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CASE REPORT

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ARMC5 mutations in primary bilateral macronodular adrenal hyperplasia: a family case report

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Abstract

Background Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a rare cause of overt Cushing's syndrome (CS), which usually manifests as bilateral macronodular adrenal nodules and varying levels of cortisol secretion. Previous studies have shown that *ARMC5* play a huge role in the occurrence of PBMAH, which may be inherited to family members and lead to more severe clinical symptoms. *ARMC5* variants may be associated with meningiomas, which is also illustrated by our report.

Case presentation This is a 41-year-old male patient with high blood pressure for 10 years and multiple adrenal nodules on both sides. In addition, the patient also suffered from pituitary microadenoma and meningioma. According to the patient's clinical manifestations, laboratory tests, imaging examinations, and the results of whole exon gene testing, we diagnosed the patient with PBMAH. The patient underwent a posterior laparoscopic nephrectomy of the left adrenal gland. Pathology reported a left macronodular adrenal hyperplasia, multifocal, 2 cm to 3 cm in diameter. Molecular analysis of DNA extracted from the patient's peripheral blood revealed an *ARMC5* heterozygous mutation, which was classified as likely pathogenic.

Conclusion Screening of family members of PBMAH patients with *ARMC5* germline mutations and active monitoring of family members carrying *ARMC5* variants are recommended.

Keywords Primary bilateral macronodular adrenal hyperplasia, Cushing's syndrome, *ARMC5* gene, Meningiomas

Background

Patients with PBMAH have different levels of cortisol secretion, which can lead to asymptomatic, subclinical and overt CS. Patients with overt CS only account for about 2-6.2% of all CS patients [1, 2]. Therefore, the clinical manifestations of patients with PBMAH are not typical, and accurate diagnosis is difficult. Patients are often diagnosed because of the discovery of bilateral adrenal incidental tumors or the clinical manifestations of cortisol excess.

Scholars have conducted a large number of studies on the pathogenesis of PBMAH and have made some achievements. Abnormal expression of membrane G protein-coupled receptors, abnormal activation of cAMP/PKA and wnt/ b-catenin signaling pathways, and inappropriate autonomous or paracrine secretion of ACTH are all possible mechanisms of nodule development and hormone dysregulation [3]. Pathogenic variants in *ARMC5*(Armadillo repeat containing 5) are responsible for 20–25% of PBMAH [4]. *ARMC5* is a protein

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that contains an armadillo domain that contains multiple ARM repeats at its middle end and a BTB domain at its c terminus. ARMC5 has been shown to act as an adaptor for the cullin-RING E3 ubiquitin ligase complex to recruit protein substrates for ubiquitination, including itself. Gene mutation of *ARMC5* affecting the above mechanisms and causing PBMAH [3, 5]. In addition to *ARMC5* germline mutations, somatic mutations are frequently detected in patients with PBMAH, which supports *ARMC5* as a "double-hit" model of tumor suppressor gene. A second somatic mutation or second hit may induce tumorigenesis or promote greater nodule progression [6].

PBMAH with *ARMC5* mutation have an autosomal dominant mode of inheritance, but the penetrance is incomplete [7]. Here, we report a PBMAH family with *ARMC5* mutation, in which two family members had meningioma, and the inheritance pattern was also an autosomal dominant inheritance pattern.

Case presentation

Patient history

A 41-year-old male patient was admitted to the hospital due to multiple bilateral adrenal nodules. He had a history of hypertension for more than 10 years, and was currently treated with irbesartan and hydrochlorothiazide. Physical examination showed thin dry skin, central obesity, plethora and moon face, and multiple ecchymosis. After admission, enhanced CT examination of the adrenal glands showed that the shape of both adrenal glands was irregular, and multiple cyst-like low- density shadows with bed-like changes were seen locally, which was considered as multiple nodular hyperplasia. Laboratory tests showed that the patient had abnormal cortisol rhythm, increased cortisol secretion, and suppressed adrenocorticotropic hormone (Fig. 1). The patient's father had been diagnosed with adrenal hyperplasia and pituitary tumor, which underwent adrenalectomy, and his mother died of an accident. Based on the results of various examinations and clinical manifestations, we diagnosed the patient as PBMAH.

Examination results

Further examination was performed. Pituitary magnetic resonance imaging (MRI) showed a possible pituitary microadenoma and meningioma. Laboratory tests showed increased secretion of parathyroid hormone, progesterone and prolactin. The results of genetic testing also ruled out MEN1. After consideration, total adrenalectomy on the larger left side was performed. Pathology reported a left macronodular adrenal hyperplasia, multifocal, 2 cm to 3 cm in diameter. Immunohistochemical results: CK (-), CgA (-), Syn (-), Vim (+), Melan-A (+), Ki67 (+1%), Inhibinα (+). In contrast to adrenocortical adenomas, a small number of Ki67 values were reported.

Genetic testing

All participants and parents of minors provided written informed consent. We used DNA from the patient's peripheral blood as the detection material. First, the DNA was interrupted and a library was prepared, and then the DNA in the exon region of the target gene was captured and enriched by capture probes. Finally, high-throughput sequencing platform was used for mutation detection. We found a heterozygous mutation, NM_001105247.2:c.943 C>T (p.Arg315Trp), at chr16: 31,473,811, in the *ARMC5* gene, which was classified as likely pathogenic according to the ACMG standards. Although this mutation site has been reported by scholars, it has not been linked to pituitary tumor and meningioma [8]. In addition, no pathogenic or likely pathogenic variants were found in 78 genes related to

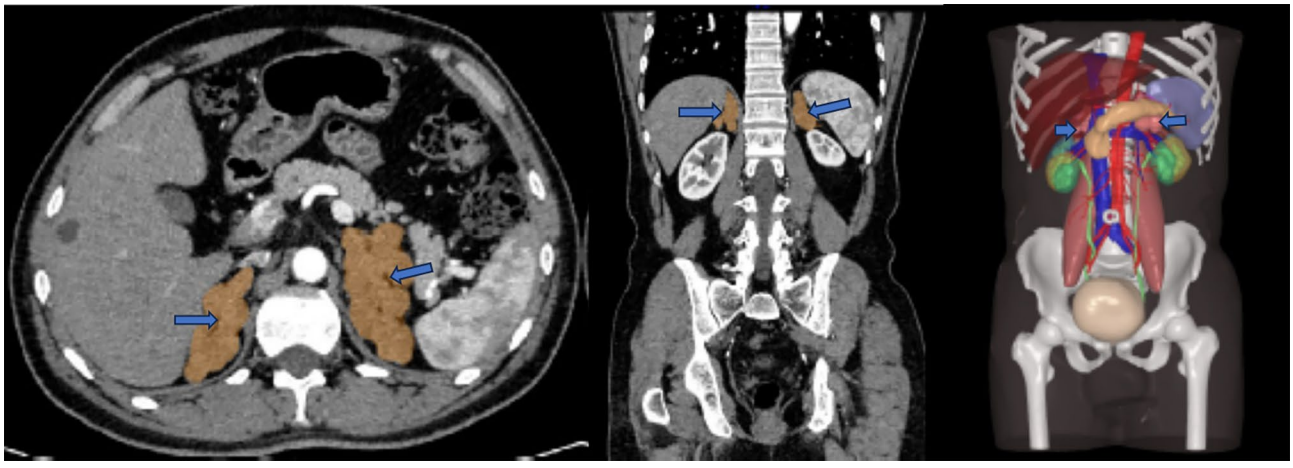

Fig. 1 CT examination revealed multiple adrenal nodules, many of which were larger than 1 cm in diameter. Blue arrows point to bilateral adrenal multiple nodules

monogenic genetic diseases. Subsequently, we performed targeted ARMC5 sequencing on his father, brother and two daughters, and found that the father and one of the daughters had the same gene mutation (Fig. 2). The daughter was doing well, with no manifestations of disease, but required active monitoring (Fig. 3). We recommended that she undergo CT of the adrenal gland and testing for cortisol and adrenocorticotropic hormone annually.

Discussion

PBMAH is a heterogeneous disease with a variety of clinical, hormonal, and imaging manifestations. Although sporadic cases are more common, it has also been linked to genetic syndromes such as multiple endocrine neoplasia type 1 (MEN1), familial adenomatous polyposis (FAP), or hereditary leiomyomatosis and renal cell carcinoma (HLRCC) [9]. The patient's clinical presentation, laboratory tests, imaging studies, and postoperative pathological findings all support the diagnosis of PBMAH, and whole-exome genetic testing helped us to rule out many genetic syndromes, although we did not perform genetic testing of adrenal glands, pituitary adenomas, or meningiomas. The incidence of CS ranges from 1.8 to 3.2 per million per year and the prevalence from 57 to 79 per million. About 20-30% of CS are caused by adrenal diseases, and CS caused by PBMAH is even rarer [10, 11]. PBMAH is thought to account for less than 2% of cases in a given series of CS patients [1]. *ARMC5* germline mutations are responsible for the majority of familial cases of PBMAH, while the *ARMC5* mutation rate is approximately 20-25% in sporadic index cases of PBMAH. *ARMC5* variants are present in 55% of PBMAH patients with severe CS [12]. Through comparison and research, scholars have confirmed that the condition of most patients with *ARMC5* mutations is more obvious than that of PBMAH patients without mutations, including cortisol secretion, adrenal morphology and metabolic complications [4].

ARMC5 germline mutations occur in combination with somatic heterozygous deleterious change of ARMC5, including copy-neutral loss of heterozygosity

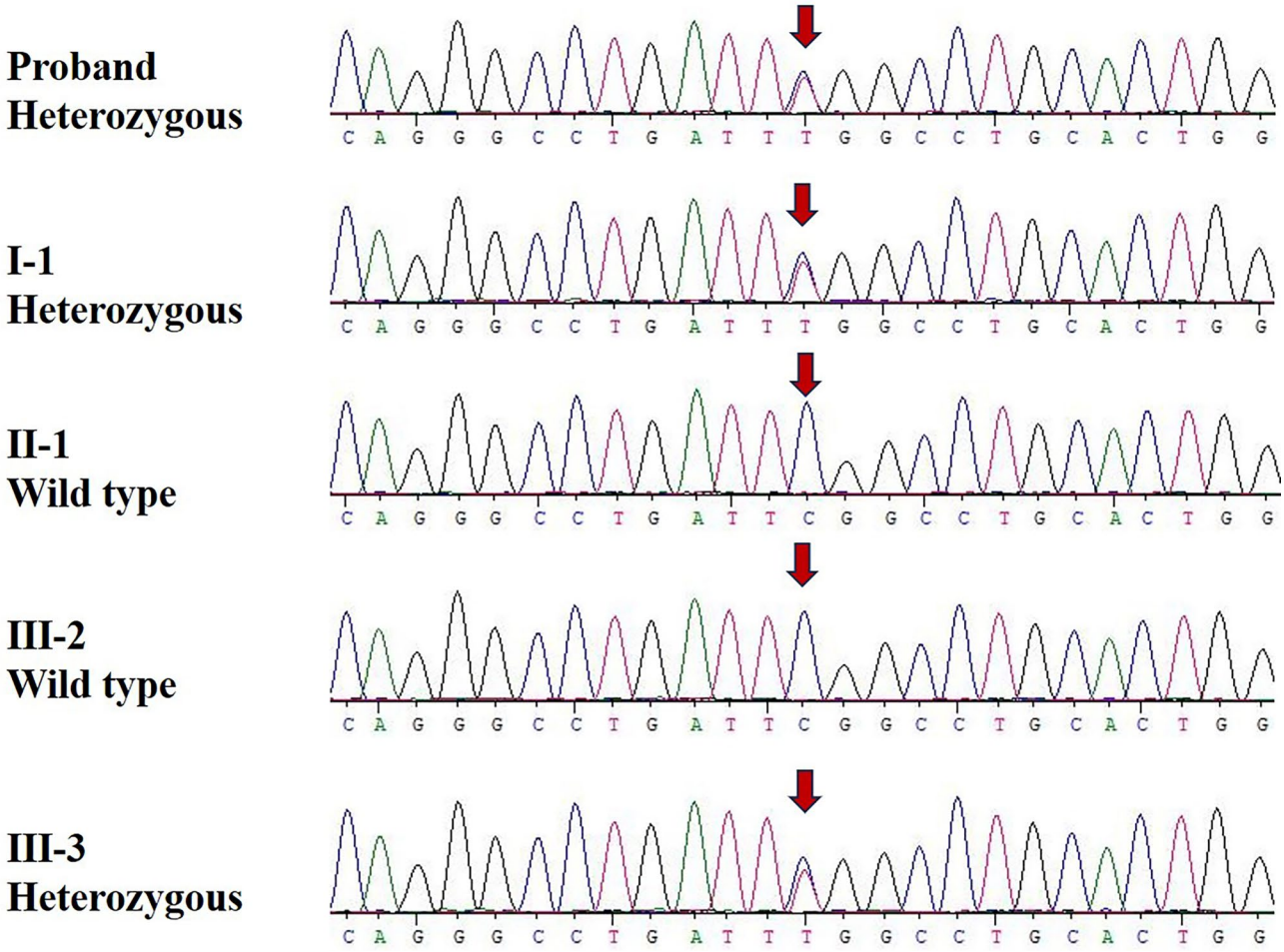

Fig. 2 *ARMC5* sequencing results. Heterozygous represent *ARMC5* mutation carriers. Wild type indicates no variation. The red arrow points to the mutation site

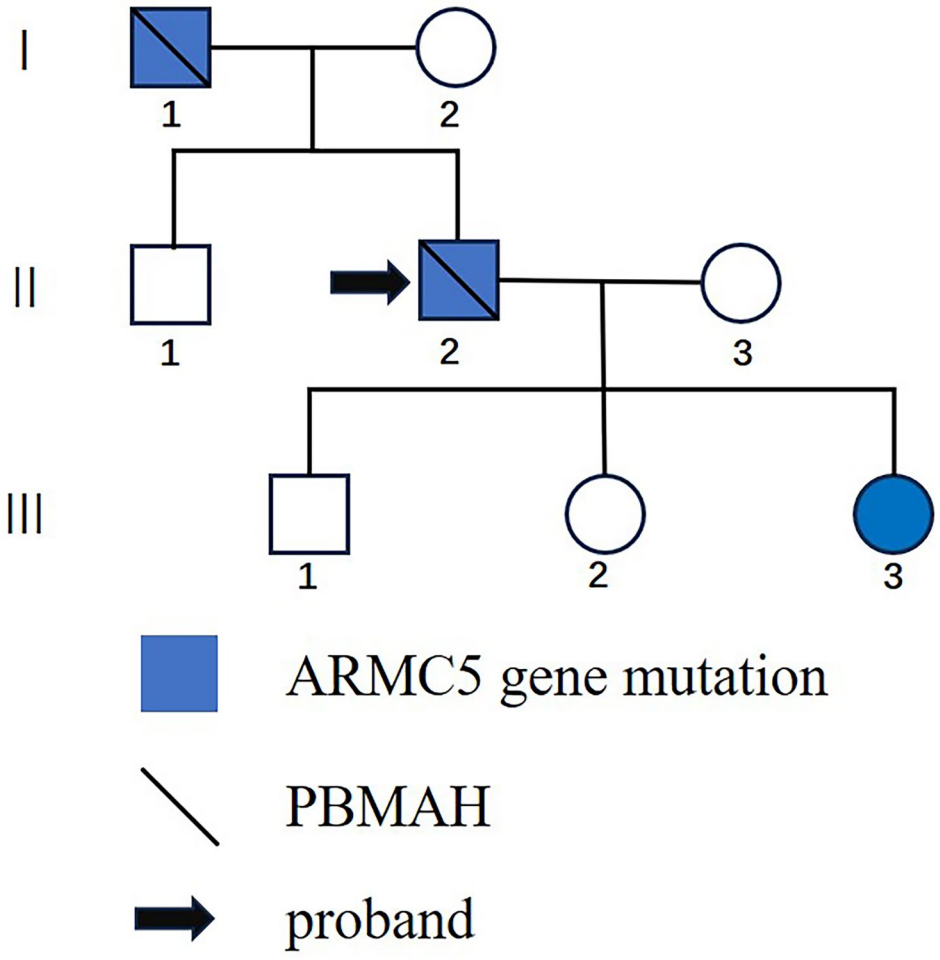

Fig. 3 Family tree. Black arrow points to proband. The proband had meningioma and pituitary microadenoma. I-1 is proband's father. He had Pituitary tumor

of chromosome 16p or point mutations, resulting in a bi-allelic inactivation of ARMC5, consistent with the tumor suppressor gene model [3]. It has been found that 16 of 20 adrenal cortical nodules have a second somatic variant in addition to the germline mutation. Even in a single patient, each adrenal nodule may contain unique somatic mutations [6].

ARMC5 as an adaptor of an ubiquitin ligase complex, which participates to the ubiquitination of many different substrates, including RPB1, sterol regulatory element-binding transcription factors (SREBF) and nuclear respiratory factor 1 (NRF1). *ARMC5* deletion caused a significant reduction of RBP1 ubiquitination leading to an accumulation of RPB1 protein, and hence an enlarged Pol II pool in normal tissues and organs. And such an enlarged Pol II pool and gene dysregulation was correlated to adrenal hyperplasia [13]. In addition to this, it has been confirmed when *ARMC5* protein mutations affect genetic variation in its BTB or Armadillo domains, leading to impaired ubiquitination of SREBF and NRF1, which leads to their stabilization and accumulation, and then affects transcription, steroidogenesis, and redox homeostasis [14, 15]. Cavalcante et al. cultured *ARMC5*-silenced PBMAH cells and found that their steroidogenic enzyme gene expression was reduced and their proliferation ability was enhanced [16]. This suggests that *ARMC5* inactivation leads to hyperplasia of adrenal tissue with a large increase in the total number of cells. Although the ability of the cells to produce steroids is reduced, the increase in the number of cells results in steroid overproduction. This may also explain why patients show no clinical signs in the early stages and are not detected until they are between the ages of 40 and 70 [17].

Conclusions

In conclusion, screening of family members of PBMAH patients with *ARMC5* germline mutations and active monitoring of family members carrying *ARMC5* variants are recommended, and relevant examinations should include brain imaging for early detection and early

treatment. The pattern of autosomal dominant inheritance is also supported by our report.

Abbreviations

PBMAH	Primary bilateral macronodular adrenal hyperplasia
CS	Cushing's syndrome
ARMC5	Armadillo repeatcontaining 5
MRI	Magnetic resonance imaging
MEN1	Multiple endocrine neoplasia type 1
FAP	Familial adenomatous polyposis
HLRCC	Hereditary leiomyomatosis and renal cell carcinoma
SREBF	Sterol regulatory element-binding transcription factors
NRF1	Nuclear respiratory factor 1

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Author contributions
W.S. and Y.W. wrote the main manuscript text. Y.W. prepared Figs. 1, 2 and 3. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The case report was waived by the Medical Ethics Committee of the First Hospital of Shanxi Medical University. Our study adhered to the Declaration of Helsinki. All participants and parents of minors provided written informed consent.

Consent for publication
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. All participants and parents of minors gave written informed consent for their personal or clinical details and any identifying images to be released in this study.

Competing interests
The authors declare no competing interests.

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References

1. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet (London England). 2015;386(9996):913–27.
2. Zhou J, Zhang M, Bai X, Cui S, Pang C, Lu L, et al. Demographic characteristics, etiology, and comorbidities of patients with Cushing's syndrome: A 10-Year retrospective study at a large general hospital in China. Int J Endocrinol. 2019;2019:7159696.
3. Bertherat J, Bourdeau I, Bouys L, Chasseloup F, Kamenický P, Lacroix A, Clinical. Pathophysiologic, genetic, and therapeutic progress in primary bilateral macronodular adrenal hyperplasia. Endocr Rev. 2023;44(4):567–628.
4. Bouys L, Vaczlavik A, Jouinot A, Vaduva P, Espiard S, Assié G, et al. Identification of predictive criteria for pathogenic variants of primary bilateral macronodular adrenal hyperplasia (PBMAH) gene *ARMC5* in 352 unselected patients. Eur J Endocrinol. 2022;187(1):123–34.
5. Lao L, Bourdeau I, Gagliardi L, He X, Shi W, Hao B, et al. *ARMC5* is part of an RPB1-specific ubiquitin ligase implicated in adrenal hyperplasia. Nucleic Acids Res. 2022;50(11):6343–67.
6. Correa R, Zilbermint M, Berthon A, Espiard S, Batsis M, Papadakis GZ, et al. The *ARMC5* gene shows extensive genetic variance in primary macronodular adrenocortical hyperplasia. Eur J Endocrinol. 2015;173(4):435–40.
7. Eghbali M, Cheraghi S, Samanian S, Rad I, Meghdadi J, Akbari H et al. A novel *ARMC5* germline variant in primary macronodular adrenal hyperplasia using Whole-Exome sequencing. Diagnostics. 2022;12(12).
8. Gagliardi L, Schreiber AW, Hahn CN, Feng J, Cranston T, Boon H, et al. *ARMC5*Mutations are common in Familial bilateral macronodular adrenal hyperplasia. J Clin Endocrinol Metabolism. 2014;99(9):E1784–92.
9. Cavalcante IP, Berthon A, Fragoso MC, Reincke M, Stratakis CA, Ragazzon B, et al. Primary bilateral macronodular adrenal hyperplasia: definitely a genetic disease. Nat Reviews Endocrinol. 2022;18(11):699–711.
10. Hakami OA, Ahmed S, Karavitaki N. Epidemiology and mortality of Cushing's syndrome. Best Pract Res Clin Endocrinol Metab. 2021;35(1):101521.
11. Wengander S, Trimpou P, Papakokkinou E, Ragnarsson O. The incidence of endogenous Cushing's syndrome in the modern era. Clin Endocrinol. 2019;91(2):263–70.
12. Assié G, Libé R, Espiard S, Rizk-Rabin M, Guimier A, Luscap W, et al. *ARMC5* mutations in macronodular adrenal hyperplasia with Cushing's syndrome. N Engl J Med. 2013;369(22):2105–14.
13. Lao L, Bourdeau I, Gagliardi L, He X, Shi W, Hao B, et al. ARMC5 is part of an RPB1-specific ubiquitin ligase implicated in adrenal hyperplasia. Nucleic Acids Res. 2022;50(11):6343–67.
14. Cavalcante IP, Rizk-Rabin M, Ribes C, Perlemoine K, Hantel C, Berthon A, et al. Tumor suppressor gene ARMC5 controls adrenal redox state through NRF1 turnover. Endocrine-related Cancer. 2022;29(11):615–24.
15. Okuno Y, Fukuhara A, Otsuki M, Shimomura I. ARMC5-CUL3 E3 ligase targets full-length SREBF in adrenocortical tumors. JCI Insight. 2022;7(16).
16. Cavalcante IP, Nishi M, Zerbini MCN, Almeida MQ, Brondani VB, Botelho MLAA, et al. The role of *ARMC5* in human cell cultures from nodules of primary macronodular adrenocortical hyperplasia (PMAH). Mol Cell Endocrinol. 2018;460:36–46.
17. Berthon A, Faucz FR, Espiard S, Drougat L, Bertherat J, Stratakis CA. Age-dependent effects of *ARMC5* haploinsufficiency on adrenocortical function. Hum Mol Genet. 2017;26(18):3495–507.

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