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Two decades of presumed Liddle syndrome: biochemical reverse phenotyping reveals apparent mineralocorticoid excess despite a coexisting SCNN1B variant: a case report

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Case Report

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Abstract

Background

Apparent mineralocorticoid excess (AME) is a rare autosomal recessive disorder caused by deficiency of 11β-hydroxysteroid dehydrogenase type 2, in which cortisol activates the mineralocorticoid receptor. AME is clinically and biochemically near-identical to Liddle syndrome, yet the two differ in mechanism and in optimal targeted therapy. The growing use of multigene panels increasingly yields variants of uncertain significance in genes with overlapping phenotypes, creating diagnostic ambiguity that genetic testing alone cannot resolve. We report how targeted biochemical phenotyping adjudicated a genuinely conflicting panel result.

Case presentation

A woman in her early thirties had been managed since childhood under a presumptive diagnosis of Liddle syndrome, with longstanding hypertension, recurrent symptomatic hypokalemia, metabolic alkalosis, and renal potassium wasting despite amiloride and potassium supplementation. Multigene panel testing identified a homozygous likely pathogenic *HSD11B2* variant (p.Ala237Val) together with a heterozygous *SCNN1B* variant of uncertain significance (p.Met395Ile) — two findings pointing to the two overlapping disorders. Twenty-four-hour urinary steroid profiling demonstrated a urinary free cortisol-to-cortisone ratio of 20.2 (normal approximately 0.54), providing direct biochemical evidence of impaired 11β-HSD2 activity and establishing AME as the dominant mechanism. The *SCNN1B* variant lay outside the PY motif where pathogenic Liddle-associated mutations cluster, arguing against Liddle syndrome. Addition of spironolactone to existing therapy was followed by normalization of serum potassium over three months of follow-up, consistent with the biochemical diagnosis.

Conclusions

This case demonstrates that biochemical reverse phenotyping remains essential for interpreting multigene panels when variants are found in genes with overlapping phenotypes. Urinary steroid profiling distinguished a causative *HSD11B2* variant from an incidental *SCNN1B* variant of uncertain significance, illustrating a diagnostic principle of broad relevance as genomic testing becomes routine in the evaluation of monogenic hypertension.

Background

Apparent mineralocorticoid excess (AME) is a rare autosomal recessive disorder caused by loss-of-function mutations in *HSD11B2*, encoding 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) [1–4]. Under physiological conditions, 11β-HSD2 converts cortisol to cortisone in mineralocorticoid target tissues, thereby protecting the mineralocorticoid receptor (MR) from inappropriate activation by cortisol,

which circulates at concentrations 100- to 1000-fold higher than aldosterone [1–4]. Deficiency of 11β-HSD2 permits cortisol-mediated MR activation, producing hypertension, hypokalemia, metabolic alkalosis, and renal potassium wasting [1–4].

Many deleterious *HSD11B2* mutations have been identified worldwide, predominantly in consanguineous kindreds [1]. Although classic AME typically presents during childhood with severe hypertension, low birth weight, failure to thrive, and nephrocalcinosis, nonclassic phenotypes associated with residual enzymatic activity are increasingly recognized and may present in adulthood with milder manifestations that overlap with essential hypertension [1, 4, 5]. Genotype–phenotype correlations have been established through *in vitro* expression studies and computational structural modeling, demonstrating that the biochemical severity of AME is largely determined by the degree of residual 11β-HSD2 enzymatic activity [5–8].

The expanding use of multigene hypertension panels has introduced a new diagnostic challenge: the identification of variants of uncertain significance (VUS) in genes associated with phenotypically overlapping disorders. Interpretation of such findings requires integration of genomic data with biochemical and physiological phenotyping rather than reliance on sequencing results alone. We report a patient with longstanding presumed Liddle syndrome in whom genetic testing identified both a homozygous likely pathogenic *HSD11B2* mutation and a heterozygous *SCNN1B* VUS. Biochemical reverse phenotyping using urinary steroid profiling established AME as the dominant disease mechanism. To our knowledge, the resolution of such a genuinely conflicting panel result by targeted biochemical phenotyping — with this *HSD11B2* variant diagnosed only in adulthood despite a biochemical severity within the classic AME range — has not been previously reported. Moreover, to our knowledge, this is the first reported patient homozygous for p.Ala237Val. This report follows the CARE guidelines (Additional file 1).

Case presentation

We describe a 31-year-old woman with longstanding hypokalemia and hypertension. According to historical medical records, she had carried a presumptive diagnosis of Liddle syndrome since childhood and had been treated intermittently with amiloride, potassium supplementation, and antihypertensive therapy for many years before she first presented to our institution. Documentation supporting the original diagnosis was unavailable for review.

She first presented to our institution in 2016 at age 21 with recurrent palpitations, fatigue, generalized weakness, and intermittent numbness associated with persistent hypokalemia. The earliest documented blood pressure was 140/86 mmHg in 2016, with subsequent measurements ranging between 148/82 mmHg and 172/82 mmHg over several years despite antihypertensive therapy. Body mass index was 32 kg/m². There was no known family history of early-onset hypertension, hypokalemia, endocrine disorders, or renal tubular disease. Consanguinity between the parents was unknown. Birth weight was unavailable.

Renal function remained preserved with serum creatinine approximately 80 µmol/L. Amlodipine 10 mg daily was initially prescribed. Amiloride, reportedly used since childhood for the presumed diagnosis, was continued at 20 mg once daily and documented in our electronic health record from 2016 because of persistent renal potassium wasting and hypokalemia. Potassium chloride supplementation was later added, with requirements varying between 10 and 120 mmol/day.

Twenty-four-hour urinary potassium excretion measured 55 mmol/day despite hypokalemia (serum potassium 2.3–3.5 mmol/L), with 24-hour urinary sodium of 150 mmol/day indicating adequate sodium intake, consistent with inappropriate renal potassium wasting. Serum bicarbonate values frequently ranged between 30 and 36 mmol/L, consistent with chronic metabolic alkalosis. Key biochemical findings are summarized in Table 1, and the clinical timeline is depicted in Fig. 1.

Table 1
Key biochemical findings

Parameter	Result	Reference range	Interpretation
Serum potassium	2.3–3.5 mmol/L	3.5–5.1 mmol/L	Persistent hypokalemia
Serum bicarbonate	30–36 mmol/L	22–29 mmol/L	Metabolic alkalosis
Serum creatinine	~ 80 µmol/L	Normal	Preserved renal function
24-hour urinary potassium	55 mmol/day	25–125 mmol/day	Inappropriately elevated for the degree of hypokalemia; renal potassium wasting
24-hour urinary sodium	150 mmol/day	40–220 mmol/day	Normal dietary sodium intake
Direct renin concentration	7.7 µIU/mL	4.2–59.7 µIU/mL	Low-normal; inappropriately non-elevated on amiloride
Plasma aldosterone	< 3.7 ng/dL (below detection)	Supine < 31.0; upright < 43.2 ng/dL	Low
Urinary free cortisol (UFF)	83 µg/24 h	3.5–45 µg/24 h	Elevated
Urinary free cortisone (UFE)	4.1 µg/24 h	17–129 µg/24 h	Markedly suppressed
UFF/UFE ratio	20.2	0.54 ± 0.05	Markedly elevated; consistent with AME

AME apparent mineralocorticoid excess, UFF urinary free cortisol, UFE urinary free cortisone

Plasma direct renin concentration was 7.7 µIU/mL (supine reference 4.2–59.7 µIU/mL; upright 5.3–99.1 µIU/mL), within the lower part of the reference range and inappropriately non-elevated given chronic amiloride therapy, while plasma aldosterone was below the limit of detection (< 3.7 ng/dL; supine

reference < 31.0 ng/dL, upright < 43.2 ng/dL). Because amiloride raises renin and aldosterone, these values likely underestimate the true degree of suppression.

Genetic testing, reported in 2024, used a commercial next-generation sequencing kidney disease panel with copy-number analysis (CentroNephro, CENTOGENE, Rostock, Germany), with *SCNN1A*, *SCNN1B*, and *SCNN1G* specifically targeted to evaluate Liddle syndrome. It identified a homozygous likely pathogenic *HSD11B2* variant (NM_000196.3:c.710C > T; p.(Ala237Val), exon 4; ACMG class 2) together with a heterozygous *SCNN1B* variant of uncertain significance (NM_000336.2:c.1185G > A; p.(Met395Ile), exon 8; ACMG class 3). The *HSD11B2* variant had a gnomAD allele frequency of 0.000004, was predicted to be damaging by PolyPhen-2, SIFT, and MutationTaster at a highly conserved position, and is listed in HGMD as disease-causing for AME and in ClinVar as of uncertain significance (Variation ID 800834). The *SCNN1B* variant was absent from gnomAD, the Exome Sequencing Project, and the 1000 Genomes Project, had not been reported previously, and had conflicting in silico predictions (PolyPhen-2 benign; SIFT deleterious; MutationTaster disease-causing). Coverage of *SCNN1A* and *SCNN1G* was 100% at > 20×, and no other clinically relevant variants were detected.

Twenty-four-hour urinary steroid profiling demonstrated urinary free cortisol (UFF) of 83 µg/24 h (reference 3.5–45 µg/24 h) with urinary free cortisone (UFE) of 4.1 µg/24 h (reference 17–129 µg/24 h), yielding a UFF/UFE ratio of 20.2 (normal approximately 0.54 ± 0.05) [9]. This ratio is consistent with values reported in adult patients with classic (type I) AME, in whom the mean UFF/UFE ratio was 17.7 ± 19.6 [10]. The collection was obtained in 2025 over 24 hours with a total volume of 2,300 mL. She was not receiving exogenous glucocorticoids and reported no licorice intake at the time of collection.

Echocardiography demonstrated preserved cardiac structure and function without left ventricular hypertrophy. CT imaging demonstrated normal kidneys and adrenal glands without obstructive uropathy.

Because of persistent hypokalemia despite chronic amiloride therapy, spironolactone 25 mg daily was initiated in 2026, with amiloride 20 mg daily and modified-release potassium chloride 32 mmol/day in two divided doses continued. Serum potassium was monitored closely because two potassium-sparing agents were combined with potassium supplementation. Spironolactone was well tolerated, with no adverse effects reported. Serum potassium subsequently stabilized within the normal range at 5.0, 4.4, and 4.0 mmol/L over the following three months, with no further episodes of critical hypokalemia such as those that had characterized her earlier course, **and average office blood pressure decreased modestly from 153/92 mmHg before to 142/91 mmHg after spironolactone but remained above target (**Fig. 1**).** This response was consistent with, and supportive of, the biochemical diagnosis of AME.

Discussion and Conclusions

This case illustrates how biochemical reverse phenotyping can resolve diagnostic uncertainty created by multigene panel testing when variants are identified in genes associated with phenotypically overlapping disorders. In our patient, integration of urinary steroid profiling, genetic findings, and clinical course established apparent mineralocorticoid excess (AME) as the dominant disease mechanism. The

longstanding presumptive diagnosis of Liddle syndrome reflects the substantial clinical overlap between these disorders and the historical absence of disease-specific biochemical testing.

The patient demonstrated the classical biochemical features of AME, including hypokalemia, metabolic alkalosis, renal potassium wasting, suppressed aldosterone, and markedly abnormal cortisol–cortisone metabolism. The UFF/UFE ratio of 20.2 was profoundly elevated compared with normal values (0.54 ± 0.05) and provided direct biochemical evidence of impaired 11β-HSD2 activity [9, 10]. The UFF/UFE ratio is considered a sensitive marker of renal 11β-HSD2 activity because it directly reflects renal cortisol-to-cortisone conversion rather than hepatic cortisol metabolism [9, 10]. Together with the suppressed aldosterone physiology and characteristic clinical phenotype, these findings strongly supported the diagnosis of AME.

The identified *HSD11B2* p.Ala237Val variant has been previously characterized *in vitro*. Nunez et al. reported that the A237V mutant retained approximately 72% of wild-type activity in intact cells but only about 3% in cell lysates, suggesting impaired protein stability rather than complete loss of catalytic activity [8, 11]. Yau et al. subsequently demonstrated through computational structural modeling that mutations producing indirect disruption of substrate interactions or modest alterations in intramolecular structure tend to be associated with milder (type 2 AME) phenotypes, whereas mutations directly affecting substrate binding, cofactor interactions, or dimerization produce severe (type 1) AME [6]. Residual activity in intact cells might predict a milder phenotype; however, our patient had manifestations from childhood, and the correct diagnosis was established only in adulthood. Indeed, the markedly abnormal urinary steroid profile (UFF/UFE ratio of 20.2, within the range reported in classic type I AME) suggests that the physiological consequences of this variant *in vivo* may be substantially greater than predicted from *in vitro* activity assays alone, emphasizing the importance of biochemical assessment in addition to molecular characterization [8].

The p.Ala237Val variant has been reported only rarely. It was first described by Nunez et al. in a child with AME who was compound heterozygous for p.Ala237Val and p.Ala328Val, and was characterized functionally as described above [8]; a 2022 review of genetically confirmed AME likewise lists p.Ala237Val only in the compound heterozygous state [7]. It has since been included in structural analyses of 11β-HSD2: Manning et al. predicted that the substitution lies close to hydrophobic residues of the partner subunit and may perturb the dimer interface [11], and Yau et al. placed Ala237 at the dimer interface, where the valine substitution increases hydrophobicity and stabilizes the inactive dimeric state, a mechanism they associated with severe AME [6]. This structural prediction is concordant with the classic-range urinary steroid profile in our patient, despite the partial activity observed in intact cells. We identified no previous report of a patient homozygous for p.Ala237Val; to our knowledge, the present case provides the first clinical and biochemical description of this variant in the homozygous state. In the Arabian Peninsula, AME has been described in Omani kindreds [12] and in two Saudi families, including siblings homozygous for p.Arg208Cys [13] and a family with three affected children reported earlier [14], all of whom presented in childhood; by contrast, our patient was not correctly diagnosed until adulthood, after two decades of treatment for presumed Liddle syndrome.

The coexistence of a heterozygous *SCNN1B* p.Met395Ile variant created a plausible alternative explanation for the phenotype and illustrates a common challenge encountered with multigene panel testing. Because both AME and Liddle syndrome present with low-renin hypertension, hypokalemia, metabolic alkalosis, and suppressed aldosterone levels, identification of an *SCNN1B* variant could easily generate diagnostic uncertainty. Because Liddle syndrome is inherited in an autosomal dominant manner, a heterozygous *SCNN1B* variant is not by itself inconsistent with that diagnosis; the case against a causal role therefore rests on variant location, biochemistry, and treatment response. Several observations argued strongly against Liddle syndrome as the primary diagnosis. First, the p.(Met395Ile) variant lies within the large extracellular domain of β-ENaC, remote from the PY motif (PPPXY sequence) in the cytoplasmic C-terminus, where the vast majority of pathogenic Liddle-associated *SCNN1B* mutations occur [15–17]. This PY motif is critical for Nedd4-2-mediated ENaC ubiquitination, internalization, and degradation, and disruption of this motif represents the principal mechanism underlying constitutive ENaC activation in Liddle syndrome [15, 16]. Second, the markedly elevated UFF/UFE ratio is characteristic of impaired 11β-HSD2 activity and would not be expected in Liddle syndrome, where cortisol–cortisone metabolism is normal. Third, the clinical course following mineralocorticoid receptor antagonism was more consistent with AME, in which cortisol-mediated MR activation is the primary mechanism [2, 4, 18], whereas Liddle syndrome characteristically responds to ENaC blockade rather than to MR antagonism [15, 16]. Collectively, these findings indicate that the *SCNN1B* variant was not the primary driver of the phenotype, although a modest modifying effect cannot be entirely excluded.

Important causes of low-renin hypokalemic hypertension include AME, Liddle syndrome, primary aldosteronism, licorice-induced (acquired) AME, congenital adrenal hyperplasia (11β-hydroxylase and 17α-hydroxylase deficiency), and glucocorticoid resistance syndrome [19, 20]. Table 2 compares AME with the three disorders most likely to mimic it in this patient. In the present case, the markedly elevated UFF/UFE ratio, homozygous *HSD11B2* mutation, and suppressed aldosterone physiology **collectively supported AME over other causes. Glucocorticoid suppression with dexamethasone is an established alternative or adjunct to mineralocorticoid receptor antagonism in AME** [2, 18]; **in our patient, mineralocorticoid receptor antagonism was considered sufficient, and chronic glucocorticoid exposure and its potential adverse effects were avoided. Dexamethasone remains an option should hypertension or hypokalemia persist.**

Table 2
Important causes of low-renin hypokalemic hypertension

Feature	AME	Liddle syndrome	Primary aldosteronism	Licorice excess
Renin	Low	Low	Low	Low
Aldosterone	Low	Low	High	Low
Potassium	Low	Low	Low	Low
Acid–base status	Metabolic alkalosis	Metabolic alkalosis	Metabolic alkalosis	Metabolic alkalosis
Urinary K wasting	Present	Present	Present	Present
Cortisol:cortisone ratio	Elevated	Normal	Normal	Elevated
Mechanism	11β-HSD2 deficiency	ENaC activation	Autonomous aldosterone secretion	11β-HSD2 inhibition
Key gene(s)	*HSD11B2*	*SCNN1A*, *SCNN1B*, *SCNN1G*	Mostly sporadic; familial forms: *CYP11B1/CYP11B2* chimera, *CLCN2*, *KCNJ5*, *CACNA1H*	Not applicable (acquired)
Response to spironolactone	Often beneficial	None	Strong	Beneficial
Response to amiloride	Beneficial	Strong	Partial	Beneficial
Typical age	Childhood to adulthood	Childhood/young adult	Adult	Any
Distinguishing feature	Elevated urinary cortisol:cortisone ratio	ENaC mutation/PY motif	Elevated aldosterone	Licorice exposure history

AME apparent mineralocorticoid excess, ENaC epithelial sodium channel, 11β-HSD2 11β-hydroxysteroid dehydrogenase type 2

This case also highlights an increasingly important principle in contemporary genomic medicine: genetic findings must be interpreted in the context of biochemical and physiological phenotyping. As multigene panels become more widely adopted, clinicians will increasingly encounter variants of uncertain significance in genes associated with overlapping phenotypes [7, 20]. In such situations, biochemical reverse phenotyping can serve as a critical adjudicating tool, distinguishing causative mutations from incidental findings and establishing the dominant disease mechanism.

The principal strengths of this report are the integrated diagnostic approach and the convergence of biochemical, genetic, and clinical evidence on a single mechanism. Limitations include the retrospective

nature of data collection and several incomplete historical variables: documentation of the original childhood diagnosis was unavailable, birth weight and parental consanguinity could not be confirmed, family members were not available for genetic screening, the urinary steroid profile was obtained on a single occasion, renin and aldosterone were measured during amiloride therapy, blood pressure values were office measurements because home blood pressure monitoring was not available, and follow-up after spironolactone was limited to three months, with blood pressure remaining above target. These limitations do not alter the convergent evidence supporting AME as the dominant mechanism.

In conclusion, biochemical reverse phenotyping remains indispensable for resolving diagnostic uncertainty when multigene panel testing identifies variants in genes associated with phenotypically overlapping monogenic hypertension syndromes. Integration of urinary steroid profiling, genetic findings, and clinical course established AME due to homozygous *HSD11B2* p.Ala237Val as the dominant disease mechanism despite a coexisting *SCNN1B* variant of uncertain significance. As multigene testing becomes routine in the evaluation of monogenic hypertension, biochemical phenotyping will remain essential for distinguishing causative mutations from incidental genetic findings.

Abbreviations

AME: Apparent mineralocorticoid excess

11β-HSD2: 11β-hydroxysteroid dehydrogenase type 2

MR: Mineralocorticoid receptor

ENaC: Epithelial sodium channel

UFF: Urinary free cortisol

UFE: Urinary free cortisone

VUS: Variant of uncertain significance

Declarations

Ethics approval and consent to participate

This case report was reviewed and approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard Health Affairs (MNG-HA), Riyadh, Saudi Arabia (IRB approval number 00000411626; study number NRR26/081/8; approval date 10 April 2026; National Committee of Bioethics registration number H-01-R-005). The study was granted expedited review. Written informed consent to participate was obtained from the patient.

Consent for publication

Written informed consent for publication of this case report and any accompanying de-identified clinical data was obtained from the patient. A copy of the signed consent form is available for review by the Editor on request.

Availability of data and materials

All data generated or analysed during this case are included in this published article. Further de-identified details are available from the corresponding author on reasonable request, subject to institutional data-protection policy.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EAME conceived and supervised the report and critically revised the manuscript. HMA and ZAH collected and interpreted the clinical data and drafted the manuscript. AA verified the laboratory and genetic findings and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

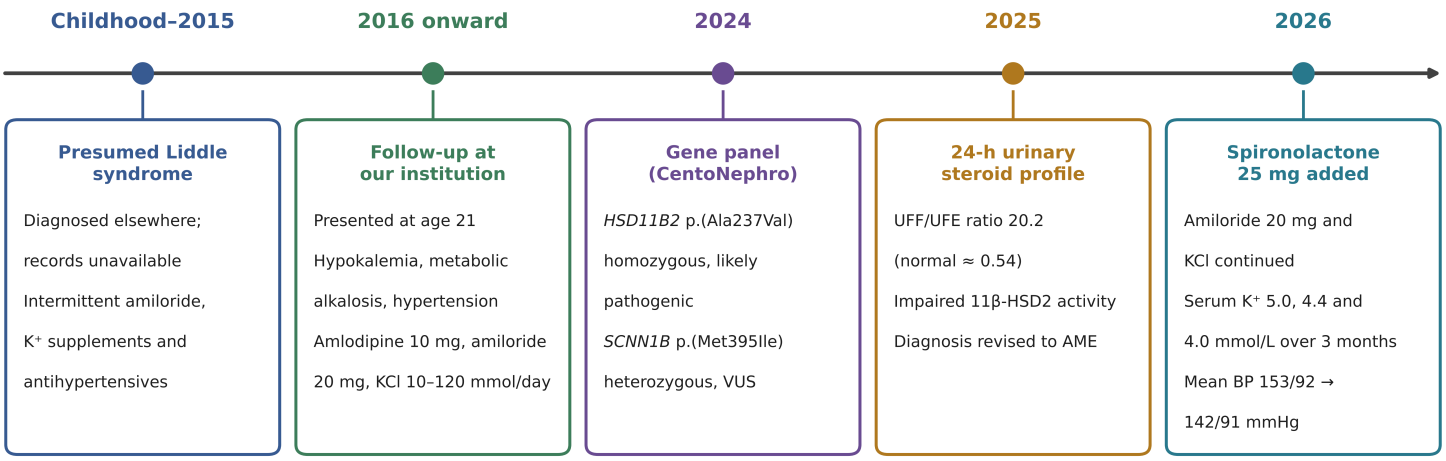


Figure 1

Timeline of diagnostic evaluation and management. The timeline illustrates the transition from a long-standing presumed diagnosis of Liddle syndrome to biochemical confirmation of apparent mineralocorticoid excess and targeted therapy with mineralocorticoid receptor antagonism. All dates are shown by year only in accordance with institutional de-identification requirements. AME, apparent mineralocorticoid excess; KCl, potassium chloride; UFF/UFE, urinary free cortisol-to-cortisone ratio; VUS, variant of uncertain significance; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2.

Supplementary Files

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- Additionalfile1CAREchecklist.docx