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CTNNB1 Mutation in Aldosterone Producing Adenoma

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Discoveries of somatic mutations permit the recognition of subtypes of aldosterone-producing adenomas (APAs) with distinct clinical presentations and pathological features. Catenin β1 (*CTNNB1*) mutation in APAs has been recently described and discussed in the literature. However, significant knowledge gaps still remain regarding the prevalence, clinical characteristics, pathophysiology, and outcomes in APA patients harboring *CTNNB1* mutations. Aberrant activation of the Wnt/β-catenin signaling pathway will further modulate tumorigenesis. We also discuss the recent knowledge of *CTNNB1* mutation in adrenal adenomas.

Keywords: CBTNN1; KCNJ5; Primary aldosteronism; Aldosterone producing adenomas; Taiwan Primary Aldosteronism Investigator

INTRODUCTION

Primary aldosteronism is the most common cause of secondary hypertension with a prevalence of 5% to 10% in hypertensive patients and 20% in patients with treatment-resistant hypertension [1-4]. In aldosterone-producing adenoma (APA), the majority of somatic mutations were potassium voltage-gated channel subfamily J member 5 (*KCNJ5*) mutations (ranging from 52.9% to 76.8% in Asia) [5-7]. Recently, the prevalence of a novel catenin β1 (*CTNNB1*) mutation in APAs was 3.7% to 5.1% [5,8]. We integrate the studies of APAs and show the prevalence of reported somatic mutation in APAs (Fig. 1) [6-22]. *CTNNB1* mutations were associated with stabilized β-catenin and increased AXIN2 (axis inhibition protein 2) expression, suggesting the activation of Wnt signaling [23]. In APA, *CTNNB1* mutations occurred mutually exclusively from *KCNJ5*, ATPase Na^+/K^+ transporting subunit α1 (*ATP1A1*), ATPase plasma membrane Ca^{2+} transporting 3 (*ATP2B3*), and calcium voltage-gated channel subunit α1 D (*CACNA1D*) mutated tumors, implying that aberrant Wnt activation plays a pivotal role in APA formation [24]. Accordingly, tumors with *CTNNB1* mutations were associated with relatively large adenomas and predominantly expressed in females [8].

PATHOGENIC MECHANISM OF *CTNNB1* MUTATION IN THE ADRENAL GLAND

The Wnt signaling pathway, through β-catenin signaling, is important for the normal development and maintenance of the adrenal cortex, and more specifically, the zona glomerulosa (ZG) within the cortex [25,26]. Somatic mutations of *CTNNB1* have been found in 27% of adrenocortical adenomas and 31% of adrenocortical carcinomas [27]. Exon 3 of the *CTNNB1* gene (encoding β-catenin) contains specific serine and threonine residues, where phosphorylation marks β-catenin for degradation [28]. Mutations or deletions of exon 3, leading to the aberrant

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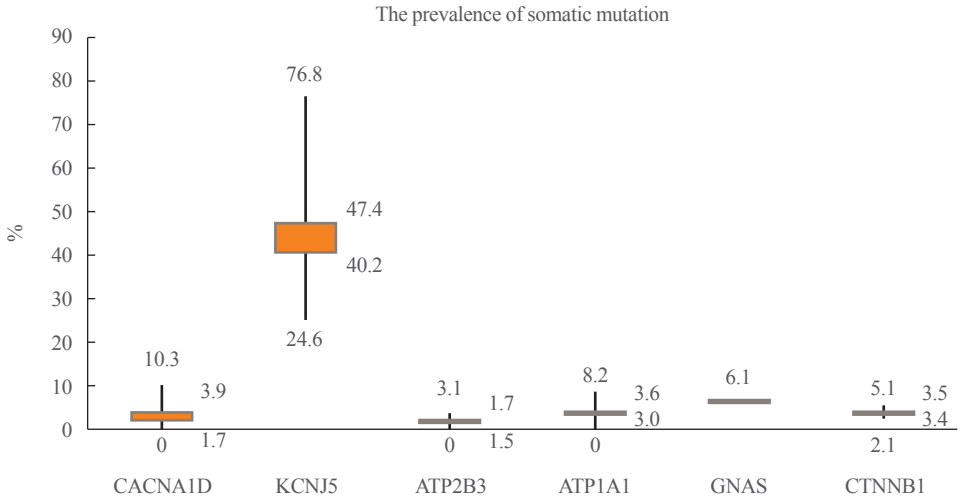

Fig. 1. The prevalence of the most known mutation of aldosterone producing adenoma. This box plot displays the full range of variation (from maximum, mean, medium to minimum, accordingly) in each index somatic mutation. CACNA1D, calcium voltage-gated channel subunit α1 D; KCNJ5, potassium voltage-gated channel subfamily J member 5; ATP2B3, ATPase plasma membrane Ca^{2+} transporting 3; ATP1A1, ATPase Na^{+}/K^{+} transporting subunit α1; GNAS, guanine nucleotide binding protein, α stimulating; CTNNB1, catenin β1.

activation of Wnt signaling, subsequently inhibits the phosphorylation of β-catenin [29]. Due to alterations in exon 3 of the *CTNNB1* gene, mice with activating Wnt signaling develop hyperaldosteronism and adrenocortical tumors [24]. Mutations in *CTNNB1* also cause increased and abnormal Wnt activation in human adrenocortical tumors [27,30], and augment the Wnt signaling pathway, leading to tumor formation [31]. In one recent series, cases of APAs harboring activating mutations of β-catenin were described in three women (two during pregnancy and one postmenopausal), who had a heterozygous somatic mutation (C→G, p.Ser33Cys in case 1, C→T, p.Ser45Phe in case 2, and G→A, p.Gly34Arg in case 3) in exon 3 of *CTNNB1*. All three mutations are predicted to affect a GSK-3β (glycogen synthase kinase 3β) phosphorylation consensus motif and could thus impair β-catenin degradation and up-regulate Wnt activity, resulting in elevated levels of active β-catenin [32].

CTNNB1 AND THE TWO HIT THEORY DEPICT TUMOR FORMATON IN ALDOSTERONISM

In the peritumoral tissue of APA, important remodeling of the adrenal cortex has also been observed with reduced vascularization, ZG hyperplasia, and increased nodulation that were not correlated with cytochrome P450 family 11 subfamily B member 2 (*CYP11B2*) expression [33]. A recent study showed that somatic mutations in the *KCNJ5*, *ATP1A1*, or *CACNA1D* genes are not limited to APAs, but are also found in the more frequent multinodular adrenals [34]. However, in a multinodular gland, the mutation was found in only one nodule, showing that mutation and nodule formation are independent processes [35]. These data demonstrate that the processes of nodule formation and aldosterone hypersecretion can be dissociated in pathological adrenals, suggesting a two-hit model for APA formation. The primary hit, consisting of somatic mutation of one of the known genes in about 60% of cases and of other unknown genetic mutation in the remaining patients, can cause aldosterone hypersecretion. The secondary hit would lead to alterations in the normal balance between adrenocortical cell proliferation and apoptosis, triggering nodule formation (Fig. 2) [36,37]. Of note, activation of the Wnt/β-catenin pathway further modulates the two hits required for both adrenal nodule formation and increased aldosterone secretion [23,38]. APAs harboring *CTNNB1* mutation could display *CYP11B1* or *CYP11B2* heterogeneous expression [8], or in both CYP11B2-positive and CYP11B2-negative regions [39]. It is also consistent with our result that the Wnt/β-catenin pathway activates downstream cyclin D1 transcription, which is a gene involved in cell growth [40] in adenomas with *CTNNB1* mutations compared with wild-type APA adenomas. All of these findings, together with the reported higher prevalence of *CTNNB1* mutations among other adrenal adenomas [41] and adrenal cancers [23], suggest that *CTNNB1* mutations may be more related to tumor cell growth (tumorigenesis), rather than to actual aldosterone production.

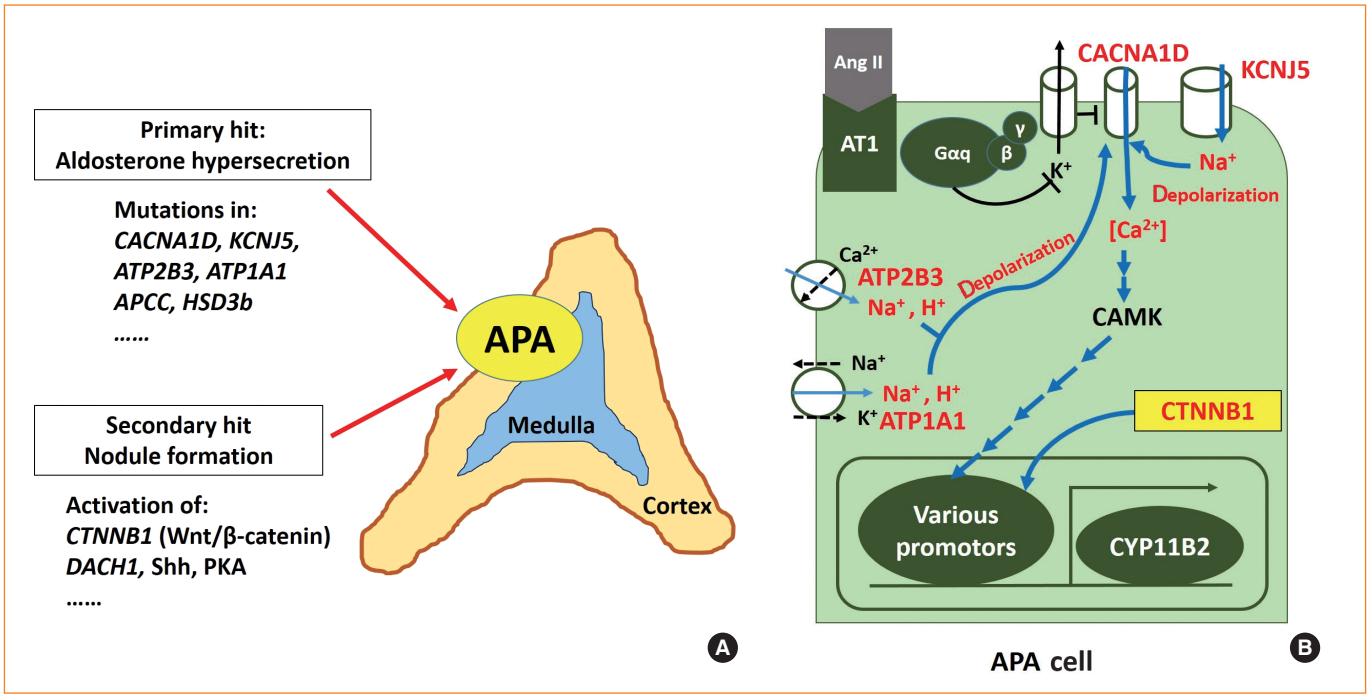

Fig. 2. A two-hit model for the pathogenesis of aldosterone-producing adenoma (APA). (A, B) Primary hit: Somatic mutations in *CACNA1D*, *KCNJ5*, *ATP2B3*, *ATP1A1*, and possibly other genetic alterations produce cell depolarization, increased cytoplasmic calcium level and increased CYP11B2 expression, causing aldosterone hypersecretion. Secondary hit: Aberrant activation of signaling pathways (such as Wnt/β-catenin, Shh, PKA, etc.) causes imbalances between cell proliferation and death in the adrenal, leading to adenoma formation. (A) Adapted from Lalli et al., with permission from Elsevier [36]. (B) Adapted from Seidel et al. [37]. CACNA1D, calcium voltage-gated channel subunit α1 D; KCNJ5, potassium voltage-gated channel subfamily J member 5; ATP2B3, ATPase plasma membrane Ca^{2+} transporting 3; ATP1A1, ATPase Na^+/K^+ transporting subunit α1; APCC, aldosterone-producing cell clusters; HSD3b, hydroxy-δ-5-steroid dehydrogenase, 3β- and steroid δ-isomerase cluster; CTNNB1, catenin β1; DACH1, dachshund family transcription factor 1; Shh, sonic hedgehog; PKA, protein kinase A; Ang II, angiotensin II; AT1, Ang II type 1; CAMK, Ca2+/calmodulin-dependent protein kinase; CYP11B2, cytochrome P450 family 11 subfamily B member 2.

CYP11B1, CYP11B2, LHCGR, AND GNRHR EXPRESSION IN APAs HARBORING *CTNNB1* MUTATIONS

Two subgroups of APAs were observed: one with diffuse *CYP11B2* expression with concomitantly low *CYP11B1* expression, and one with low *CYP11B2* and high *CYP11B1* expressions [8]. APAs harboring *CTNNB1* mutations have shown variable expression of *CYP11B1* and *CYP11B2* [5,8,32]. Of note, APAs harboring *CTNNB1* mutations could express luteinizing hormone/choriogonadotropin receptor (LHCGR) and gonadotropin releasing hormone receptor (GNRHR), encoding gonadal receptors, at levels that were more than 100 times higher than the levels in other APAs in one report [32]. Constitutive activation of the Wnt signaling pathway in ZG-like adenomatous cells could lead to de-differentiation toward the common adrenal-gonadal precursor cell type, and to the aberrant expression of gonadal receptors LHCGR and/or GNRHR [5]. However, GNRHR could present diffuse cytoplasmic, membranous, and nuclear expression in adenomas, and was especially enhanced in adenomas harboring *CTNNB1* mutations from female patients. GNRHR was attenuated in *KCNJ5* mutated adenomas. LHCGR was diffusely expressed in adrenal tissues and was prominent in adenomas harboring *CTNNB1* mutations [5]. Compared with *KCNJ5* mutated APAs, no difference in *CYP11B1* expression levels were observed, but significantly higher *CYP11B2* expression was observed in *CTNNB1* mutated tumors in a single report [8].

CLINICAL CHARACTERISTICS OF PATIENTS WITH TUMORS HARBORING *CTNNB1* MUTATIONS

CTNNB1 mutated APAs were more often observed in female patients (60% to 75%) [5,8] and older patients, with a shorter

duration of hypertension [5]. There were no significant differences in preoperative aldosterone levels, tumor size at surgery, and the ratio of parental hypertension in patients with tumors harboring *CTNNB1* mutations compared to those with tumors harboring *KCNJ5* mutations [5,8]. However, *CTNNB1* mutations led to higher serum potassium and creatinine levels compared to *KCNJ5* mutations in one study [5].

Patients with tumors harboring *CTNNB1* mutation have a small but increased risk of malignant transformation [27]. Experiments using β-catenin mutated mice which develop benign tumors can transition to malignancy, indicating the requirement of additional epigenetic changes [24,42]. This is consistent with the multistep progression model seen in patients with familial adenomatous polyposis [43]. However, most APAs rarely increase in size and the transition to aldosterone-producing carcinomas is extremely rare [44]. Adrenal carcinomas harboring *CTNNB1* mutation are also extremely rare.

CLINICAL OUTCOMES AFTER ADRENALECTOMY IN APA PATIENTS HARBORING *CTNNB1* MUTATIONS

According to our study, *CTNNB1* mutation carriers had a higher possibility (87.5%) of residual hypertension than other APA patients after adrenalectomy [5]. Compared with *KCNJ5* mutation carriers (12.5% vs. 79.3%, $P<0.001$), *CTNNB1* mutation carriers had a much lower chance of recovery from hypertension, even after 1-year follow-up. One of the possible explanations of the higher postadrenalectomy residual hypertension among patients harboring *CTNNB1* mutations could be that age-related essential hypertension plays an important role in the hypertension observed in these patients.

CTNNB1 MUTATION OCCUR IN CUSHING'S SYNDROME AND CORTISOL PRODUCING ADENOMAS

CTNNB1 mutations and activation of the Wnt/β-catenin pathway are also found in other benign and malignant adrenocortical neoplasms that do not produce aldosterone, including cortisol producing adenomas (CPA) [45-47]. As previously stated, activated Wnt/β-catenin signaling contributes to adrenal tumorigenesis [48]. *CTNNB1* mutation has been described in a 4-month-old Thai infant with Cushing's syndrome secondary to bilateral adrenal tumors with hepatic metastasis [49]. Following molecular investigations, a deletion mutation of β-catenin involving codons 44 to 45 was detected in the right adrenal tumor and peripheral blood of this patient, which indicates systemic mutation. Immunohistochemistry showed nuclear accumulation of β-catenin on the right adrenal tumor together with the metastatic nodule in the liver and the left adrenal tumor harbored wild-type β-catenin.

For CPAs, mutations in the catalytic subunit of protein kinase A (PKA) were identified and shown to occur mutually exclusively to *CTNNB1* mutations [50,51]. The PKA pathway has paramount importance in the regulation of adrenocortical growth and hormone secretion. Activating mutations in PKA led to constitutively activated cyclic adenosine monophosphate (cAMP) signaling, causing increased cortisol production and tumor formation. Expression analysis revealed the increased expression of genes involved in the biosynthesis and metabolism of steroids in tumors with protein kinase cAMP-activated catalytic subunit α (*PRKACA*) mutation [50]. Somatic gain-of-function mutations in the *PRKACA* have been found in cortisol-producing adrenocortical adenomas [50-53], but the presence of genetic alterations in genes involved in the PKA pathway in APA is currently unknown. *ARMC5* (armadillo repeat containing 5) is a gene found to be mutated in macronodular adrenal hyperplasia and has a connection with the PKA pathway [54].

CONCLUSIONS

CTNNB1 mutations in a subset of APAs are predominant with aberrant β-catenin accumulation. Tumors harboring these mutations have a variable histological and *CYP11B2/B1* expression pattern, and show different clinical characteristics, such as female gender dominance and a higher risk of postadrenalectomy residual hypertension. *CTNNB1* mutations in APAs could relate to tumorigenesis rather than aldosterone production by activating Wnt/β-catenin signaling.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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