thrive | GH, TSH, PRL | APH | Catch-up growth |
| Sobrier et al., 2016 | Case series of 9 patients | Homozygous c.10C > T (p.Q4*) | M | 11.5 | Failure to thrive | GH, TSH, PRL | APH | – |
| Birla et al., 2016 | Case control study | 3 family, 5 patients Homozygous/ heterozygous c.605-1G > A | – | 1.6-9 | Failure to thrive | GH, TSH, PRL | APH | – |
| | | 1 family, 1 patient Homozygous c.605 delele | – | 5.0 | Failure to thrive | GH, TSH, PRL | APH | – |
| | | 2 family, 2 patients Heterozygous c.1-59 T > A | M | 15-18 | Failure to thrive | GH, TSH, PRL, LH | EPP | – |
| | | 1 family, 1 patient Heterozygous c. + 8C > T | M | 8.0 | Failure to thrive | GH, TSH, PRL, LH | EPP | – |
| | | Cohort study: 1 patient Homozygous IVS2-3insa | F | 0.5 | Failure to thrive | GH, TSH, PRL | APH | – |
| De Rienzo et al., 2015 | Cohort study | 1 family, 2 patients Homozygous p.V153F | F | 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, LH | APH | – |
| | | 1 sporadic patient Homozygous p.Q4X | M | 0.5 | Failure to thrive | GH, TSH, PRL, LH | APH | – |
| | | 1 sporadic patient | | 8.0 | Failure to thrive | GH, TSH, PRL, LH | APH | – |
| | | Case report Compound heterozygosity: IVS1 + 3 mtA > G/c.793C > T (p.R265W) | M | 8.0 | Failure to thrive, global developmental delay, midline facial defect, microenphis | GH, TSH, PRL | APH | Catch-up growth, improved neurodevelopment |
| Tenenbaum-Rakover, Sobrier, & Amsellem, 2011 | Case report | Homozygous c.502insT (p.Thr168IlefsX7) | M | 0.8 | Failure to thrive, prolonged jaundice, constipation, hypoglycemia, seizure, midline facial defect, microenphis, delay puberty | GH, TSH, PRL | APH | Short stature |
| Lee et al., 2011 | Case report | Homozygous c.698 T > C (p.F233S) | F | 2.2 | Failure to thrive | GH, TSH, PRL | – | – |

(continued on next page)
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 would gradually develop into cretinism. If GHD was present, 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 the gonadotropin releasing hormone stimulation test at an appropriate timing. Our patient had good response to hormone supplementation, as

| Writer, publish date | Study type and case | Gene mutation of POU1F1 | Sex | Age at diagnosis (year) | Presentation | Influenced hormone | MRI | Follow up |
|----------------------|---------------------|------------------------|-----|------------------------|--------------|--------------------|-----|-----------|
| De Graaff et al., 2010 | Cohort study: 1 patient | P.R271W | M | 18.0 | Failure to thrive, midline facial defect, cretinism | GH, TSH, PRL | – | Poor compliance, Kocher-Debre-Semelaigne syndrome |
| Snabboon et al., 2008 | Case report | Homozygous IVS4 + 1G > A | M | 4.0 | Failure to thrive, poor feeding | GH, TSH, PRL | APH | Short stature |
| Miyata et al., 2006 | Case report | Homozygous p.S179R | M | 0.1–0.3 | Failure to thrive | GH, TSH, PRL | APH | – |
| Turton et al., 2005 | Case report | Compound heterozygosity: c.688G > A (p.E230K); c.515G > A (p.R172Q) | M | 1.4–2.3 | Failure to thrive | GH, TSH, PRL | APH | Short stature |
| Rainbow et al., 2005 | Cohort study | Homozygous p. R271W | M | 1.7 | Failure to thrive, midline facial defect, normal psychomotor development | GH, TSH, PRL | APH | Poor compliance, short stature, hypothyroidism |
| Ward et al., 1998 | Case report | Homozygous p. F233L | M | 0.9–1.3 | Failure to thrive, optic nerve hypoplasia | GH, TSH, PRL | Normal | – |
| Rodrigues Martineli, Braga, De Lacerda, Rankin, & Graf, 1998 | Case report | Heterozygous c.811C > T (p.R271W) | M | 3.8 | Failure to thrive | GH, TSH, PRL | – | Catch-up growth |
| Fofanova et al., 1998 | Cohort study | Heterozygous p. R271W | F | 14.0 | Failure to thrive, normal psychomotor development, delay puberty | GH, TSH, PRL | Reduce size of pituitary | Short stature |
| Pfafl et al., 1992 | Case report | Homozygous c.527C > G (p.A158P) | M | 1.0 | Failure to thrive, psychomotor retardation, short upper limbs, delayed psychomotor development | 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.

Table 1 (continued)
presented a patient of congenital hypopituitarism with \textit{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, we 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 writing 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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