

REVIEW

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Apparent mineralocorticoid excess: comprehensive overview of molecular genetics

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Abstract

Apparent mineralocorticoid excess is an autosomal recessive form of monogenic disease characterized by juvenile resistant low-renin hypertension, marked hypokalemic alkalosis, low aldosterone levels, and high ratios of cortisol to cortisone metabolites. It is caused by defects in the *HSD11B2* gene, encoding the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which is primarily involved in the peripheral conversion of cortisol to cortisone. To date, over 50 deleterious *HSD11B2* mutations have been identified worldwide. Multiple molecular mechanisms function in the lowering of 11 β -HSD2 activity, including damaging protein stability, lowered affinity for the substrate and cofactor, and disrupting the dimer interface. Genetic polymorphism, environmental factors as well as epigenetic modifications may also offer an implicit explanation for the molecular pathogenesis of AME. A precise diagnosis depends on genetic testing, which allows for early and specific management to avoid the morbidity and mortality from target organ damage. In this review, we provide insights into the molecular genetics of classic and non-classic apparent mineralocorticoid excess and aim to offer a comprehensive overview of this monogenic disease.

Keywords Apparent mineralocorticoid excess, *HSD11B2* gene, 11 β -HSD2, Genetic testing, Hypertension, Non-classic

Introduction

Apparent mineralocorticoid excess (AME, OMIM: 218030) is a rare form of monogenic hypertension that is transmitted as an autosomal recessive trait. The clinical symptoms of AME were first reported in 1974 by Werder et al. in a 3-year-old girl with low birth weight, delayed growth, polydipsia, polyuria, and hypertension. In 1977, New et al. identified patients with similar symptoms, characterized their biochemical profiles, and named the disease AME [1, 2]. Initially, it was speculated that

HSD11B1 (encoding 11 β -hydroxysteroid dehydrogenase type 1 [11 β -HSD1]) was the causative gene but no mutation was detected in AME patients; thus, the focus was shifted to other candidate genes [3]. In 1995, Wilson et al. identified the first *HSD11B2* mutation in several siblings with typical characteristics of AME from a consanguineous Iranian family, unraveling the genetic defects of AME [4]. The molecular pathogenesis of AME primarily results from a deficiency in the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which is involved in the peripheral metabolism of cortisol [5, 6]. In 1999, Nunez et al. summarized the AME genotype–phenotype correlation by studying 14 affected children and proposed that clinical and/or biochemical parameters and enzyme activity were closely related [7].

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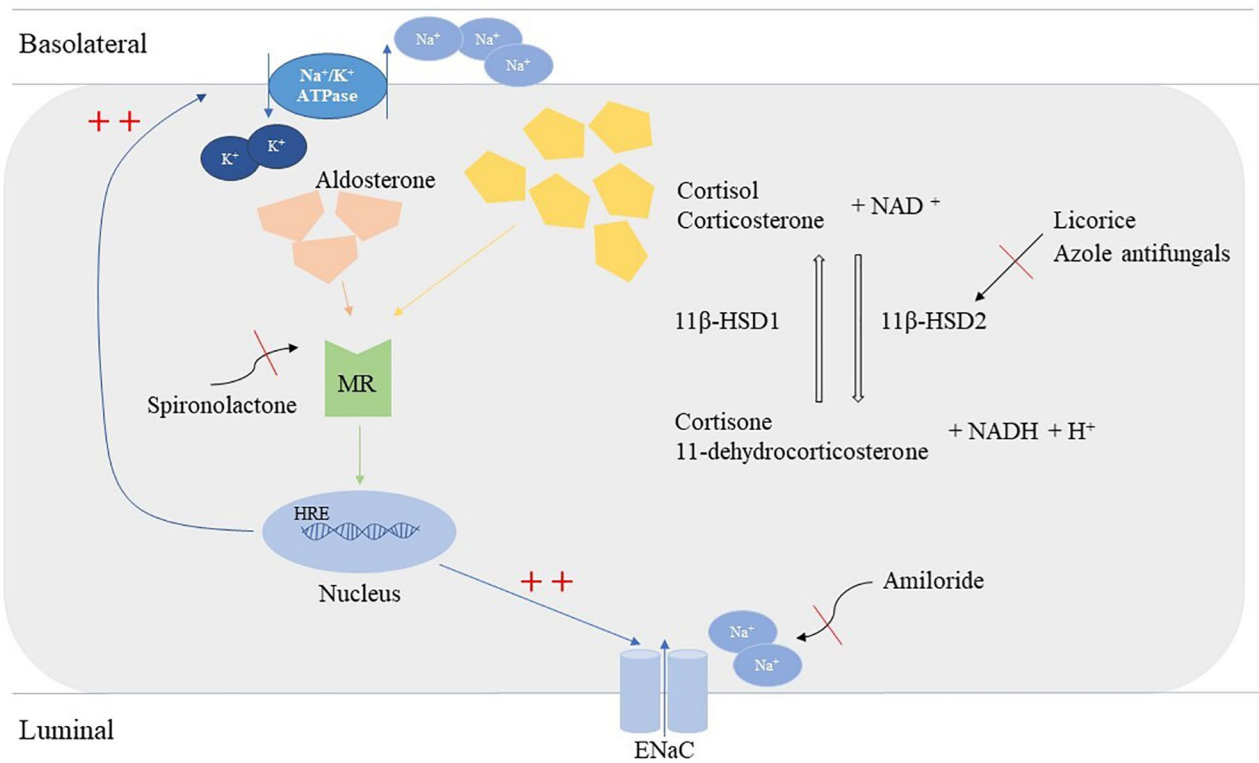


Fig. 1 Mechanisms of apparent mineralocorticoid excess syndrome. 11β-HSD2 enzyme facilitates the conversion from active cortisol to inactive metabolite form, cortisone; 11β-HSD1 has an opposing function. Physically, aldosterone and cortisol are both ligands of mineralocorticoid receptors, which results in binding to nuclear hormone response elements, leading to transcription of Na⁺/K⁺ ATPase and ENaC channels. The deficiency of 11β-HSD2 fails in the metabolism of cortisol and results in excessive mineralocorticoid, so as the over-ingestion of licorice and azole antifungals causes the same effects. Mineralocorticoid receptor blocker, spironolactone, could block the hyperactivation of mineralocorticoid receptors while amiloride blocks ENaC remarkably.

A timely diagnosis of AME is pivotal because continuous poor management of blood pressure and potassium can cause end organ damage such as early stroke, hypertensive myocardial hypertrophy, hypertensive retinopathy, and deterioration of renal function [8]. Genetic analysis, regarded as a unique method for the accurate diagnosis of disease, continually broadens the genetic spectrum of AME [9]. In recent decades, great progress has been made in understanding the pathogenesis of AME, which aids the development of targeted therapy [10] and a novel clinical condition with a mild phenotypic spectrum named non-classic AME was identified. Examining *HSD11B2*-related genetic or non-genetic determinants has important implications in understanding the special condition. This review summarizes the clinical presentation, pathophysiology, molecular genetic basis, and genetic testing of AME.

Pathophysiology

Cortisol is a hormone secreted by the zona fasciculata of the adrenal cortex, which plays a crucial role in cognition, development, metabolism, the immune system, and

the stress response [11, 12]. Cortisol levels are regulated by two isoforms of 11β-HSD: 11β-HSD1 and 11β-HSD2. 11β-HSD2 is widely distributed in various tissues, such as the brain, placenta, kidney, and colon [13], and facilitates the conversion of active steroid cortisol to its inactive metabolite form, cortisone; 11β-HSD1 has the opposing function (Fig. 1). Both cortisol and aldosterone are ligands of mineralocorticoid receptors (MRs). In vitro, MRs have equal affinity for both cortisol and aldosterone while in vivo MRs are much stronger for aldosterone than cortisol [14]. The role of 11β-HSD2 in cortisol metabolism is to mediate the ligand selectivity of aldosterone for MRs, and the full abolishment or partial activity loss of 11β-HSD2 leads to the continuous accumulation of cortisol and MR overstimulation following the upregulation of sodium reabsorption, increased potassium loss, and low-level renin [5, 15]. In addition, following the failure of the conversion of cortisol, the excretion of urinary cortisol metabolites tetrahydrocortisol (THF) and allo-THF increases and the cortisone metabolite tetrahydrocortisone (THE) decreases [16]. Moreover, it is worthy to note that 11β-HSD2 distributes more widely in the fetus than

after birth [17]. Feto-placental 11β -HSD2 is regarded as a 'glucocorticoid barrier' which ensures most maternal cortisol inactivated strictly determining the fetal homeostasis of cortisol [18]. Abolished 11β -HSD2 in the placenta causes the fetus to be over-exposed to maternal glucocorticoids, leading to the phenotype of intrauterine growth restriction associated to glucocorticoid receptor [19, 20].

Additionally, excessive ingestion of exogenous 11β -HSD2 inhibitors such as licorice and azole antifungals results in MR induced hypertension; thus, taking a detailed personal and pharmacological history is beneficial when identifying acquired forms of AME [21–23].

Phenotype of AME

AME is a rare disorder and the prevalence of AME across the hypertensive population has yet to remain unclear. Consistent with the nature of autosomal recessive inheritance, predominant causative mutations occur in consanguineous or endogamous groups or in families affected by a founder effect (Table 1) [8, 24–27]. Moreover, no sex predominance is distributed for the disease [28]. Depending on its phenotypic severity, AME can be divided into two forms: classic AME and non-classic AME (Table 2) [29].

Classic AME

Despite the abolishment of 11β -HSD2 leads to deranged cortisol metabolism and decreased urinary excretion of cortisol metabolites, patients with AME have normal serum cortisol concentration and don't present with clinical features of Cushing's syndrome or Addison's disease [14, 30]. Presumably, the prolonged cortisol half-life may result in the low rate of cortisol secretion because of normal hypothalamic-pituitary-adrenal axis (HPA) regulation effect [14, 31]. Classic AME usually starts in infancy to juvenile and typically manifests as low birth weight, refractory hypertension, delayed growth, polyuria and polydipsia, failure to thrive [32]. Marked hypokalemia, metabolic alkalosis, suppressed plasma renin activity, low levels of aldosterone, and increased urinary or serum cortisol to cortisone ratios are typical characteristics of classic AME. Additionally, nephrocalcinosis and renal cysts are common, possibly ascribing to chronic long-standing hypokalemia [33, 34].

Non-classic AME

Patients with non-classic AME, also known as AME type 2, present with milder phenotypes including slight hypertension and subtle biochemical disturbances, which is proposed as a novel clinical condition different from classic AME [32]. In the literature, non-classic AME is commonly presented in adolescents or adults which develops much later than classic AME. Mainly, non-classic AME is characterized by a high urinary cortisol/cortisone

ratio and low cortisone level [35]. Different from classic AME, blood pressure level of non-classic AME is normal or slightly elevated, approximately 141.0/88.5 mm Hg [36]. Recently, a cross-sectional study identified a partial defect of 11β -HSD2 in 7.1% of a primary care cohort in Chile [37].

These patients are often undetected, and the disease is not usually diagnosed until adulthood. By analyzing metabolic changes of non-classic AME patients and healthy controls, Tapia-Castillo et al. found gamma-L-glutamyl-L-methionine sulfoxide and 5-sulfoxymethylfurfural might be sensitive biomarker of non-classic AME [36]. Moreover, high levels of inflammatory markers, microalbuminuria, high-sensitivity C-reactive protein, plasminogen activator inhibitor-1 are indicated in non-classic AME [37].

Of note, some heterozygous AME subjects with a single pathogenic mutation display various manifestations, ranging from normal to mild or moderate phenotype [38, 39]. It is either haploinsufficiency or the dominant mutant negative effect that partially explain this phenotypic variability [38, 40].

Treatment and long-term follow-up

For the nature of AME is a kind of salt-sensitive hypertension, salt-limited diet is necessary for both classic and non-classic AME patients [41, 42]. Targeting the pathogenic pathway, MR antagonist (spironolactone or eplerenone) combined with potassium sparing diuretics are strongly recommended for both AME individuals with satisfactory curative effects. Generally, MR antagonist for classic AME at doses ranging from 2 to 10 mg/kg/day while low dose of MR antagonist (12.5–25 mg/day) is advised for non-classic AME [43, 44]. Glucocorticoids also have been administered for suppressing the secretion of endogenous adrenocorticotrophic hormone-mediated corticosteroid in adult classic AME patients [45]. Moreover, kidney transplantation has also been reported in classic AME patients which was shown to "cure" AME [46, 47]. So far, there is few data regarding the long-term follow-up of classic AME patients. Razzaghy-Azar et al. followed an Iranian family of three sibs affected with classic AME for 20 years and found that the eldest sibling with the longest delay in diagnosis developed left ventricular dysfunction and renal failure who had to undergo renal transplantation while other two sibs didn't suffer from end-organ damage [47]. In 2017, Yau et al. reported long-term follow-up results of a large series comprising 36 classic AME patients, including cardiovascular mortality (19%), persistence of nephrocalcinosis (89%), and kidney failure (15%) [28]. The long-term outcome associated with non-classic AME patients remains unclear.

Table 1 Clinical manifestations, biochemical profile of AME patients identified by genetic analysis

Patient	Family	Ethnicity	Consanguinity	Mutation	Gender	LBW	Clinical manifestations				Biochemical profile					Reference		
							Early-onset HT	GR	Hx of FTT	Hx of	PAC/PRA/PRC	MA	u	u F/E	Others			
1	1	Iranian	Y		F	Y	Y	Y	N	N	hypertensive ne-	↓	-	↑	-	-	[4, 8, 28]	
2	1	Iranian	Y		F	Y	Y	Y	Y	N	-	↓	↓	-	↑	-	[4, 8, 28]	
3	1	Iranian	Y		M	Y	Y	Y	Y	N	-	↓	↓	-	↑	-	[4, 8, 28]	
4	2	Indian	Y		M	-	Y	-	-	Y	LVH, Hx of hypokalemic paralysis	↓	↓	-	-	-	albuminuria	[76]
5	2	Indian	Y		M	-	Y	-	-	Y	LVH, Hx of hypokalemic paralysis	↓	↓	-	-	-	-	[76]
6	3	Native	-		M	-	Y	-	-	-	-	-	-	-	↑	-	-	[5]
7	4		N		M	Y	Y	Y	-	Y	facial palsy	↓	↓	Y	↑	-	-	[28, 78]
8	4		N		M	Y	Y	Y	-	Y	facial palsy	↓	↓	Y	↑	-	-	[28, 78]
9	5	Saudi Arabian	Y		F	Y	Y	Y	Y	Y	mild LVH	↓	↓	Y	-	↑	hypercalciuria	[79]
10	5	Saudi Arabian	Y		F	Y	Y	Y	-	Y	-	↓	↓	Y	-	↑	hypercalciuria	[79]
11	5	Saudi Arabian	Y		M	Y	Y	Y	-	Y	-	↓	↓	Y	-	↑	hypercalciuria	[79]
12	6	-	Y		F	Y	Y	Y	Y	Y	LVH, hypertensive retinopathy	↓	↓	Y	-	-	-	[80]
13	7	Native	-		F	-	Y	Y	Y	-	retinal vasoconstriction	↓	↓	-	↑	-	-	[5, 81]

Table 1 (continued)

Patient	Family	Ethnicity	Consanguinity	Mutation	Gender	LBW	Clinical manifestations					Biochemical profile					Reference		
							Early-onset HT	GR	Hx of FTT	Hx of				PAC/PRA/PRC	MA	u		u F/E	Others
14	7	Native	-		F	-	Y	Y	Y	Y	-	-	↓	-	-	↑	-	-	[5, 81]
15	8	Algerian	Y		M	N	Y	-	-	Y	Y	moderate LVH	↓	↓	Y	↑	-	hypercalciuria	[39]
16	9		N		F	Y	Y	-	-	-	Y	renal failure	↓	↓	Y	↑	-	-	[39]
17	10	Chilean	Y		F	Y	Y	-	-	-	Y	LVH	N	↓	-	↑	↑	-	[35]
18	11	Native	-		F	-	Y	-	-	-	-	-	-	-	-	↑	-	-	[5]
19	12	Native	-		M	-	Y	-	-	-	-	-	-	-	-	↑	-	-	[5]
20	13	Native	-		M	-	Y	-	-	Y	-	pyloric stenosis	↓	↓	Y	↑	-	-	[5, 81]
21	14	Native	Y		M	-	Y	Y	-	-	Y	-	↓	↓	-	↑	-	-	[78]
22	15	East Indian	N		M	Y	Y	Y	Y	Y	Y	LVH, hypertensive retinopathy	↓	↓	Y	↑	-	-	[5, 82, 83]
23	16	Iranian	N		M	Y	Y	-	-	-	N	-	↓	↓	-	↑	-	-	[28, 78]
24	17		N		M	-	Y	N	-	Y	N	-	↓	↓	-	↑	-	-	[78]
25	18		N		M	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28, 78]
26	19	Mexican/	-		F	-	HT	-	-	-	-	-	-	-	-	↑	-	-	[5]
27	20	Irish/	-		M	-	Y	-	-	-	-	-	-	-	-	↑	-	-	[5]
28	21	African	N		F	Y	Y	N	-	-	Y	hypertensive retinopathy, LVH	↓	↓	Y	↑	↑	-	[28, 78, 82]
29	21	African	N		F	N	Y	N	-	-	Y	LVH, cerebral palsy, deafness	↓	↓	Y	↑	↑	-	[28, 78, 82]
30	22	Brazilian	Y		M	Y	Y	Y	Y	Y	Y	mild LVH	↓	N	Y	-	-	hypercalciuria	[84]
31	23	Native	N		F	Y	Y	Y	Y	N	N	died of LVH	↓	↓	Y	↑	-	-	[2, 78]

Table 1 (continued)

Pa-tient	Fam-ily	Eth-nic-ity	Con-san-guini-ty	Mu-ta-tion	Gen-der	LBW	Clinical manifestations					Biochemical profile					Ref-er-ence		
							Ear-ly-onset HT	GR	Hx of FTT	Hx of	Hx of	Hx of	PAC/PRA/PRC	MA	u	u F/E		Oth-ers	
32	24	Asian	Y		M	-	Y	Y	Y	Y	Y	LVH, DI	↓	↓	Y	↑	↑	hy-per-calci-uria	[20, 85]
33	24	Asian	Y		M	-	Y	Y	-	Y	Y	-	↓	-	-	↑	-	hy-per-calci-uria	[20, 85]
34	24	Asian	Y		M	-	-	-	-	-	-	still-birth at 28	-	-	-	-	-	-	[20, 85]
35	24	Asian	Y		M	-	-	-	-	-	-	still-birth at 28	-	-	-	-	-	-	[20, 85]
36	25	Iranian	Y		M	-	Nor	-	Y	-	Y	-	↓	-	Y	-	-	-	[74]
37	26		N		F	Y	Y	-	-	-	-	di-lated aorta de-scen-dens,	↓	↓	Y	↑	-	-	[86]
38	26		N		M	Y	Y	Y	Y	Y	-	reti-nop-athy, sub-lux-ation of the ocu-lar lens-es, LVH, hy-dro-ne-phro-sis	↓	↓	Y	↑	-	-	[86, 87]
39	27	Bra-zilian	Y		F	-	Y	Y	Y	Y	-	noc-turia, reti-nop-athy, LVH	↓	↓	Y	↑	-	-	[88, 89]
40	28	Por-tu-	Y		M	N	Y	-	-	-	-	LVH, renal corti-cal atro-phy	↓	↓	N	↑	-	-	[39]

Table 1 (continued)

Pa-tient	Fam-ily	Eth-nic-ity	Con-san-guini-ty	Mu-ta-tion	Gen-der	LBW	Clinical manifestations					Biochemical profile					Ref-er-ence		
							Ear-ly-onset HT	GR	Hx of FTT	Hx of			PAC/PRA/PRC	MA	u	u F/E		Oth-ers	
41	28	Portu-	Y		M	N	Y	Y	-	-	-	LVH	↓	↓	N	↑	-	pro-tein-uria, hypercalci-uria	[39]
42	29	Japa-nese	N		M	N	Y	-	-	Y	-	reti-nop-athy, LVH	↓	↓	Y	↑	-	-	[49, 90]
43	30	Ital-ian/Mo-roc-can	N	L250R	M	Y	Y	N	Y	Y	Y	LVH, I-	↓	↓	Y	↑	-	hy-percalci-uria	[8]
44	31	Turk-ish	N		M	N	Y	N	Y	Y	Y	con-ge-ni-tal left ptosis	↓	↓	Y	↑	↑	-	[8, 28]
45	32	Italian	Y		F	-	HT	-	-	-	-	-	↓	-	-	↑	-	-	[91]
46	32	Italian	Y		M	-	Y	Y	-	Y	Y	-	↓	-	-	↑	-	-	[91]
47	32	Italian	Y		F	-	Y	Y	-	Y	Y	-	↓	-	-	↑	-	-	[91]
48	32	Italian	Y		F	-	HT	-	-	-	-	-	↓	-	-	↑	-	-	[91]
49	33		Y		F	N	Y	N	N	N	N	-	N	↓	N	↑	-	-	[28, 32]
50	34	Japa-nese	-		F	Y	Y	-	-	-	-	DI, paral-ysis	↓	-	-	↑	-	-	[7]
51	35	Cau-ca-sian/Aus-tra-lian	-	L179R	M	Y	Y	-	Y	-	Y	DI, LVH	↓	-	-	↑	↑	-	[7]
52	36	Cau-ca-sian	-		M	N	Y	-	-	-	-	-	↓	-	-	↑	↑	-	[7]
53	37	Cau-ca-sian	N		M	N	Y	-	-	Y	Y	mild LVH, renal cysts	↓	↓	Y	↑	-	-	[33]
54	38	Mex-ican-	-		F	N	Y	-	Y	-	-	DI	↓	-	-	↑	↑	-	[7]
55	39	-	Y		F	-	Y	Y	-	-	Y	LVH	↓	↓	Y	↑	↑	hy-percalci-uria	[55]
56	39	-	Y		M	-	Y	Y	-	-	Y	LVH	↓	↓	Y	↑	↑	hy-percalci-uria	[55]

Table 1 (continued)

Pa- tient	Fam- ily	Eth- nic- ity	Con- san- guin- ity	Mu- ta- tion	Gen- der	LBW	Clinical manifestations				Biochemical profile					Ref- er- ence			
							Ear- ly- onset HT	GR	Hx of FTT	Hx of	PAC/ PRA/ PRC	MA	u	u F/E	Oth- ers				
57	40		Y		M	Y	Y	-	Y	Y	Y	cardiac arrest (3.5 y)	↓	-	Y	↑	-	-	[9]
58	41	Cau- ca- sian	-		M	-	HT	-	-	Y	Y	nocturia, cardiac arrest (21 y), Ill-	↓	↓	-	↑	-	-	[38, 92]
59	42	Italian	N		F	-	Y	-	-	-	-	cerebral aneurysm	↓	↓	-	↑	↑	-	[38]
60	43	Cau- ca- sian	-		M	-	Y	-	-	-	-	type 1 diabetes, hypertensive renal damage	↓	↓	-	↑	-	-	[38]
61	44	Chil- ean	-		M	-	Y	Y	Y	Y	Y	-	↓	↓	-	-	-	[40]	
62	45	Ku- waiti	Y		F	Y	Y	Y	-	Y	Y	-	↓	↓	Y	↑	-	-	[44]
63	45	Ku- waiti	Y		F	N	Y	Y	-	-	Y	-	↓	-	Y	↑	-	-	[44]
64	46	-	-		F	Y	Y	-	Y	-	-	DI	↓	-	Y	-	-	-	[93]
65	47		Y	R74G	M	N	Y	-	Y	Y	Y	-	↓	-	Y	↑	-	-	[9]
66	47		Y	R74G	M	Y	Y	-	-	-	-	mild LVH, congestive heart failure (0.5y)	↓	-	Y	-	-	-	[9]
67	48		-	R74G	M	Y	Y	-	-	Y	N	mild LVH	↓	-	Y	↑	-	-	[9]
68	49		Y		M	Y	Y	-	Y	Y	N	mild LVH, respiratory failure (4.2 y)	↓	-	Y	↑	-	-	[9]
69	49		Y		F	Y	Y	-	Y	Y	N	-	↓	-	Y	↑	-	-	[9]
70	49		Y		F	Y	Y	-	-	-	Y	-	N	-	N	↑	-	-	[9]

Table 1 (continued)

Pa-tient	Fam-ily	Eth-nic-ity	Con-san-gui-nity	Mu-ta-tion	Gen-der	LBW	Clinical manifestations				Biochemical profile					Ref-er-ence			
							Ear-ly-onset HT	GR	Hx of FTT	Hx of	PAC/PRA/PRC	MA	u	u F/E	Oth-ers				
71	49		Y		F	Y	Y	-	Y	Y	N	-	↓	-	-	↑	-	-	[9]
72	50		-		M	Y	Y	-	Y	Y	-	mild LVH	↓	-	Y	↑	-	-	[9]
73	50		-		F	Y	Y	-	-	-	-	mild LVH	↓	-	-	-	-	-	[9]
74	51	Paki-stani	Y		F	Y	Y	-	-	-	Y	dila-tion of the aortic root, reti-nop-athy	↓	↓	Y	↑	-	-	[50]
75	52		N		M	N	Y	Y	-	-	N	LVH, te-tanic con-vul-sions	↓	↓	N	↑	-	-	[39]
76	53		-		F	Y	Y	-	-	-	N	LVH	N	↓	N	↑	-	-	[39]
77	54		-		F	-	Y	-	Y	Y	Y	Cof-fin-Siris syn-	↓	↓	Y	-	-	-	[94]
78	55	Mo-roc-can	Y		M	N	Y	N	-	-	Y	mild LVH	↓	↓	Y	↑	-	-	[39]
79	56		-		F	Y	Y	Y	Y	Y	-	end-stage renal fail-ure, sub-	↓	↓	-	Plas-ma ↑	Plas-ma ↑	-	[1, 52]
80	57		Y		M	N	Y	N	-	-	N	-	↓	↓	Y	-	-	-	[95]
81	58		Y		M	N	Y	N	-	-	N	mild LVH	↓	↓	-	↑	-	-	[25]
82	58		Y		M	N	Y	N	-	-	-	-	↓	↓	-	↑	-	-	[25]
83	59	Qatari	Y	G89D	F	Y	Y	Y	Y	-	-	LVH, cyst fibro-sis	↓	↓	Y	-	-	-	[24]
84	59	Qatari	Y	G89D	M	Y	Y	Y	-	-	-	distal ileal ob-struc-tion, LVH, cyst fibro-sis	↓	↓	Y	-	-	-	[24]
85	60		Y		M	Y	Y	-	Y	Y	Y	aortic root dila-tion	↓	↓	N	-	-	-	[56]

Table 1 (continued)

Patient	Family	Ethnicity	Consanguinity	Mutation	Gender	LBW	Clinical manifestations					Biochemical profile					Reference		
							Early-onset HT	GR	Hx of FTT	Hx of	Hx of	PAC/PRA/PRC	MA	u	u F/E	Others			
96	65	-		F367I	F	Y	Y	Y	-	Y	Y	renal medullary cysts, LVH	↓	-	N	-	-	-	[98]
97	-		Y		F	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28]
98	-		Y		F	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28]
99	-		Y		M	Y	Y	-	-	-	Y	-	↓	↓	N	↑	-	-	[28]
100	-		Y		F	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28]
101	-		Y		M	Y	Y	-	-	-	Y	-	↓	↓	Y	-	-	-	[28]
102	-		Y		M	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28]
103	-		Y		M	Y	Y	-	-	-	N	-	↓	↓	N	-	-	-	[28]
104	-		Y		M	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28]
105	-		Y		M	Y	Y	-	-	-	Y	-	↓	↓	N	↑	-	-	[28]
106	-		Y		F	Y	Y	-	-	-	Y	-	↓	PAC ↓ PRA ↑	N	-	-	-	[28]
107	-		Y		F	Y	Y	-	-	-	Y	-	↓	↓	N	-	-	-	[28]
108	-		Y		M	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28]
109	-		Y		F	Y	Y	-	-	-	Y	-	↓	↓	Y	-	-	-	[28]
110	-		Y		M	Y	Y	-	-	-	Y	-	↓	↓	Y	↑	-	-	[28]

AME, apparent mineralocorticoid excess; *Italic mutations* mean compound heterozygous mutations; -, not available; Y, yes; N, normal; M, male; F, female; LVH, left ventricular hypertrophy; PAC, plasma aldosterone concentration; PRC, plasma renin concentration; PRA, plasma renin activity; MA, metabolic alkalosis; LBW, low birth weight (defined as less than 2.5 kg); early-onset hypertension is defined as an increase in blood pressure aged 18 years or less; Hx of FTT, history of failure to thrive; Hx of polyu/polyd, history of polyuria/polydipsia; GR, growth retardation; DI, nephrogenic diabetes insipidus; u THFs/THE, urinary (tetrahydrocortisol + 5 α -tetrahydrocortisol)/ tetrahydrocortisol or urinary (tetrahydrocortisol + allo-tetrahydrocortisol)/ tetrahydrocortisol; u F/E, urinary cortisol to cortisone; the italics represent complex heterozygous mutations

Genetics of AME

HSD11B2 gene

The *HSD11B2* gene is located on chromosome 16q22.1, has an approximate length of 6.2 kb, and consists of five exons [48]. Since the first *HSD11B2* mutation (p.Arg337Cys) was identified, a total of 51 deleterious mutations have been reported that are causative of AME (Fig. 2) [4]. Most pathogenic mutations occur in exons 3–5, indicating that these regions are critical for maintaining stable activity of 11 β -HSD2 and/or have an active tendency to mutate [49]. Missense mutations at single points are the most frequent mutation type, although nonsense, frameshift, and splicing mutations leading to truncated, inactive proteins, have also been discovered at low rates. Several harmful splicing mutations have been reported that have varying effects on enzyme activity. For example, the nucleotide substitution of C to T in intron 3 (*IVS3+14 C>T*) changes the structure of the pre-mRNA, affects normal splicing, and results in the absence of exon 4 which encodes the catalytic domain; thus, the translated 11 β -HSD2 protein is inactive [5, 7, 40]. The *IVS3+1G>A* mutation affects the splice donor

site, causing incomplete expression of exon 3. This allows some normal splicing thus constituting moderate impairment of 11 β -HSD2. However, the mutant partially reserves some normal splicing process followed by a moderate impairment in 11 β -HSD2 [38]. Although the *de novo* mutation c.771 C>G, identified in a Caucasian family, is silent (p.Val254Val), the mutant minigene contains an aberrant consensus donor splice site that results in a premature truncation in exon 5 [38].

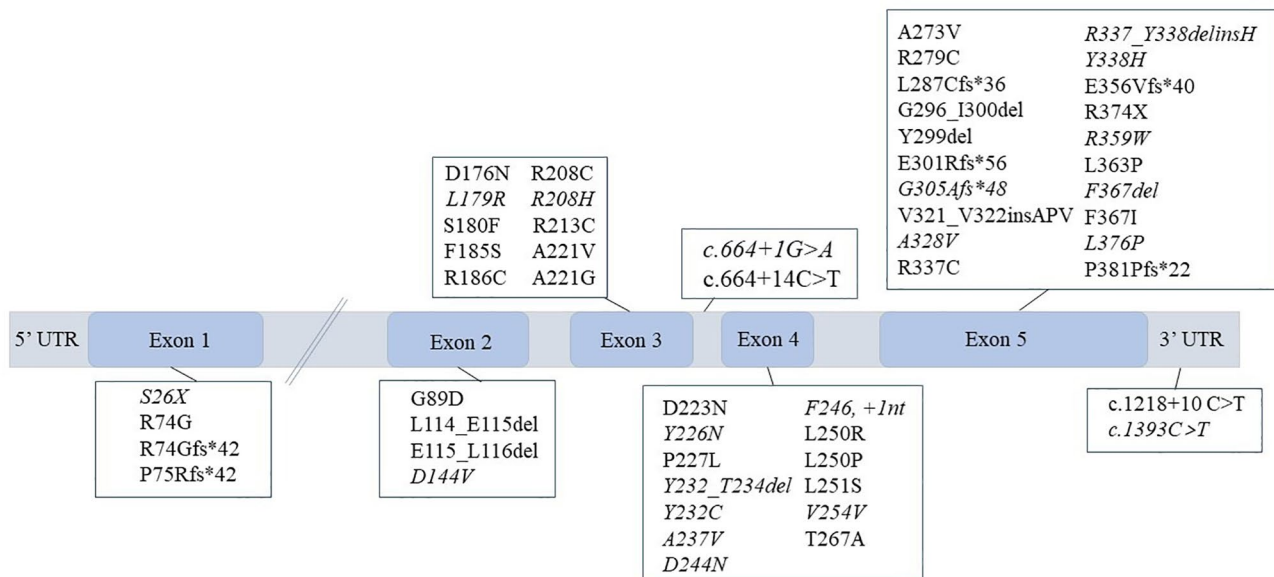
Molecular pathogenesis of classic AME

11 β -HSD2 is a nicotinamide adenine dinucleotide (NAD)-dependent dehydrogenase of 405 amino acids that contains two main domains: the cofactor (NAD⁺) binding region and the substrate binding region. 11 β -HSD2 only functions in its catalytic role when the coenzyme binding site binds to NAD⁺ and the substrate binding site binds to cortisol. Previous work established mutant transfectants to investigate enzyme activity and expression in vitro or used an *in silico* model to predict potential impacts on protein function, thereby identifying possible pathogenic mechanisms [40, 50, 51]. Any mutations potentially influencing protein stability, the affinity

Table 2 Indicative symptoms and markers suggested for classic AME and non-classic AME

	Classic AME	Non-classic AME
Phenotypes		
Range of age at diagnosis	Infant to juvenile	Adolescent to adult
Blood pressure	III grade hypertension or higher	Normal /mild hypertension
History of polyuria and polydipsia	Y	N
Pre- and postnatal growth failure	Y	N
Failure to survive	Y	N
Markers		
Electrolyte	Hypokalemia	Normal
Plasma renin activity	Low	Low
Plasma aldosterone level	Low	Normal
Urinary F/E	High	Slightly increased
Urinary THF + allo-THF/THE	High	Normal/slightly increased
Others	Exosomal urinary HSD11B2 mRNA	Microalbuminuria, plasminogen activator inhibitor-1, sensitivity c-reactive protein, L-dopachrome, gamma-L-glutamyl-L-methionine sulfoxide, 5-sulfoxymethylfurfural, S-phenylmercapturic acid, bilirubin, L-iditol, deoxyribose 1-phosphate, citric acid TNF

AME, apparent mineralocorticoid excess; Y, yes; N, normal; F, cortisol; E, cortisone; THF, tetrahydrocortisol; THE, tetrahydrocortisone

**Fig. 2** Mutant spectrum of *HSD11B2* gene. The italics represent compound heterozygous mutations, and the rest are homozygous mutations.

to the substrate or cofactor, and the dimer interface have been found to impair enzymatic activity and cause classic AME [38, 51–53]. Moreover, genetic polymorphism, environmental factors as well as epigenetic modifications may also offer an implicit explanation for the molecular pathogenesis of non-classic AME by having an increased salt appetite or affecting *HSD11B2* expression.

Impaired stability of 11 β -HSD2 protein

The loss of 11 β -HSD2 protein stability accelerates its degradation rate in a pathway thought to contribute to the development of classic AME. The functional validation of mutant 11 β -HSD2 in vitro by Nunez et al. revealed a more significant reduction in the enzymatic activity of mutants Ser180Phe, Ala237Val, and Ala328Val in cell lysates than in whole cells, indicating impaired enzyme stability [7]. The Arg/Tyr amino acid cluster (residues

335–339) has been shown to be of great importance for 11 β -HSD2 stability [52]. Several AME cases carrying mutations at this cluster have been reported to have significantly decreased 11 β -HSD2 activity [4, 5, 49, 52]. As enzymatic stability decreases, the mutant protein degradation rate increases, and its half-life reduces. Compared with wild-type 11 β -HSD2 with a half-life of 21 h, Tyr338His and Arg337Cys mutations reduce the half-life to 3 and 4 h, respectively [52]. Of note, the Tyr338His mutation disrupted the normal endoplasmic reticulum and microsome localization of 11 β -HSD2, and the mutant protein was detected in perinuclear bodies which also may influence its stability [52].

Attenuated affinity for the substrate

The substrate binding region of 11 β -HSD2 is composed of a chain of highly conserved residues, and it is thought that the catalytic activity mechanism may rely on the interaction between specific hydrophobic residues with cortisol. Pizzolo et al. identified the novel homozygous Ala221Gly substitution, which had a severely deleterious effect on 11 β -HSD2 activity [25]. As shown in an *in silico* model, the hydrophobic side chain of Ala221 causes it to be closely associated with the substrate binding site. However, the conversion of alanine to the polar hydrophilic amino acid glycine destroys the local hydrophobic environment and attenuates the affinity of 11 β -HSD2 for cortisol [25]. Similarly, the Tyr226Asn mutation alters the hydrophobic side chain to a hydrophilic one, which attenuates hydrophobic interactions and disrupts the substrate interaction [28]. Recently, Wang et al. showed that the substrate–protein interaction site might be located in a shallow pocket within residues 357–367 [54]. They also detected a novel missense mutation, Leu363Pro, with decreased affinity for cortisol that appears due to lack of local hydrophobicity [54].

Blunted affinity to the cofactor

Specific mutations associated with the coenzyme binding pocket in 11 β -HSD2 enzyme weaken its affinity for NAD⁺. In 2001, Odermatt identified a consecutive deletion mutation (Leu114_Glu115del) in *HSD11B2*, which is the first site shown to decrease the affinity of the protein for the coenzyme. They found that the negative charge of glutamic acid at position 115 reduced the binding preference for NAD⁺. Moreover, the loss of amino acids Leu114 and Glu115 led to an abnormal conformation of the coenzyme binding region and disturbed the transformant efficiency of the electron [55]. More recently, Yau et al. observed that the hydroxyl side chain of threonine at site 267 interacts with the amide nitrogen of the coenzyme to form a hydrogen bond, which helps the NAD⁺ localize with coenzyme binding domain. The Thr267Ala missense mutation impairs the hydrogen bond structure,

thus affecting the alignment of NAD⁺ in the coenzyme binding pocket [56]. By constructing a model of the Asp223Asn mutant protein structure, Carvajal et al. found that alterations in the electrostatic potential of the enzyme surface contribute to weakening its affinity for NAD⁺ [40].

Disruption of the dimer interface

11 β -HSD2 functions as a monomer, or a homodimer under inactive conditions [57, 58]. The dimer interface consists of a portion of helix, including vital residues such as Arg186, Ala237, Asp244, and Leu251 and so on [28, 51]. By disrupting inter-subunit ion pair interactions, hydrogen bond interactions, or salt bridge interactions at the interface, mutations can enhance the formulation of homodimers, thus abolishing the activity of 11 β -HSD2 [28].

Other potential mechanisms associated with non-classic AME

Excessive dietary salt intake is a known risk factor and the appetite for salt is susceptible to the activity of 11 β -HSD2 in the brain. In the adult brain, the only site where MRs and 11 β -HSD2 are co-expressed is inside the nucleus of the solitary tract, while the subcommissural organ and the ventromedial hypothalamic nucleus merely express 11 β -HSD2 [59]. Notably, all of these regions are involved in modulating the appetite for salt [59–61]. Previously, Ingram et al. reported a case of AME with an increased salt appetite [62]. Moreover, animal model observed that basal blood pressure of brain-specific *HSD11B2* knockout mice was similar to that of healthy control mice, but they gradually went on to develop hypertension for a three-fold increased salt consumption that could be inhibited by spironolactone [63]. It has been speculated that defective 11 β -HSD2 in both central and renal systems simultaneously affects sodium homeostasis and contributes to the phenotype of hypertension [63].

As well as genetic deficiencies, epigenetic modifications also play a crucial role in regulating *HSD11B2* expression in the onset of hypertension with underlying defects in 11 β -HSD2 [64]. By analyzing *HSD11B2* expression *in vitro* and *in vivo* in rats, Alikhani-Koopaei et al. found that high methylation of CpG islands in the *HSD11B2* promoter reduced gene expression, which was potentially associated with hypertension, and that the inhibition could be reversed by inducing demethylation [65]. A close relationship exists between the extent of *HSD11B2* promoter DNA methylation and adverse birth outcomes, such as low birth weight and insufficient gestational age at delivery, emphasizing the inhibiting effect of placental DNA methylation in fetal intrauterine growth [66, 67]. In addition, it is reported that the downregulation expression of miRNA (miR-192-5p and miR-204-5p) in urinary

exosomes also plays a potential role regulating the phenotype [68]. Santis et al. identified that the expression level of exosomal urinary *HSD11B2* mRNA was closely associated with the hypertension phenotype [69].

In terms of genetic polymorphism, Alikhani-Koupaei et al. found that frequent G209A polymorphism was associated with salt sensitivity that reduced the transcription and expression of *HSD11B2* by hindering the binding of nuclear factor 1 and glucocorticoid receptor to its promoter [70]. Collectively, genetic or epigenetic modifications as well as environmental factors (age, sodium intake) may compose multiple hits, responsible for the molecular genetics of AME phenotypic differences [71–73].

Genetic testing for AME

If not diagnosed and treated in time, chronic hypertension and hypokalemia alkalosis may cause extensive, severe consequences, including diseases of the renal, central nervous, cardiovascular, and retinal systems, or even sudden fatality [8]. We suggest that patients with clinical symptoms resembling AME should undergo 24-h urinary steroid quantification to determine the profile of cortisol and cortisol metabolites. Traditional laboratory evaluation findings have been shown to be ambiguous in terms of ruling out other monogenic disorders with similar clinical and hormonal patterns, such as Liddle syndrome, Batter syndrome and primary glucocorticoid resistance [10, 74, 75].

Identifying specific causative mutations utilizing genetic testing is a confirmatory tool in the diagnosis of AME. Because 11 β -HSD2 can be deficient in low-renin hypertensives, genetic testing of *HSD11B2* is required to screen for AME, especially in patients with a clinical history or increased cortisol to cortisone ratios [32]. Moreover, with an increasing number of asymptomatic cases detected among individuals with a positive family history, it is necessary to conduct genetic counseling in affected families to clarify genetic involvement [56]. Patients with high-risk pathogenic mutations require close monitoring to ensure that the disease is well controlled [8, 38]. Initially, Wilson et al. designed the intron and exon derived primer sequences of the targeted gene for repeat PCR amplification of exons and discovered an identical mis-sense mutation site in two affected siblings [4]. Since then, more causative mutations have been discovered. Promisingly, as next-generation sequencing technology becomes more common, whole exome sequencing has emerged as a cost-effective tool to detect pathogenic mutations, and to be particularly suitable in patients with atypical and overlapping clinical features or for whom biochemical profiles are unavailable [74, 76, 77].

Conclusion

In summary, AME is an autosomal recessive form of infant or juvenile low-renin hypertension caused by deleterious mutations in *HSD11B2*. Such mutations disrupt the stability of the protein or dimer interface, and cause a loss of affinity for substrate and/or cofactor, thus attenuating or abolishing 11 β -HSD2 activity. Because of the heterogeneity of AME clinical manifestations, it is challenging to accurately diagnose the disease early in clinical practice. Genetic testing is pivotal in the precise identification of AME and guides subsequent treatment to prevent end organ damage and sudden death. Considering the potential mechanisms of non-classic AME, genetic polymorphism, environmental factors as well as epigenetic modifications associated with *HSD11B2* should be highlighted.

Abbreviations

11β-HSD2	11 β -hydroxysteroid dehydrogenase type 2.
AME	Apparent mineralocorticoid excess.
11β-HSD1	11 β -hydroxysteroid dehydrogenase type 1.
MRs	Mineralocorticoid receptors.
NAD	Nicotinamide adenine dinucleotide.

Authors' contributions

YTL and XLZ were responsible for conceiving the ideas. YTL, QYZ, DZ, ZMZ wrote different parts of the manuscript. All authors read and approved the final manuscript.

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Data Availability

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Declarations

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

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