



Case Report

Neonatal presentation of familial glucocorticoid deficiency with a MRAP mutation: A case report☆

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ABSTRACT

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder in which the adrenal cortex fails to respond appropriately to stimulation by adrenocorticotrophic hormone (ACTH) to produce cortisol. The disease is characterized in laboratory testing by glucocorticoid deficiency and markedly elevated ACTH levels. FGD may present in infancy or early childhood with symptoms related to low cortisol and high ACTH, such as hyperpigmentation, severe hypoglycemia, failure to thrive and recurrent infections. Mutations in the MC2R accessory protein (MRAP) cause FGD types 2, which accounts for approximately 15–20% of FGD cases. Here, we report a female neonate of Chinese Han origin, who presented with noted hyperpigmentation at birth. Laboratory investigations revealed hypocortisolemia (cortisol <1.0 µg/dl) and elevated plasma ACTH (1051 pg/ml). She responded to hydrocortisone treatment. Genetic studies confirmed the diagnosis showing homozygous deletion (c.106 + 1delG) in intron 3 of MRAP gene, a mutation already reported as responsible for FGD type 2. This mutation can cause complete lack of ACTH response thus explaining the early presentation in this case. Her parents and maternal grandmother were heterozygous for the same mutation. To our knowledge, this is the first Chinese Han patient reported with FGD type 2 due to a known MRAP mutation.

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1. Introduction

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder resulting from adrenal unresponsiveness to adrenocorticotrophic hormone (ACTH). This disease is characterized by low serum cortisol concentrations in the presence of grossly elevated plasma ACTH levels. Affected individuals typically present with hyperpigmentation, hypoglycemic seizures, failure to thrive, failure to thrive and recurrent infections [1]. Causal mutations of FGD have been identified in MC2R [2], MRAP [3], MCM4 [1], TXNRD2 [4], STAR [5] and NNT [4]. MC2R accessory protein (MRAP), a 19-kDa single-transmembrane domain protein, is essential for trafficking of MC2R from the endoplasmic reticulum (ER) to the cell surface and subsequent signaling in response to ACTH [6]. Mutations in MRAP are responsible for 15–20% of FGD cases, named FGD type 2 [7]. Until now, this mutation has not been reported in Chinese Han cases of FGD. In the current paper, we describe a

Chinese Han child who presented with isolated hyperpigmentation at birth and a homozygous splice mutation (c.106 + 1delG) in MRAP.

2. Case presentation

A female infant was referred to our neonatal unit at the age of nine days for evaluation of hyperpigmentation of the skin. She was the product of an uncomplicated pregnancy and was born by caesarian section for concerning cardiocographic changes during labor. She is second born of non-consanguineous Chinese Han parents. Her sibling had died on the third day of life with hyperpigmentation of the skin. Medical history revealed that she had generalized severe hyperpigmentation of the skin after birth. Birth size was normal (weight 2800 g, −0.99 SDS; length 46 cm, −1.69 SDS; head circumference 33 cm, −0.74 SDS) and Apgar scores was 8 and 9 at 1st and 5th minute, respectively. On physical examination, weight was 2740 g (−1.31 SDS), length 47 cm (−2.47 SDS), and head circumference was 34.5 cm (−1.5 SDS). Blood pressure was 70/39 mm Hg. She had normal female genitalia. Hyperpigmentation of the skin was noted (Fig. 1A). There were no signs of alacrima or achalasia. Other examination findings were unremarkable. Serum electrolytes and blood glucose were normal. Endocrine investigations revealed low baseline 8 am serum cortisol (<1.0 µg/dl) with extremely elevated ACTH (1250 pg/ml). Testosterone, 17-OH progesterone, estradiol, progesterone, luteinizing hormone, folliculin, and prolactin, free

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Fig. 1. Image of the patient (consent obtained). (A) Severe generalized hyperpigmentation of the patient at presentation in the neonatal period (indicated by the arrow). (B) Hyperpigmentation was resolved on her most recent visit, at the age of 12 months (Her father is holding her as their skin color is being compared).

T4, and TSH levels were normal. Cortrosyn stimulation test was not done. Magnetic resonance imaging (MRI) reveals normal adrenal glands.

Based on these findings, a familial glucocorticoid deficiency was suspected and oral hydrocortisone treatment at dose of 20 mg/m² per day was started. Hydrocortisone dose (varying from 10 to 15 mg/m² per day) adjustment was based on ACTH and cortisol concentrations. After 4 weeks, ACTH level was 278.0 pg/ml and cortisol level was 42.4 µg/dl, and hydrocortisone dose was reduced to 15 mg/m² per day (given in divided doses twice daily). The ACTH level was suppressed to slightly above the normal limit and the cortisol level is normal during the follow-up period. On her most recent visit, at the age of 12 months, hydrocortisone dose was 11 mg/m² per day (5 mg was given once daily in the morning), the ACTH level was 25.10 pg/ml and cortisol level was 33.4 µg/dl, and her skin was slightly lightened (Fig. 1B). Her weight

was 10 kg (0.84 SDS), length 70 cm (−1.67 SDS), and head circumference was 46.5 cm (1.12 SDS). She achieved all milestones at an appropriate age with normal neurodevelopment.

Genomic DNA was extracted from peripheral blood leucocytes from the infant and her family after informed consent was obtained. For the molecular diagnosis, a custom panel-based next-generation sequencing approach has been used to sequence all known adrenal gland diseases-associated genes in this child. We found a homozygous deletion of one nucleotide at the canonical 5α donor splice site (c.106 + 1delG) in intron 3 of MRAP gene. This would result in the skipping of exon 3 and a prematurely terminated translation product ((1)). PCR and Sanger sequencing confirmed the mutation. Her parents and maternal grandmother were found to be heterozygous carrier for the same mutation (Fig. 2). They had normal cortisol and ACTH levels.

An informed consent for publication was taken from the parents.

3. Discussion

We report a case of FGD with homozygous mutation of MRAP in a Chinese Han neonate. This girl presented with isolated hyperpigmentation, have low cortisol and high ACTH with normal electrolytes. A homozygous splice mutation (c.106 + 1delG) of MRAP confirmed the diagnosis of FGD type 2. Her parents and maternal grandmother had the same mutation. Until now, this mutation has not been reported in Chinese Han cases of FGD.

FGD is a rare autosomal recessive disorder characterized in laboratory testing by glucocorticoid deficiency and markedly elevated ACTH levels. Patients with FGD usually present during neonatal period to late childhood with symptoms related to cortisol deficiency and ACTH excess. In the neonatal period, these symptoms may include hyperpigmentation, hypoglycemia, irritability, jitteriness, lethargy, respiratory distress, cyanosis, apnea, hypotonia, seizures, shock, or sudden death [8]. Newborns can present with a positive family history of early-unexplained infant deaths or other affected family members supports a diagnosis [8].

The severe pigmentation of the skin is due to the over-stimulation of MC1R (cutaneous MSH receptors) by high circulating MSH which is a byproduct of ACTH synthesis from proopiomelanocortin [9]. This hyperpigmentation fades once proper treatment is initiated with glucocorticoids, which reduce ACTH concentrations [10]. Our patient was severely hyperpigmented at birth. This would suggest that the fetal corticotrophs could produce excessive plasma ACTH in response to low fetal cortisol, which in turn acts on melanocytes to promote

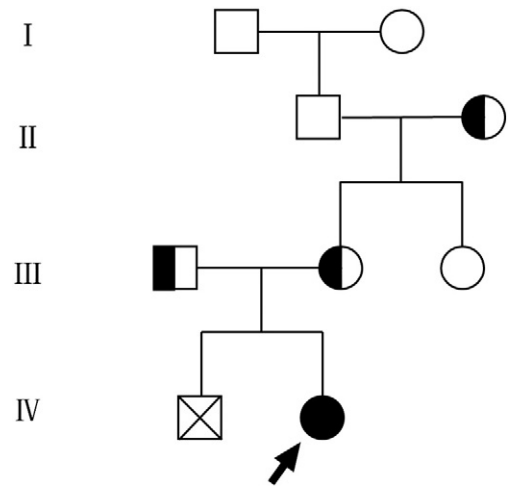


Fig. 2. Pedigree of the family. The proband is the second child of the family (indicated by the arrow). The first baby had died on the third day of life with hyperpigmentation of the skin. Her parents and maternal grandmother were heterozygous MRAP mutation carriers.

eumelanin synthesis before birth. In most of the FGD patients suppression of ACTH levels is difficult, and therefore is not used as a goal for therapy [11]. In this case, replacement treatment with hydrocortisone suppressed ACTH level to slightly above the normal limit and partially resolved the hyperpigmentation.

Acquired causes of adrenal insufficiency such as adrenal hemorrhage, trauma and infections were excluded by history and laboratory findings. Congenital adrenal hyperplasia was excluded by hormone analysis; congenital adrenal hypoplasia was also unlikely, because she had normal serum 17-OH progesterone and no mutation of the DAX1 gene. Allgrove syndrome was excluded because the baby had normal esophageal patency and tearing. ACTH receptor gene sequences were normal in our patient excluding FGD type 1.

Type 2 FGD is due to mutations in MRAP. MRAP, located at 21q22.1, is a small single-pass transmembrane domain protein, which is essential for the processing of the ACTH receptor (melanocortin 2 receptor, MC2R) and its trafficking from the ER to the cell surface [6]. The transmembrane domain of MRAP encoded by exon 3 is responsible for MC2R interaction [2]. This mutation will lead to skipping of exon 3 and early truncation of the protein and the absence of the MC2R interacting transmembrane domain [8]. As a result, MC2R is retained within the ER and fails to reach the cell surface which lead to ACTH resistance and adrenal insufficiency. Mutations in MRAP causing FGD2 were first described in 2005 [3]. So far over 9 different mutations of MRAP in FGD type 2 patients have been documented all of which are splice site or nonsense mutations and are predicted to produce proteins lacking the transmembrane domain essential for interaction with MC2R [6,7]. In our patient, we found a newborn with FGD type 2, presenting with severe hyperpigmentation. She was found to have a splice-site mutation in the MRAP gene, hence explaining the early presentation seen in the case.

In their study, Metherell et al. [3] identified the 1-bp deletion, c. 106 + 1delG, in 6 individuals from 5 families with glucocorticoid deficiency, making this the second frequent mutation causing FGD unrelated to defects in the MC2R gene. To our current knowledge, 1-bp deletion (c. 106 + 1delG) in intron 3 of MRAP gene, identified in the DNA of the patient, can be regarded as the cause of FGD type 2.

FGD is a rare autosomal recessive condition with no racial predilection. Cases of the condition have been reported in white [4,12], black, Indian [5], and Middle Eastern [13] populations. To our knowledge, our patient is the first reported Chinese Han patient with FGD type 2, with a known MRAP mutation. The patient was the offspring of non-consanguineous parents and her sibling had died in the neonatal period, possibly due to glucocorticoid insufficiency. Prolonged ACTH excess or glucocorticoid deficiency increases linear growth [7], while early diagnosis and appropriate therapy in this case enabled the patient to achieve normal developmental milestones. Clinical awareness of this condition is of considerable prognostic and therapeutic significance. Further

studies describing new cases and mutations causing FGD will contribute to understanding the mechanism of this rare and potentially life-threatening disease.

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