Novel Melanocortin 2 Receptor Variant in a Chinese Infant With Familial Glucocorticoid Deficiency Type 1, Case Report and Review of Literature

Kuerbanjiang Abuduxikuer†, Zhong-Die Li†, Xin-Bao Xie, Yu-Chuan Li, Jing Zhao and Jian-She Wang*

Department of Hepatology, Children’s Hospital of Fudan University, Shanghai, China

Familial glucocorticoid deficiency type 1 (FGD1) is an autosomal recessive disorder caused by mutations in the melanocortin 2 receptor (MC2R) gene, characterized by a low or undetectable serum cortisol level and a high adrenocorticotropic hormone (ACTH) level. Clinical manifestations include hypoglycemia, seizure, skin hyperpigmentation, hyperbilirubinemia, cholestasis, and a tall stature. Some dysmorphic features such as, a prominent forehead with hypertelorism, a broad nasal bridge, and small tapering fingers, have been reported. Children with FGD1 may have other isolated endocrine abnormalities. To date, no patient with FGD1 has been reported in mainland China. Here we report on a Chinese patient with FGD1 having a novel MC2R gene variant, a mild transverse palm crease, hypertelorism, and subtle/transient endocrine abnormalities relating to all three zones of the adrenal cortex and thyroid gland. We also reviewed cases with dysmorphic features or additional endocrine abnormalities.

Keywords: melanocortin 2 receptor (MC2R), familial glucocorticoid deficiency (FGD) type 1, cholestasis, skin hyperpigmentation, hypoglycemia, cortisol, adrenocorticotropic hormone (ACTH), linear overgrowth

INTRODUCTION

Familial glucocorticoid deficiency type 1 (FGD1) (OMIM #202200) is an autosomal recessive disorder caused by mutations in the melanocortin 2 receptor (MC2R) gene (OMIM *607397), characterized by a low or undetectable serum cortisol level and high adrenocorticotropic hormone (ACTH) level. Clinical manifestations include hypoglycemia, seizure, skin hyperpigmentation, hyperbilirubinemia, cholestasis, and a tall stature (1–6). Other dysmorphic features, such as a prominent forehead with hypertelorism (7), and a broad nasal bridge with small tapering fingers (8), have been reported. Children with FGD1 may have other isolated endocrine abnormalities (4, 6–17). Here we report on the first FGD1 patient from China with a novel MC2R gene variant, a mild transverse palm crease, hypertelorism, and subtle/transient endocrine abnormalities relating to all three zones of the adrenal cortex and thyroid gland.
CASE PRESENTATION

The female infant was born to healthy non-consanguineous parents (25-year-old father, and 22-year-old mother) after an uncomplicated first pregnancy and 40 weeks of gestation. A Cesarean section was performed due to a failed vaginal delivery, but the Apgar score until 15 min after birth and birth weight was normal (3,300 g). The patient was intubated after developing progressive tachypnea, moaning, and severe hypoglycemia (0.9 mmol/L). The patient developed hyperbilirubinemia that was unresponsive to phototherapy, but the parents took the baby home, for home care at the age of 9 days.

At the age of 1.4 months, the patient was admitted to a provincial hospital for jaundice, vomiting, afebrile seizures, and pneumonia. The lowest blood glucose level during the hospital stay was 1.4 mmol/L. The serum cortisol levels were extremely low (13.8–29.3 nmol/L, normal range 138–690 nmol/L) while adrenocorticotropic hormone levels were slightly lower or normal (6.0–18.5 pg/ml, normal range 6.4–40 pg/ml). A cortisol deficiency was diagnosed, but parents refused hormone replacement therapy. The patient was discharged after the pneumonia was resolved and blood glucose levels were stabilized.

At the age of 3.2 months, the patient was presented to our hospital for cholestasis without obvious symptoms of hypoglycemia, infection, alacrima, or achalasia. Repeated morning serum cortisol levels were extremely low (8.8–10.6 nmol/L, normal range 138–690 nmol/L), while ACTH was extremely elevated (1656.9–1911.8 pg/ml, normal range 6.4–40 pg/ml). Upon physical examination, significant jaundice, skin hyperpigmentation and slight hepatosplenomegaly (liver 2–2.5 cm below the right costal margin, and 2.5 cm below the xiphoid process; spleen 1.5–2.0 cm below the left costal margin) were observed. Slight dysmorphic features such as a transverse palmar crease in the right hand, a prominent forehead, hypertelorism (inner canthal distance greater than the palpebral fissure length) were noted. The palmar crease, and the changes in skin pigmentation are presented in Figure 1. Written informed consent was obtained from the parents for the publication of this case report and related images. Changes in body weight/length, complete blood count, procalcitonin, serum biochemistry, blood coagulation, and endocrine profiles throughout the disease course are provided in Table 1.

Genetic screening for abnormalities related to congenital adrenal hyperplasia (list of 44 genes are provided in Table 3), and multiplex ligation-dependent probe amplification (MLPA) analysis of the CYP21A2 gene were performed by a commercial genetic testing company (Customized target capture sequencing, http://www.mygenostics.com/ServiceTechnology.aspx?nid=263&pid=268). The result showed compound heterozygous

![Image](image.png)

**FIGURE 1** | Skin pigmentation and palmar creases. Higher skin pigmentation of the hand compared to parents at 3.5 months (A,B), a slight transverse palmar crease on the right hand (C) but not on the left hand (D). Changes in skin pigmentation at 0.7 months (E), 1.6 months (F), 3 months (F), and 4.9 months (H, 1.5 months after hydrocortisone therapy and resolution of cholestasis). Written informed consent was obtained from the parents for the publication of personal images.
variants in the melanocortin 2 receptor (MC2R) gene, but the result of the CYP21A2 gene MLPA analysis was negative for hot-spot mutations and copy number variants (Supplementary Figure 1). We conducted protein modeling with SWISS-model (https://www.swissmodel.expasy.org) using the most similar structure (5jtb.1.A, Adenosine receptor A2a), and polar contacts of wild-type and mutated amino acid residues were compared with Pymol software (https://pymol.org/2/). The c.433C>T/p.R145C was reported in the dbSNP152 (http://www.ncbi.nlm.nih.gov/snp/rs139218324), and gnomAD (http://gnomad-old.broadinstitute.org/variant/18-13885085-G-A), but not in the 1000 Genome Database (http://www.1000genomes.org/) and Exome Variant Server (http://evs.gs.washington.edu/EVS/). The c.712C>T/p.H238Y variant was not reported in

| TABLE 1 | Changes in body weight/length, complete blood count, procalcitonin, serum biochemistry, blood coagulation, and endocrine profiles. |
|----------|----------------------------------------------------------------------------------------------------------------------------------|
| Age (d, day; m, month) | 2 d | 7 d | 1.4 m | 1.7 m | 3.2 m | 3.4 m<sup>a</sup> | 3.8 m | 4.2 m<sup>b</sup> | 0.9 m<sup>c</sup> | 8.1 m<sup>d</sup> |
| Weight Kg | 3.3 | – | 4.0 | – | 6.3 | 6.6 | – | – | 9.0 | 13.0 |
| WHO percentile | 38th | – | 6th | – | 39th | 24th | – | – | 96th | >99th |
| Length Cm | 51.0 | – | – | – | – | – | – | – | 70.0 | 77.0 |
| WHO percentile | 65th | – | – | – | 96th | – | – | – | 98th | >99th |
| Serum biochemistry (reference range) | | | | | | | | | | |
| Albumin (35–55 g/L) | 28.9 | 31.2 | 34.0 | 33.4 | 37.9 | 36.1 | 41.9 | 42.3 | 44.9 | 39.0 |
| Globulin (20–30 g/L) | 18.4 | 19.6 | 16.6 | 14.4 | 17.5 | 19.5 | 24.6 | – | 18.3 | 18.9 |
| Alanine aminotransferase (0–40 IU/L) | 7 | 14 | 14 | 42 | 101 | 101 | 70 | 78 | 119 | 40 |
| Aspartate aminotransferase (0–40 IU/L) | 50 | 34 | 56 | 167 | 320 | 359 | 155 | 66 | 83 | 61 |
| Total bilirubin (5.1–17.1 umol/L) | 172.0 | 290.9 | 147.1 | 79.4 | 100.6 | 104.1 | 71.0 | 24.3 | 12.8 | 6.9 |
| Direct bilirubin (0–6umol/L) | 13.6 | 16.2 | 37.3 | 46.5 | 63.1 | 68.6 | 47.3 | 15.5 | 7.0 | 1.8 |
| γ-Glutamyl transferase (7–50 IU/L) | 377 | 306 | 274 | 192 | 54 | 49 | 68 | 59 | 67 | 12 |
| Total bile acid (0–10 umol/L) | – | – | – | – | – | 441 | 375 | – | – | – |
| Alkaline phosphatase (42–383 IU/L) | 146 | 171 | 373 | 376 | 742 | 812 | 342 | 283 | – | – |
| Blood glucose (3.9–5.8 mmol/L) | 2.65 | 6.6 | 1.44 | 3.0 | 101 | 78 | 24.3 | 12.8 | 6.9 | 39.0 |
| Lactic acid (0–2 mmol/L) | – | – | – | – | – | – | – | – | – | – |
| Ammonia (10–47 umol/L) | – | – | – | – | – | 18.3 | 18.9 | – | – | – |
| Total cholesterol (3.1–5.2 mmol/L) | 3.09 | – | 2.6 | 3.0 | 17.4 | 7.7 | 13.4 | – | – | – |
| Triglyceride (0.56–1.70 mmol/L) | 0.8 | – | – | – | – | – | – | – | – | – |
| Creatine kinase (22–270 U/L) | 1,259 | 292 | – | – | – | – | – | – | – | – |
| Creatine kinase-MB (2–28 U/L) | 40 | – | – | – | – | – | – | – | – | – |
| Total bile acid (0–10 umol/L) | – | – | – | – | – | – | – | – | – | – |
| Dehydroepiandrosterone sulfate (35–430 ug/dl) | – | – | – | – | – | – | – | – | – | – |
| Total testosterone (0–1.08 nmol/L) | – | 18.3 | 113.8 | 192.7 | – | – | – | – | – | – |
| Renin (4–24 ng/ml/hour) | – | – | – | – | – | 263 | – | – | – | – |
| Aldosterone (10–160 pg/ml) | 253.6 | – | 113.8 | – | 192.7 | – | – | – | – | – |
| Angiotensin II (25–129 pg/ml) | – | – | – | – | – | 149.5 | – | – | – | – |
| Dehydroisoandrosterone (1–11.7 umol/L) | – | – | – | – | – | 0.1 | – | – | – | – |
| 17-alpha hydroxyprogesterone (0.8–16.6 ng/ml) | – | – | – | – | – | 0.4 | – | – | – | – |
| Androstenediol (0.3–3.3 ng/ml) | – | – | – | – | – | <0.3 | – | – | – | – |
| Dehydroandrosterone (1–11.7 umol/L) | – | – | – | – | – | – | – | – | – | – |
| Testosterone (0–1.08 nmol/L) | 150 | 0.23 | 0.67 | 2.09 | – | – | 0.46 | – | – | – |
| Progesterone (0.1–0.33 ng/ml) | >60 | 0.18 | 0 | – | – | – | 0.04 | – | – | – |
| Dehydroepiandrosterone sulfate (35–430 ug/dl) | – | – | – | – | – | – | – | – | – | – |
| C peptide (0.3–3.73 ng/ml) | 0.23 | – | 0.03 | – | – | – | – | – | – | – |
| Insulin (4.03–23.46 uIU/ml) | 4.86 | 0.34 | – | – | – | – | – | – | – | – |
| Thyroid-stimulating hormone (0.25–7.31 mIU/L) | 10.61 | 4.15 | – | – | 4.81 | – | – | – | 4.87 |
| Serum thyroxine (57.92–198.2 nmol/L) | – | – | – | – | – | 131.11 | – | – | – | – |
| Free thyroxine (6.44–29.6 pmol/L) | 18.28 | 13.26 | – | – | 11.49 | – | – | – | – | – |
| Serum triiodothyronine (1.08–3.38) | – | – | – | – | – | 2.2 | – | – | – | – |
| Free triiodothyronine (2.73–8.6 pmol/L) | 4.62 | 4.55 | – | – | 4.77 | – | – | – | – | – |

<sup>a</sup>Oral hydrocortisone was started at 30 mg/m<sup>2</sup> body surface area per day after the blood test.
<sup>b</sup>Blood was drawn before hydrocortisone intake.
<sup>c</sup>Blood was drawn 1 h after hydrocortisone intake.
<sup>d</sup>Follow-up testing results 3 weeks after stopping oral hydrocortisone therapy. ACTH, Adrenocorticotropic hormone; –, not available.
TABLE 2 | Carrier frequency and in-silico pathogenicity prediction results of MC2R gene variants.

| Variant/Amino-acid (physical location) | Change | c.433C>T/p.R145C<sup>a</sup> (chr18:13885085G>A) | c.712C>T/p.H238Y (chr18:13884806G>A) |
|----------------------------------------|--------|-----------------------------------------------|--------------------------------------|
| Carrier frequency (number of heterozygous/homozygous carriers) | 1000G 0 | 0 | 0 |
|                                     | EXAC 0 | 0 | 0 |
|                                     | EXAC (East Asians) 0 | 0 | 0 |
|                                     | EXAC (South Asians) 0 | 0 | 0 |
|                                     | gnomAD 0.00007219 (2/0) | 0 | 0 |
|                                     | gnomAD (East Asian) 0 | 0 | 0 |
|                                     | gnomAD (South Asian) 0 | 0 | 0 |
|                                     | gnomAD (African) 0.00004163 (1/0) | 0 | 0 |
|                                     | gnomAD (European, non-finns) 0.00007901 (1/0) | 0 | 0 |

In-silico pathogenicity prediction (pathogenicity threshold)

| Prediction | Score | Prediction | Score |
|------------|-------|------------|-------|
| Mutation taster (probability) | Disease causing | 0.999 | Disease causing | 1.000 |
| SIFT (<0.05) | Damaging | 0.014 | Damaging | 0.000 |
| Provean (<=-2.5) | Deleterious | -6.19 | Deleterious | -5.77 |
| Polyphen-2 (>0.8) | Probably damaging | 0.999 | Probably damaging | 1.000 |
| Revel (>0.5) | Benign | NA | NA |
| M-CAP (>0.025) | Non-pathogenic | 0.405 | Pathogenic | 0.842 |
| M-CAP (>0.025) | Likely benign | 0.009 | Possibly pathogenic | 0.056 |
| CADD (>20) | Pathogenic | 24.1 | Pathogenic | 26.8 |

<sup>a</sup>Known disease mutation at this position (HGMD CM116421), rs139218324. URLs of in-silico prediction tools: Mutation taster (http://www.mutationtaster.org); SIFT&Provean (http://provean.jcvi.org/genome_submit_2.php); Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/); Revel (Rare Exome Variant Ensemble Learner software); MutPred2 (http://mutpred.mutdb.org); M-CAP (http://bejerano.stanford.edu/MCAP/); CADD (https://cadd.gs.washington.edu/score).

the dbSNP152, gnomAD, 1000 Genome Database, and Exome Variant Server. The c.433C>T/p.R145C variant of maternal origin caused the change of arginine (polar, basic) at the amino acid position of 145 to cysteine (non-polar, neutral). R145 is a relatively conserved amino acid residue, and five out of eight in-silico prediction tools (Table 2) predicted this variant as pathogenic. This is a known disease-causing variant (HGMD CM116421, rs139218324), and reported to be associated with FGD1 in an adopted Chinese girl (18). Protein modeling showed no effect of R145C residue change on polar contact with V149. The c.712C>T/p.H238Y variant of paternal origin caused the change of amino acid residue histidine (polar, basic) at the position of 238 to tyrosine (polar, neutral). H238 is a strictly conserved residue, and all eight in-silico prediction tools predicted this variant as pathogenic (Table 2). Protein modeling showed that the H238Y mutation changed polar contact of the amino acid residue in the position of 238 with adjacent residues, and polar contact with N261 in the transmembrane domain (TMD) 7 was lost. Confirmation with Sanger sequencing, conservation status of amino acid residue that have been affected, protein modeling results, and in-silico pathogenicity prediction results for both MC2R variants are provided in Figure 2 and Table 2.

Extensive etiologic evaluations from birth until the last follow-up (4.9 months) are provided in Table 3. After ruling out other causes of hypoglycemia, cholestasis, and adrenal deficiency, a diagnosis of FGD1 was made. Oral hydrocortisone was started at a dose of 30 mg/m<sup>2</sup> body surface area (divided into three doses) at the age of 3.4 months. Cholestasis was resolved at 4.9 months, skin hyperpigmentation was improved, and no further episodes of hypoglycemia occurred. Morning serum cortisol levels 1 h after hydrocortisone intake was normal, while ACTH levels returned to near normal levels. However, parents decided to stop the medication at the age of 7.4-months, and serum cortisol/ACTH levels returned to extreme levels at the age of 8.1-months (Table 1).

DISCUSSION

ACTH unresponsiveness was first described by Shepard et al. (19) in 1959, melanocortin receptors were cloned in 1992 (20), and the first FGD1 caused by the MC2R gene mutation was reported by Clark et al. (2).

Hypothyroidism had been reported in an FGD1 patient with compound heterozygous L46fs/V49M mutation. The TSH level of 13.9 mIU/L at 3-months of age was normalized after a week of L-thyroxine therapy and remained normal when the medicine was stopped after 3 months (6). Our patient had hypothyroidism (TSH 10.61 mIU/L) during the neonatal period, but the repeated TSH levels without hormone
replacement therapy at the age of 1.4 months was normal. Partial or complete deficiency of sex hormones such as 17-alpha hydroxyprogesterone, androstenediol, dehydroisoandrosterone, testosterone, progesterone, and dehydroepiandrosterone sulfate (DHES) had been reported in several FGD1 patients (4, 7, 9, 10, 13–15, 17). Besides low levels of androstenediol, DHES, and 17-alpha-hydroxyprogesterone, our patient also had lower levels of dehydroisoandrosterone and progesterone, as well as higher levels of testosterone. Although FGD1 patients may experience delayed development of pubic hair, other sexual characteristics did not seem to be affected. Slight abnormalities in renin or aldosterone levels have been reported (7, 8, 11, 13, 14), but angiotensin II levels have never been reported to be elevated in FGD1 patients. Renin, aldosterone, and angiotensin II levels were slightly elevated in our patient without any abnormalities in serum electrolytes, blood pressure, and kidney function. Patients with severe or homozygous truncating mutations in the MC2R gene, mild disturbances in renin–angiotensin–aldosterone axis may need temporary replacement of mineralocorticoid but did not cause long-term mineralocorticoid deficiency after stopping the intervention (11, 12).

A tall stature in the presence of normal growth hormone levels is one of the features of FGD1 (7, 8, 10, 14, 15, 17) accompanied by some dysmorphic features (such as hypertelorism, relative frontal prominence, epicanthic folds, large head circumference, and small tapering fingers) (7, 8). *In vitro* studies indicated that excess levels of ACTH increases chondrocyte precursors leading to chondrogenic phenotypes (21), and low levels of cortisol may fail to inhibit the synthesis of insulin-like growth factor-binding protein-5 (22). A single transverse palmar crease was associated with 107 genes and 172 disease entities (http://www.geneontology.org/formats/oboInOwl?id: HP:0007598), but not with the MC2R gene or FGD1. Since none of the transverse palmar associated genes were screened in this patient, we cannot rule out the possibility that variants in other genes may have caused this phenotype. Our patient had a normal body weight and length percentiles until hydrocortisone treatment, but both weight and length percentiles exceeded the 95th percentile 1.5 months post-treatment. This might be due to inadequate suppression and a prolonged effect of elevated ACTH. A tall stature is believed to return to normal after continuous treatment with hydrocortisone. However, growth parameters should be monitored in patients with FGD1, and

![FIGURE 2](image-url)

**FIGURE 2** | Sanger sequencing results with conservation status of amino acid residues (A), and protein modulation (B,C).
TABLE 3 | Diagnostic evaluation.

| Etiological assessment                | Investigations performed (normal unless otherwise indicated)                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Infections                           | Complete blood count; Blood culture for bacteria and fungus; Serology for human Legionella, hepatitis B, hepatitis C, HIV, syphilis, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex viruses (HSV) I/II, toxoplasmosis, rubella virus, mycoplasma, chlamydia, tuberculosis, and respiratory syncytial virus; Complete blood count (slightly increased reticulocyte percentage) (Table 1). PCR for serum DNA detection for EBV, CMV, and HSV I/II; Elevated procalcitonin levels; Routine urine and fecal analyses. |
| Radiology and ultrasonography        | Echocardiography (atrial septal defect, 3.7 mm), electroencephalography, electrocardiography, brain MRI, contrast MRI scan of the pituitary gland, chest X-ray (pneumonia), computed tomography scan of the brain. Bilateral hip ultrasound (possible hip dysplasia at when 5-5 days old, normal at 1.5 months); Abdominal ultrasound: slight hepatomegaly with decreased echogenicity (2–2.5 cm below the right costal margin, and 2.5 cm below the xiphoid process), slight splenomegaly (1.5–2.0 cm below the left costal margin); normal looking portal vein, pancreas, kidneys, and adrenal glands. |
| Immunology and coagulation profiles  | Coomb's test at 5 days; Glucose-6-phosphate dehydrogenase (G6PD) activity at 5 days; INR and prothrombin time: slight elevation during newborn period, but normal afterwards; D-dimer (0.7–2.84 mg/L, normal range 0–0.3 mg/L); Activated partial thromboplastin time (46.1–51.5 s, normal range, 28.0–44.5 s); Fibrinogen (1.44–1.89 g/L, normal range, 2–4 g/L); Fibrinogen degradation products; Thrombin time. |
| Biochemical, metabolic and endocrine profiling | Liver function test (hyperbilirubinemia during newborn period, cholestasis), serum electrolytes, creatinine, uric acid, urea nitrogen, cholesterol, triglyceride (slightly elevated at 3.8 months) (Table 1) | Serum creatine kinase (significantly elevated when 2 days old, normal afterwards), creatine kinase-MB, lactate dehydrogenase (slight elevation). Serum ceruloplasmin level at 1.5 months; Slightly elevated lactate and ammonia levels; Blood mass spectrometry at 1.6 months: elevated levels of oxalic acid (15.66 μM, normal range 0–0.1 μM), sebacic acid (24.38 μM, normal range 0.4–7 μM), 3-hydroxyglutaric acid (16.76 μM, normal range 0–0.5 μM), palmatine acid (95.22 μM, normal range 0–13.8 μM). Low levels of 25-hydroxy vitamin D3 (10.41 ng/ml, normal range 15–35 ng/ml), and elevated levels of alphafetoprotein (7,575 ng/ml, normal range <77.1 ng/ml) at 3.5 months. Serum amino acid and acyl-carnitine profiles at 3.5 months were normal except for slightly elevated threonine (126.35 μM, normal range 17–90 μM), and CO2 (54.28, normal range 10–50 μM). Urine organic acid analysis (qualitative) at 3.5 months: significant elevation of citric acid, and slight elevation of 2-oxoglutaric acid and lactic acid. Glucose profiling (hypoglycemia); Low to normal levels of Insulin and C-peptide; Slightly elevated Serum lactate (Tables 1, 2; Hemoglobin A1c (2.2%, normal range 3.8–5.8%). Extremely low levels of serum protein; Extremely high levels of serum ACTH; Lower level of 17α-hydroxyprogesterone, androstenediol, dehydroisoandrosterone; Higher levels of renin, aldosterone, angiotensin II, and dehydroepiandrosterone sulfate; Normal to higher levels of testosterone; Transient hypothryroidism (Table 2). Genetic disorders | Genetic panel for screening for congenital adrenal hyperplasia including NR0B1, PRKACA, DHC7, GSK2, PDE8B, LH4X, ARMCO5, MC2R, GIK, H6PD, CDKN1C, CYP11B1, ABCD1, SOX3, GNAS, MRAP, POMC, HSD11B1, MCR1, CYP21A2, NNT, RXRA, RARA, HESX1, HSD3B2, GLCC11, TPS3, CYP11B2, POR, RXR, PDE11A, PRD1, and STAR gene (compound heterozygous variants in MC2R gene, Table 2. Figure 2; Multiplex ligation-dependent probe amplification (MLPA) analysis of CYP21A2 gene. |

growth hormone levels together with bone maturity should be evaluated when necessary. We also observed slight dysmorphic features, such as a prominent forehead, and hypertelorism, but no epicantelic folds were observed in our patient. Other endocrine abnormalities, and dysmorphic features in previously reported cases are summarized in Table 4.

The underlying mechanism of the MC2R gene mutations causing FGD1 is ACTH resistance, either due to the trafficking failure of the receptor from the endoplasmic reticulum to the cell surface, or due to ineffective binding to ACTH (5), according to the last published review in 2018 (23), a total of 28 missense mutations, three non-sense mutations, and eight small insertion/deletions in the MC2R gene were reported in the literature. Most naturally occurring or site-directed mutants cause defective trafficking of the MC2R protein toward the cell membrane while others may lead to defective binding with ACTH (Figure 3). R145C found in our patient was previously reported in an adopted Chinese FGD1 child (18) and a known disease-causing variant in HGMD (CM116421), but no functional study was conducted to evaluate its effect in protein function. Located in the transmembrane domain 4 (TMD4), R145C is adjacent to R146H, which is also a naturally occurring disease causing mutant that causes decreased binding to ACTH and defective membrane trafficking. Site directed mutagenesis of another adjacent residue (T147D) resulted in a trafficking defect, but T147A did not affect protein trafficking toward the cell membrane (24). TMD4 plays a critical role in the activation of the rainbow trout melanocortin-2 receptor (25). R145C may have caused abnormal MC2R protein function by affecting receptor localization in the cell membrane, or activation of the receptor itself. H238Y (located in the TMD6) in our patient is a novel variant in a highly conserved residue not only among different species, but also among other melanocortin receptors. An in vitro study of site directed mutagenesis at the same amino acid residue (H238A) caused a 1.4-fold decrease in membrane trafficking of the MC2R protein from Golgi apparatus toward the cell membrane. H238 residue is also a component of the proposed ACTH binding site consisting of E80, D104, D107, F168, F178, F235, H238, and F258 (26). These findings suggest that the H238Y variant may affect cortisol production by affecting the MC2R localization and ACTH binding. Further functional studies are...
| Cases | Amino acid change in MC2R protein | Gender, age (y, years; m, months; d, days) | Additional endocrine abnormalities | Other features |
|-------|----------------------------------|------------------------------------------|-----------------------------------|----------------|
| Current report | R145C/H238Y | Female, 4.9 m | | |
| Weber et al. (15) | S74I/R128C | Male, 8 y, 6 m | N N –  | Down  | N – N – | – – – | Tall stature |
| | I44M/L192fs | Female, 2 y | N N – | Down  | Down  | Down | – | – | Tall stature |
| | R146H/R146H | Female, 3 y, 4 m | – | – | – | – | – | – | – |
| Tsigos et al. (16) | Y254C/Y254C | Female, 2 y, 3 m | N N – | – | – | – | – | – | Developmental delay |
| Naville et al. (13) | C251F/G217fs | Male, 2 y | N ↑ – | Down  | – | – | – | – | – |
| | D107N/D107N | Male, 3 y | N ↑ – | Down  | – | – | – | – | – |
| Slavotinek et al. (8) | R146H/R146H | Female, 5 y, 9 m | ↑ N – N – | – | – | – | – | Tall stature, broad nasal bridge, small tapering fingers |
| Elias et al. (7) | T159K/T159K | Male, 8 d | N ↑ – | Down  | – | – | – | – | Tall stature |
| | T159K/T159K | Male, 3 m | N ↑ – | – | – | – | – | – | – |
| | T159K/D103N | Male, 2 y | N ↑ – | Down  | – | – | – | – | – |
| | S74I/1052 delC | Male, 3 y | ↑ N – | Down  | – | – | – | – | – |
| | S74I/S74I | Male, 6 y | ↓ – | – | – | – | – | – | – |
| | S74I/T159K | Female, 13 y, 8 m | N – | – | N | – | Down  | N | – | – | Short stature |
| Selva et al. (17) | C21Y/R146H | Female, 2 y | – | – | – | – | – | – | Tall stature |
| Matsuura et al. (10) | C21Y/R146H | Female | – | – | – | – | – | – | – |
| | S74I/S74I | Male, 1 y, 7 m | ↑ – | – | N | – | – | – | – | – | failure to thrive |
| | R146H/560delT | Female, 1 y | N ↓ – | – | – | – | – | – | – |
| | S79–581delTGT | Male, 2 m | ↑ ↓ – | – | – | – | – | – | – | – |
| | S79–581delTGT | Male | ↑ ↓ – | – | – | – | – | – | – |
| Artigas et al. (14) | G217fs/A26S | Male, 2 y | ↑ – – | Down  | – | – | Down | – | – | N | Tall stature |
| Mazur et al. (6) | L468fs/V49M | Male, 3 m | N – – N – – – – | – | – | – | ↑ | Constipation, muscle weakness |
| Akin et al. (4) | L225R/L225R | Male, 7 d | N N | ↓↓ | ↓↓ | – | – | – | ↓↓ | – | – |

N, normal; ↑, increased levels; ↑↑, significantly increased levels; ↓, decrease levels; ↓↓, significantly decrease levels; -, not available or not provided;
needed to prove variants found in our patient affect the MC2R protein function.

In conclusion, we reported on the first child with FGD1 from mainland China, carrying a novel MC2R variant, and reviewed previously reported cases with additional features.

INFORMED CONSENT

Written informed consent was obtained from the parents of the participant for the publication of this case report.

ETHICS STATEMENT

Ethical Committee of Children’s Hospital of Fudan University approved the study.

AUTHOR CONTRIBUTIONS

J-SW designed the report and approved the final submission. KA and Z-DL collected data. KA analyzed relevant information and conducted protein modeling. Z-DL analyzed the next generation sequencing data. J-SW, KA, Z-DL, X-BX, Y-CL, and JZ, clinically managed the patient. Both KA and Z-DL wrote the manuscript, contributed equally for this manuscript, and will be first co-authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2019.00359/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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