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综 述

醛固酮腺瘤中KCNJ5基因的研究进展

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摘 要：醛固酮腺瘤是原发性醛固酮增多症的一种亚型，随着多组学研究的深入，在基因水平上对原发性醛固酮增多症的研究取得了新的突破，与醛固酮腺瘤发病相关的KCNJ5 (potassium inwardly rectifying channel, subfamily J, member 5)基因作为原发性醛固酮增多症最常见的体细胞突变基因，受到广泛关注。本文旨在对醛固酮腺瘤发病过程中KCNJ5基因的相关研究进行证据整合，从遗传学角度加深对醛固酮腺瘤发病机制的认识，为临床诊断及治疗醛固酮腺瘤提供新思路。

关键词：醛固酮腺瘤；原发性醛固酮增多症；KCNJ5；基因突变

Research progress of KCNJ5 gene in aldosterone-producing adenoma

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Abstract: Aldosterone-producing adenoma is a subtype of primary aldosteronism. Recent advancements in multi-omics research have led to significant progress in understanding primary aldosteronism at the genetic level. Among the various genes associated with the development of aldosterone-producing adenomas, the KCNJ5 (potassium inwardly rectifying channel, subfamily J, member 5) gene has received considerable attention due to its prevalence as the most common somatic mutation gene in primary aldosteronism. This paper aims to integrate the existing evidence on the involvement of KCNJ5 gene in the pathogenesis of aldosterone-producing adenomas, to enhance the understanding of the underlying mechanisms of aldosterone-producing adenomas from the perspective of genetics, and to provide novel insights for the clinical diagnosis and treatment of aldosterone-producing adenomas.

Key words: aldosterone-producing adenoma; primary aldosteronism; KCNJ5; gene mutation

原发性醛固酮增多症 (primary aldosteronism, PA) 是由肾上腺皮质增生或肿瘤分泌过多醛固酮引起的以血压升高、血钾降低为临床表现的心血管系统代谢综合征，是常见的继发性高血压原因之一。随着诊断水平的提高，在高血压患者人群中 PA 患病率日益增长，已达 10%，在新诊断的高血压患者人群中 PA 患病率约为 4% [1,2]。PA 主要分型有醛固酮腺瘤 (aldosterone-producing adenoma, APA)、特发

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性醛固酮增多症(idiopathic hyperaldosteronism, IHA)、家族性醛固酮增多症 (familial hyperaldosteronism, FH) 三种，而随着精准医学的发展及全基因组测序的应用，又将 FH 分为 I 型、II 型和 III 型 FH [3]。APA 作为 PA 最常见的亚型，占比达 60% [4]，该亚型最常见的病因为 KCNJ5 (potassium inwardly rectifying channel, subfamily J, member 5) 基因突变，KCNJ5 基因突变携带者总体患病率达 43%，欧洲国家患病率达 35%，亚洲国家患病率高达 63% [5–8]。本文对 APA 主要病因 ——KCNJ5 基因突变相关研究进展进行综述，以期为 APA 在基因水平的诊断及治疗等方面提供新的思路。

1 醛固酮分泌机制

醛固酮是一种由肾上腺皮质球状带分泌的盐皮质激素 [9]，具有参与血压稳定、维持血容量、稳定钾钠平衡等生理功能。在健康人中，肾上腺皮质每天最多约产生 200 μg 醛固酮，其合成和分泌与肾素、血管紧张素 I (angiotensin I, Ang I)、血管紧张素 II (angiotensin II, Ang II) 及相关酶密切相关。肾素 - 血管紧张素 - 醛固酮系统 (renin-angiotensin-aldosterone system, RAAS) 是体内由肝、肾所主导的一种血压调节体系，醛固酮分泌增多是 RAAS 激活的一个重要原因，当低血压或低血清钠等刺激触发 RAAS 时，肾小球细胞分泌肾素，激发肝脏产生无活性的血管紧张素原，并在酶的作用下裂解为 Ang I [10]，通过肺循环在血管紧张素转化酶 (angiotensin-converting enzyme, ACE) 等酶的作用下使 Ang I 转化为 Ang II，后者结合肾上腺皮质细胞膜表面的血管紧张素受体，导致醛固酮产生增多 (图 1)。

醛固酮在心脏和血管的非上皮组织以及唾液腺和肾远端小管等上皮组织中表达，能够作用于一种激素依赖性转录因子 —— 盐皮质激素受体 (mineralocorticoid receptor, MR)，调节钠 / 水重吸收和钾排泄 [11]，从而激活上皮 Na^+ 通道，Na^+-K^+-ATP 酶和 NaCl 协同转运蛋白的表达导致 Na^+ 和 Cl^- 的重吸收增加，进而引起血压升高。Yokota 等人 [12] 研究显示，MR 的转录活性和醛固酮生物合成双重机

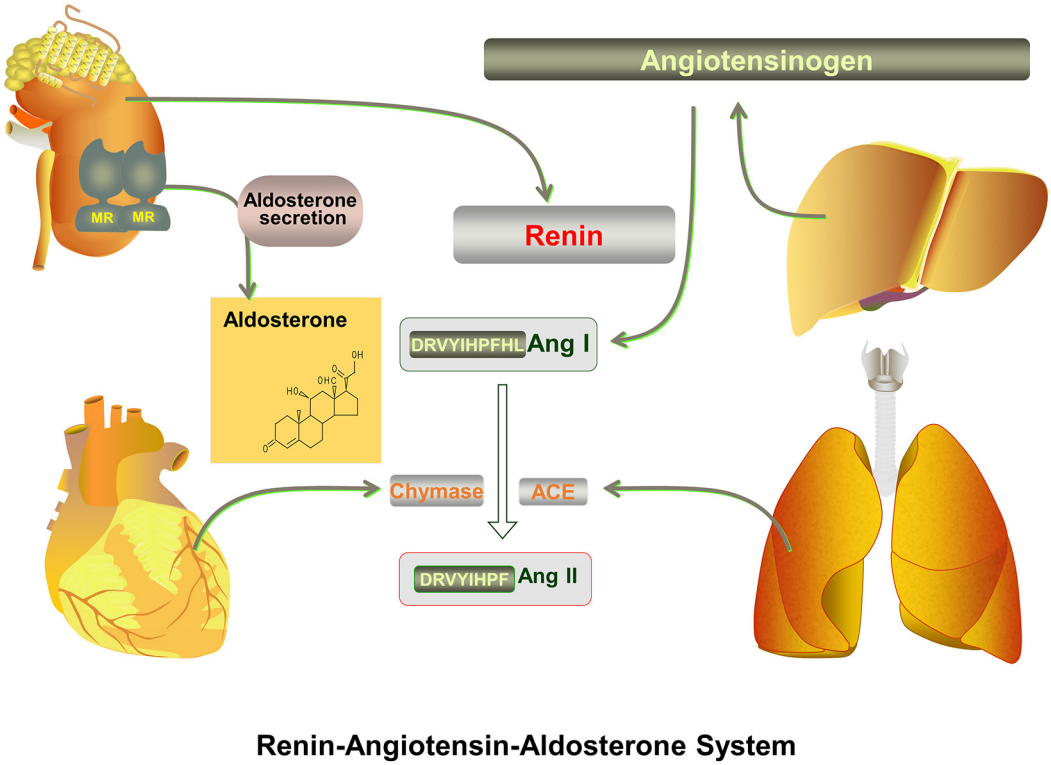

图 1. 肾素-血管紧张素-醛固酮系统(RAAS)中醛固酮(ALD)产生流程图

Fig. 1. Flow chart of aldosterone (ALD) generation in renin-angiotensin-ALD system (RAAS). When RAAS is triggered by a stimulus such as low blood pressure and low serum sodium, glomerular cells secrete renin, which stimulates the liver to produce angiotensin I (Ang I). Ang I is converted to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE), and Ang II binds to angiotensin receptors on the surface of adrenocortical cell membranes, resulting in an increase in aldosterone production. MR: mineralocorticoid receptor.

制在高血压和 PA 发生、发展中发挥关键作用，其作用机制可能与人类蓖麻锌指 1 (castor zinc finger 1, CASZ1) 基因过表达抑制肾上腺细胞中醛固酮的生物合成有关。反观 KCNJ5 基因，它是通过基因突变来调控细胞内、外离子来激活 RAAS，从而影响醛固酮产生。

2 KCNJ5

2.1 KCNJ5基因概述

KCNJ5 基因是编码细胞 G 蛋白激活内向整流钾通道 4 (G protein-activated inward rectifier potassium channel 4, GIRK4) 的基因，Choi 等首先在 APA 患者中检测到 KCNJ5 基因的体细胞突变及种系突变 [13]，此后，很多关于 PA 的发病机制被不断发现，PA 突变类型大多发生在 APA 当中。GIRK4 是一种由 G 蛋白控制的同源四聚体，其突变导致 GIRK4 对 K^+ 的选择性降低，细胞外 Na^+ 进入细胞增加，引起细胞膜去极化，使醛固酮合酶 CYP11B2 合成，导致电压门控 Ca^{2+} 通道打开，提高肾小球细胞内 Ca^{2+} 浓度，激活醛固酮的生物合成途径 RAAS，使醛固酮的生成增多 [14](图 2)。

2.2 KCNJ5基因突变位点

一项有关 PA 患者肾上腺多发性结节的研究结果显示，一个肾上腺中多个结节可能含有不同的 KCNJ5 基因突变位点，且无周围肾上腺皮质增生或轻度增生的结节比明显增生的结节更易出现 KCNJ5 基因突变，提示肾上腺结节起源于不同的复制位点 [15]。Chang 等 [16] 对 110 例 PA 患进行 KCNJ5 测序，结果显示突变位点包括 p.G151R、p.L168R、p.E145Q 和 p.T158A，其中 p.G151R、p.L168R 突变位点占 95% 以上，p.G151R 突变率高于 p.L168R [17]，且 p.E145Q 突变会导致钠离子内流，引起醛固酮水平升高 [18]，另有研究显示，将 p.G151R、p.L168R 突变精确整合到猪成纤维细胞中进行克隆，可加快 PA 动物模型的建立，表明猪适用于肾上腺研究，且更能拟合人类模型，推动了对 p.G151R、p.L168R 突变位点模型的研究 [19]。除了 p.G151R、p.L168R、p.E145Q、p.T158A 等突变位点，近年的研究还发现了 KCNJ5

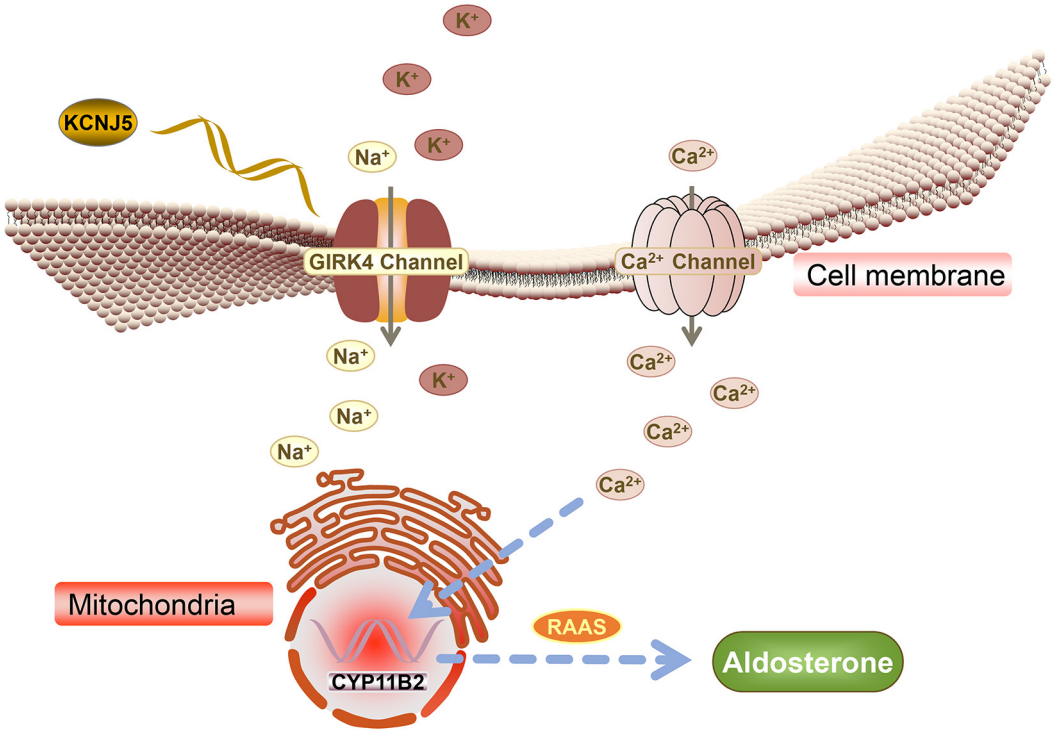

图 2. KCNJ5基因突变对GIRK4通道的影响

Fig. 2. Effects of KCNJ5 gene mutation on GIRK4 channels. Increased entry of extracellular Na^+ into the cell after the KCNJ5 mutation causes depolarization of the cell membrane, which leads to the synthesis of the aldosterone synthase CYP11B2 and the opening of the voltage-gated Ca^{2+} channel, increases the intracellular Ca^{2+} concentration in glomerular cells, activates the renin-angiotensin-aldosterone system (RAAS), and leads to an increase of aldosterone production. GIRK4: G protein-activated inward rectifier potassium channel 4, encoded by KCNJ5.

基因的 p.G151E、p.delI157、p.Y152C、p.W126R、p.R115W、p.E246G 等突变位点，其中 p.W126R 突变率处于最低状态，p.R115W 和 p.E246G 突变会影响 Kir3.4 插入细胞膜，从而导致细胞表面 Kir3.4 (即 GIRK4) 的数量减少，最终引起醛固酮的过量产生 [18, 20, 21](图 3)。

2.3 KCNJ5基因突变的临床表现

RAAS 与 APA 高血压密切相关，实验室检查结果显示，患者多表现为低肾素、高 Ang II 和高醛固酮，血浆醛固酮 / 肾素比值 (aldosterone/renin ratio, ARR) 升高可作为 APA 诊断的有效指标。临床上 KCNJ5 基因突变的 APA 患者常表现为多尿、多饮、低钾血症和难治性高血压，此类患者发生心力衰竭、心律失常等心血管疾病的风险较非 KCNJ5 基因突变的 APA 患者显著增加 [22, 23]。

肾上腺细胞异常增殖可引起腺瘤增生，加剧 APA 患者临床症状。KCNJ5 基因突变是否影响细胞的增殖尚未确定，目前仅有一项研究结果显示，KCNJ5 种系突变的细胞在体内是具备增殖能力的 [24]。研究显示，具有 KCNJ5 体细胞突变的 APA 患者肿瘤通常更大，醛固酮水平较高，血钾水平较低 [14]，进一步引起疲劳、全身无力、便秘等非特异性症状 [25]。另外，Zhao 等报告在一名双侧肾上腺皮质肿瘤的患者上，肿瘤细胞组成的异质性和 KCNJ5 的体细胞突变导致双侧肾上腺腺瘤分别分泌皮质醇和醛固酮 [26]。值得关注的是，KCNJ5 基因突变的 APA 患者腹部 CT 结果显示，患者腹主动脉增厚，但钙化并不明显 [27]。一项关于 APA 表型 - 基因型的相关性研究结果显示，KCNJ5 基因突变可导致胆固醇受体 (LDL-R) 显著降低，胆固醇 / 羊毛甾醇比值降低 (羊毛甾醇为胆固醇前体物质)，进而诱导高胆固醇血症的发生、发展 [28]。此外，KCNJ5 基因突变可使 APA 患者左心室增厚，舒张功能降低，KCNJ5 基因突变的 APA 患者左心室质量指数 (left ventricular mass index, LVMI) 较非突变患者有所升高，在行腹腔镜肾上腺全切除术 (laparoscopic total adrenalectomy, LTA) 后，相较于非突变患者，LVMI 的改善也更好 [29]。

2.4 KCNJ5基因突变诊断

2.4.1 突变诊断技术

作为首选诊断方式，测序通过测定核酸或氨基酸等生物分子序列来解读遗传密码。近年来，随着

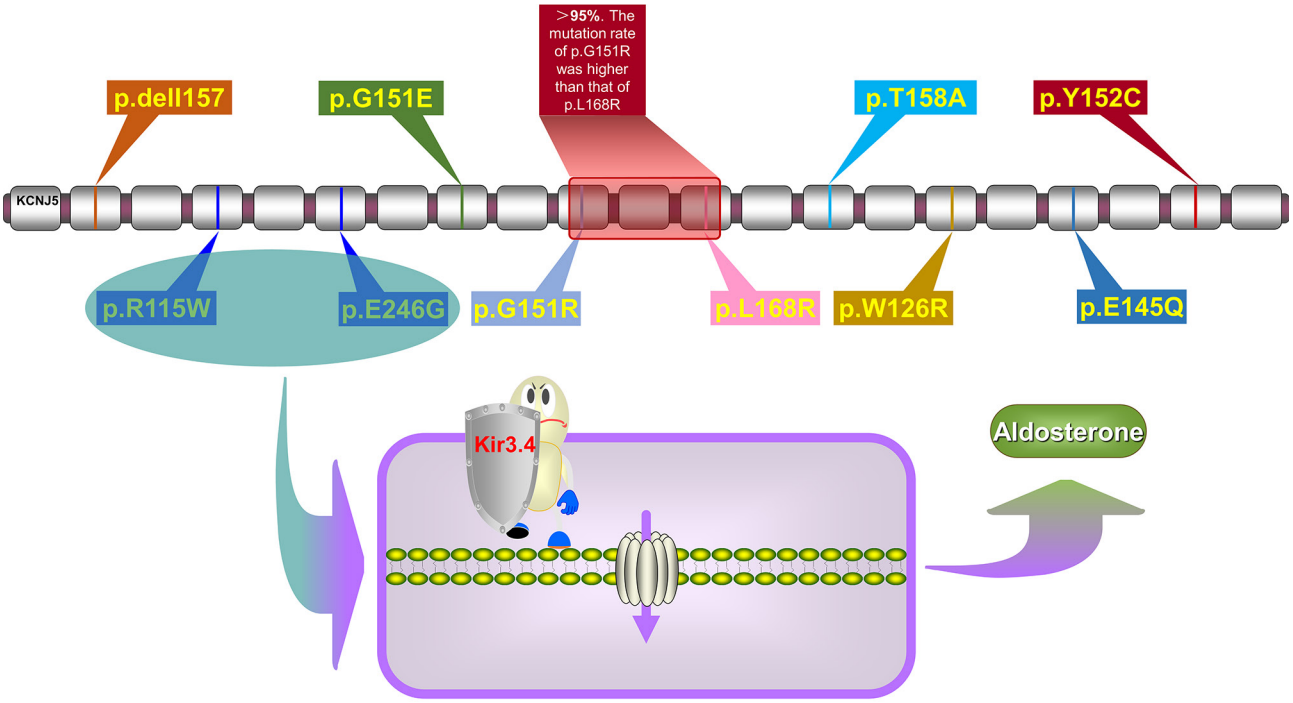

图 3. KCNJ5基因位点突变图

Fig. 3. Mutation map of KCNJ5 gene locus. p.W126R mutation rate is in the lowest state, and p.R115W and p.E246G mutations affect the insertion of Kir3.4 (i.e. GIRK4) into the cell membrane, which leads to the decreases of cell surface Kir3.4 amount, ultimately causing an overproduction of aldosterone.

测序技术的进步，KCNJ5 基因突变的诊断更加清晰，Choi 等通过外显子测序首次发现 APA 患者 KCNJ5 基因突变 [13]。Nanba 等人 [30] 通过对 PA 进行 CYP11B2 免疫组织化学法检测，并进行 DNA 测序，结果显示 45 位 APA 患者中有 35 位 (78%) 发生 KCNJ5 基因突变；Chang 等通过对 110 例 PA 患者进行基因测序发现，KCNJ5 基因突变 65 例，占所有完成基因检测标本的 59.1% [16]，由此可见，基因测序在 KCNJ5 基因突变诊断中有重要意义。随着基因序列数据库的不断涌现，基因测序已经不再是技术瓶颈，可以通过基因测序对患者进行早期干预，指导健康管理，辅助疾病诊断，制定个体化治疗方案。

2.4.2 液相色谱-串联质谱联用技术(liquid chromatography-tandem mass spectrometry, LC-MS/MS)

LC-MS/MS 结合了液相色谱仪有效分离热不稳性及高沸点化合物的分离能力与质谱仪的组分鉴定能力，是一种分离分析复杂、低丰度混合物的有效手段，通过 LC-MS/MS 检测外周血和头发中肾上腺合成相关的激素谱，可以帮助诊断 KCNJ5 基因突变的 APA 患者 [31]。该项检查基于 LC-MS/MS 的高敏感性，虽然外周血液中激素在一段时间内的波动较大，但是 APA 患者病史一般较长，头发激素谱在一段时间内的波动相对稳定，因此检测头发激素谱可以发现 KCNJ5 基因突变。Eisenhofer 等人 [32] 对外周静脉血浆类固醇进行 LC-MS/MS 检测，并结合人工智能进行分析，不仅实现了正确的 PA 亚型分类，而且还能够正确预测具有 KCNJ5 基因突变的 APA，对于诊断 PA 及 PA 亚型，特异性分别为 94% 和 97%，敏感性分别为 69% 和 85%。这一进展有助于 KCNJ5 基因突变患者的诊断。该项技术的优点就在于其较高的灵敏度和选择性，将高效液相色谱分离能力与质谱仪的检测和结构解析功能相结合，从而在不同种类的代谢产物中检测出活性化学物质，进而运用于活性天然产物的药代动力学研究中。将 LC-MS/MS 运用到 KCNJ5 基因突变患者的诊断中也是近年来检测技术的创新与突破，其存在的弊端是灵敏度太高，导致沸点和溶剂相近的活性化学物质不能准确分离，另外在分离过程中可能受到溶液中其他离子的干扰，对测试结果产生影响。

2.4.3 肾上腺闪烁显像(adrenal scintigraphy)联合单光子发射计算机断层扫描(single photon emission computed tomography, SPECT)

Lu 等以 NP-59 肾上腺闪烁显像联合 SPECT 来预测 PA 患者是否存在 KCNJ5 基因突变 [33]，为 PA 患者术前预测 KCNJ5 基因突变提供了更多的可能性，但是目前该项诊断并没有普及，一方面是只有较少的医疗机构具备该项技术，另一方面是该项实验样本量较少，其可靠性有待考证，因此不作为 KCNJ5 基因突变首选检查方法。

3 KCNJ5基因突变治疗方案

3.1 手术治疗

目前研究证实，APA 患者首选治疗方式便是手术治疗，术后患者高血压症状明显得到改善，其他临床症状得到明显缓解 [34]。研究显示，在双侧醛固酮增多症的情况下，单侧肾上腺切除术可以改善特定患者的血压控制并稳定钾水平 [35]。对于双侧 APA 患者不能或者不适宜接受手术患者，可予以 CT 引导下肾上腺射频消融术 (radiofrequency ablation, RFA)，一项随机对照研究结果显示，CT 引导下 RFA 与单侧腹腔镜肾上腺切除术的成功率相近，术后血清 K^+ 和肾素的变化接近 [36]。相比于非 KCNJ5 基因突变 APA 患者，临床上 KCNJ5 突变患者早期行 LTA 后，可改善肱动脉血管内皮功能，尤其对肱动脉舒张功能具有显著的改善 [37]。

通过对 KCNJ5 基因突变患者与非 KCNJ5 突变患者术前术后对比发现，KCNJ5 基因突变患者更年轻，女性多见，腺瘤体积较大，醛固酮水平较高，术前血钾水平相对较低，术前高血压家族史更少，术后收缩压更低，舒张压更高，血压恢复较佳，心脏功能损害严重 [5–8, 34] (表 1)。

3.2 药物治疗

3.2.1 钙通道阻滞剂(calcium channel blockers, CCB)

Wang 等给予 KCNJ5 基因突变 APA 患者不同种类的 CCB，发现贝尼地平、米贝拉地尔和硝苯地平可显著抑制原代培养的 APA 细胞中的醛固酮分泌 [38]；Zhou 等 [39] 研究显示，CCB 类药物维拉帕米可有效阻断 KCNJ5 多个突变点所致的 H295R 细胞分泌醛固酮效应，这与 Zhao 等人 [26] 的研究结果一致。研究显示，维拉帕米可以浓度依赖性减少 Ang II 诱导或 KCNJ5 突变型细胞的醛固酮合成，抑制 CYP11B2 mRNA 和相关蛋白的表达 [40]。目前为止，维拉帕米对醛固酮分泌的抑制作用明确。

3.2.2 抗生素

研究显示，大环内酯类抗生素克拉霉素和罗红

霉素可在体外特异性抑制 KCNJ5 突变位点 G151R 和 L168R，为 KCNJ5 基因突变的 APA 治疗提供新方案，并且罗红霉素和克拉霉素的抑制活性要远高于红霉素 [41, 42]。

3.3 其他治疗进展

分泌型相关卷曲蛋白 2 (secreted frizzled-related protein 2, SFRP2) 可通过抑制 β-catenin 的表达来抑制 Wnt/β-catenin 信号通路，从而控制醛固酮浓度，阻碍 APA 发展，其机制在于 SFRP2 可特异性竞争 Wnt 配体，从而阻断 Wnt/β-catenin 信号通路 [43](图 4)。除 Wnt/β-catenin 信号通路之外，KCNJ5 基因突变与雌激素、催产素等信号通路相关，女性更容

表1. KCNJ5基因突变与非KCNJ5基因突变临床患者症状及术后疗效比较

Table 1. Comparison of clinical symptoms and postoperative outcomes between patients with KCNJ5 gene mutations and non-KCNJ5 gene mutations

	KCNJ5 mutation	Non-KCNJ5 mutation
Favored population	Females	No difference with gender
Age	Younger	Older
Adenoma volume	Big	Little
Aldosterone level	Higher	Lower
Potassium level	Lower	Higher
Family history of preoperative hypertension	Less common	More commonly seen
Postoperative systolic blood pressure	Lower	Higher
Postoperative diastolic blood pressure	Higher	Lower
Degree of heart damage	Worse	Lighter
Postoperative benefits	More	Passable

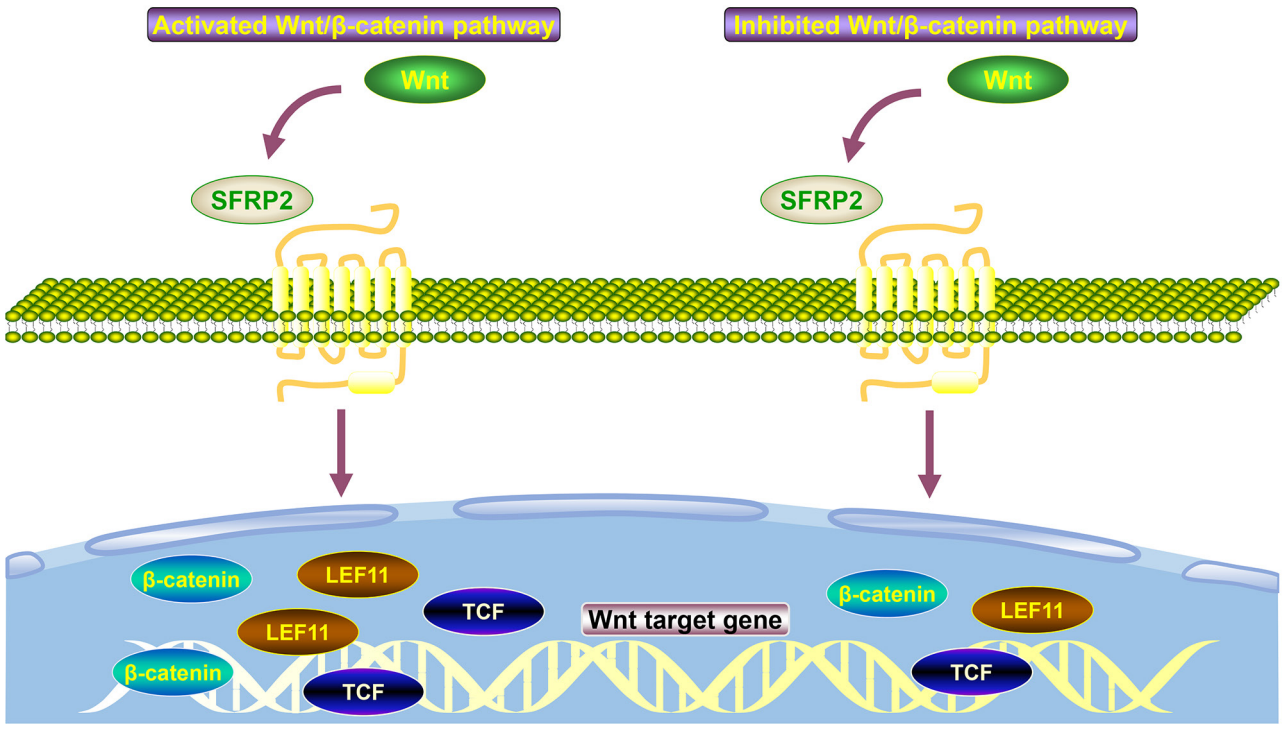

图 4. SFRP2通过Wnt/β-catenin信号通路控制醛固酮

Fig. 4. Aldosterone production controlled by secreted frizzled-related protein 2 (SFRP2) through Wnt/β-catenin signaling pathway. SFRP2 specifically competes for Wnt ligands and thus blocks the Wnt/β-catenin signaling pathway. T-cell factor/lymphoid enhancer factor 11 (TCF/LEF11) transcription factors are the major end point mediators of Wnt/β-catenin signaling, promoting transcription of downstream target genes.

表2. 与原发性醛固酮增多症(PA)相关的基因位点突变总览

Table 2. Overview of mutations in primary aldosteronism (PA)-associated gene loci

Gene	Mutant site	Marginal notes
7p22	rs1997243, D7S531, D7S2521, D7S511, D7S481 [45]	This gene fragment was likely to be genetically heterogeneous and has the highest correlation with mutations at the rs1997243 locus [45]
CACNA1D	p.Val259Asp, p.Phe747Leu, p.Ile750Me, p.Arg990His, p.Pro1336Arg, p.Met1354Ile [46]; p.Gly403Arg, p.Phe767Val, p.Ile770Met, p.Val1373Me, p.Gly403Asp [47]	Presence of germline mutations in p.Gly403Asp [46]
CYP11B2	rs1799998, Lysl73Arg rs4546, rs6414 [48]	rs1799998 increased susceptibility to hypertension in specific geographic areas [49]; Lysl73Arg was strongly associated with cardiovascular disease [48]
ATP1A1	p.Phe100-Leu104del, p.Leu104Arg, p.Val332Gly [50]; p.GluGlu-ThrAla963Ser [46]; p.Gly99Arg [51]; p.L104R[16]	ATP1A1 was highly expressed in the adrenocortical zona glomerulosa and may be realized by deletion mutations with base substitution mutations [47]
ATP2B3	Xq28, p.L425_V426del [16]; p.V426_V427del [16]	ATP2B3 was expressed throughout the adrenal cortex in the whole layer [52]
CTNNB1	p.G45R [16]	

易发生 KCNJ5 基因突变，更有可能是 KCNJ5 基因携带者 [44]。因此，对于 KCNJ5 基因突变患者，也可以通过设计更加合理的治疗方案抑制相关蛋白通路，以期达到更好的治疗效果。

4 PA其他致病基因

KCNJ5 基因突变仅仅是 PA 发病的一个单一基因研究，除此之外，PA 发病的体细胞突变基因还有 7p22、CACNA1D、CYP11B2、ATP1A1、ATP2B3、CTNNB1 (表 2)，可能还有其他导致 PA 的基因尚未被发现。需要基于更大的样本，在基因组学、代谢组学、蛋白组学及分子生物学等基础之上对 PA 进行致病基因的筛选，进一步明确该病致病基因类型以及其与各种表型之间的关系，为该病的早期诊断及个体化治疗提供有力指导和帮助。

5 总结

综上所述，本文总结了 APA 发病过程中 KCNJ5 基因的来源、突变位点、临床表现以及诊断治疗方式。新型技术的运用对阐明 PA 患者中 KCNJ5 突变导致病理性醛固酮产生的病理生理学机制做出了重要贡献，尤其是高通量测序技术的发展和广泛应用可鉴别出 PA 相关的散发型与家族型体细胞和种系突变，SPECT 的应用对 PA 进行分类诊断具有较高的准确性，通过 RFA 可以控制 APA 进展，此外，多组学结合的模式也为 APA 的治疗提供了可能的研究方向。

参考文献

1 Reincke M, Bancos I, Mulatero P, Scholl UI, Stowasser M, Williams TA. Diagnosis and treatment of primary aldosteronism. Lancet Diabetes Endocrinol 2021; 9(12): 876–892.

2 Xu Z, Yang J, Hu J, Song Y, He W, Luo T, Cheng Q, Ma L, Luo R, Fuller PJ, Cai J, Li Q, Yang S. Primary aldosteronism in patients in China with recently detected hypertension. J Am Coll Cardiol 2020; 75(16): 1913–1922.

3 Cobb A, Aeddula NR. Primary Hyperaldosteronism. Treasure Island (FL): StatPearls Publishing, 2024.

4 Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008; 93(9): 3266–3281.

5 Lenzini L, Rossitto G, Maiolino G, Letizia C, Funder JW, Rossi GP. A Meta-analysis of somatic KCNJ5 K^+ channel mutations in 1636 patients with an aldosterone-producing adenoma. J Clin Endocrinol Metab 2015; 100(8): E1089–E1095.

6 Okamura T, Nakajima Y, Katano-Toki A, Horiguchi K, Matsumoto S, Yoshino S, Yamada E, Tomaru T, Ishii S, Saito T, Ozawa A, Shibusawa N, Satoh T, Okada S, Nagaoka R, Takada D, Horiguchi J, Oyama T, Yamada M. Characteristics of Japanese aldosterone-producing adenomas with KCNJ5 mutations. Endocr J 2017; 64(1): 39–47.

7 Wang B, Li X, Zhang X, Ma X, Chen L, Zhang Y, Lyu X, Tang Y, Huang Q, Gao Y, Fan Y, Ouyang J. Prevalence and

characterization of somatic mutations in Chinese aldosterone-producing adenoma patients. Medicine (Baltimore) 2015; 94(16): e708.

8 Zheng FF, Zhu LM, Nie AF, Li XY, Lin JR, Zhang K, Chen J, Zhou WL, Shen ZJ, Zhu YC, Wang JG, Zhu DL, Gao PJ. Clinical characteristics of somatic mutations in Chinese patients with aldosterone-producing adenoma. Hypertension 2015; 65(3): 622–628.

9 Nanba K, Vaidya A, Rainey WE. Aging and adrenal aldosterone production. Hypertension 2018; 71(2): 218–223.

10 Schilbach K, Junnila RK, Bidlingmaier M. Aldosterone to renin ratio as screening tool in primary aldosteronism. Exp Clin Endocrinol Diabetes 2019; 127(2–03): 84–92.

11 Boulkroun S, Fernandes-Rosa FL, Zennaro MC. Old and new genes in primary aldosteronism. Best Pract Res Clin Endocrinol Metab 2020; 34(2): 101375.

12 Yokota K, Shibata H, Kurihara I, Itoh H, Sone M. CASZ1: a promising factor modulating aldosterone biosynthesis and mineralocorticoid receptor activity. Hypertens Res 2023; 46(2): 417–420.

13 Choi M, Scholl UI, Yue P, Björklund P, Zhao B, Nelson-Williams C, Ji W, Cho Y, Patel A, Men CJ, Lolis E, Wisgerhof MV, Geller DS, Mane S, Hellman P, Westin G, Åkerström G, Wang W, Carling T, Lifton RP. K^+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science 2011; 331(6018): 768–772.

14 Chang YY, Lee BC, Chen ZW, Tsai CH, Chang CC, Liao CW, Pan CT, Peng KY, Chou CH, Lu CC, Wu VC, Hung CS, Lin YH. Cardiovascular and metabolic characters of KCNJ5 somatic mutations in primary aldosteronism. Front Endocrinol (Lausanne) 2023; 14: 1061704.

15 Xie J, Zhang C, Wang X, Jiang Y, Wu L, Ye L, Wang X, Xie W, Xu H, Wang W. Exploration of KCNJ5 somatic mutation and CYP11B1/CYP11B2 staining in multiple nodules in primary aldosteronism. Front Med (Lausanne) 2022; 9: 823065.

16 Chang Z, Shang JW, Ren RM, Ren X, Yang SS, Guo ZS. Correlation between KCNJ5 mutation and postoperative clinical remission of unilateral primary aldosteronism. J Clin Urol 2023; 38(7): 519–524.

17 Fernandes-Rosa FL, Amar L, Tissier F, Bertherat J, Meatchi T, Zennaro MC, Boulkroun S. Functional histopathological markers of aldosterone producing adenoma and somatic KCNJ5 mutations. Mol Cell Endocrinol 2015; 408: 220–226.

18 Cheng CJ, Sung CC, Wu ST, Lin YC, Sytwu HK, Huang CL, Lin SH. Novel KCNJ5 mutations in sporadic aldosterone-producing adenoma reduce Kir3.4 membrane abundance. J Clin Endocrinol Metab 2015; 100(1): E155–E163.

19 Vohra T, Kemter E, Sun N, Dobenecker B, Hinrichs A, Burrello J, Gomez-Sanchez EP, Gomez-Sanchez CE, Wang J, Kinker IS, Teupser D, Fischer K, Schnieke A, Peitzsch M, Eisenhofer G, Walch A, Reincke M, Wolf E, Williams TA. Effect of dietary sodium modulation on pig adrenal steroidogenesis and transcriptome profiles. Hypertension 2020; 76(6): 1769–1777.

20 Wang MH (王梦卉), Cai L, Wu T, Luo Q, Zhang WW, Zhou KM, Wang GL, Zhao JW, Zhang ZH, Li NF. Analysis of variation of G151R and L168R of KCNJ5 gene and expression of sodium-calcium exchange 1 in aldosterone tumor or peritumoral tissues. Anhui Med J (安徽医学) 2021; 42(11): 1215–1219 (in Chinese).

21 Warachit W, Atikankul T, Houngngam N, Sunthornyothin S. Prevalence of somatic *KCNJ5* mutations in Thai patients with aldosterone-producing adrenal adenomas. J Endocr Soc 2018; 2(10): 1137–1146.

22 Buffolo F, Tetti M, Mulatero P, Monticone S. Aldosterone as a mediator of cardiovascular damage. Hypertension 2022; 79(9): 1899–1911.

23 Meyer KM, Malhotra N, Kwak JS, El Refaey M. Relevance of *KCNJ5* in pathologies of heart disease. Int J Mol Sci 2023; 24(13): 10849.

24 Maria AG, Suzuki M, Berthon A, Kamilaris C, Demidowich A, Lack J, Zilbermint M, Hannah-Shmouni F, Faucz FR, Stratakis CA. Mosaicism for KCNJ5 causing early-onset primary aldosteronism due to bilateral adrenocortical hyperplasia. Am J Hypertens 2020; 33(2): 124–130.

25 Gruber S, Beuschlein F. Hypokalemia and the prevalence of primary aldosteronism. Horm Metab Res 2020; 52(6): 347–356.

26 Zhao L, Wan J, Wang Y, Yang W, Liang Q, Wang J, Jin P. Different cell compositions and a novel somatic KCNJ5 variant found in a patient with bilateral adrenocortical adenomas secreting aldosterone and cortisol. Front Endocrinol (Lausanne) 2023; 14: 1068335.

27 Lee BC, Kang VJ, Pan CT, Huang JZ, Lin YL, Chang YY, Tsai CH, Chou CH, Chen ZW, Liao CW, Chiu YW, Wu VC, Hung CS, Chang CC, Lin YH. KCNJ5 somatic mutation is associated with higher aortic wall thickness and less calcification in patients with aldosterone-producing adenoma. Front Endocrinol (Lausanne) 2022; 13: 830130.

28 Harashima S, Yamazaki Y, Motomura N, Ono Y, Omata K, Tezuka Y, Morimoto R, Nakamura Y, Satoh F, Suzuki H, Kwon GE, Choi MH, Sasano H. Phenotype-genotype correlation in aldosterone-producing adenomas characterized by intracellular cholesterol metabolism. J Steroid Biochem Mol Biol 2022; 221: 106116.

29 Chang YY, Tsai CH, Peng SY, Chen ZW, Chang CC, Lee

BC, Liao CW, Pan CT, Chen YL, Lin LC, Chang YR, Peng KY, Chou CH, Wu VC, Hung CS, Lin YH. KCNJ5 somatic mutations in aldosterone-producing adenoma are associated with a worse baseline status and better recovery of left ventricular remodeling and diastolic function. Hypertension 2021; 77(1): 114–125.

30 Nanba K, Baker JE, Blinder AR, Bick NR, Liu CJ, Lim JS, Wachtel H, Cohen DL, Williams TA, Reincke M, Lyden ML, Bancos I, Young WF, Else T, Giordano TJ, Udager AM, Rainey WE. Histopathology and genetic causes of primary aldosteronism in young adults. J Clin Endocrinol Metab 2022; 107(9): 2473–2482.

31 Li PH (李沛衡). LC-MS/MS in diagnosing KCNJ5 mutant aldosterone-producing adenoma [D/OL]. Beijing: Peking Union Medical College (北京协和医学院), 2021 (in Chinese). https://kns.cnki.net/kcms2/article/abstract?v=X-lf5kQqXAOkGYMZrKmu_WPM6bjGNEX0pXsUGW-8bhDmbWQwU38x1DMS-Jg4CAnMTTuEnJmwDgXl-V5prsglMqyy86KsemEn7c5jKLPCEcxS7Y6nvpW4fI0j1S-rDrI0Eg-K&uniplatform=NZKPT

32 Eisenhofer G, Durán C, Cannistraci CV, Peitzsch M, Williams TA, Riester A, Burrello J, Buffolo F, Prejbisz A, Beuschlein F, Januszewicz A, Mulatero P, Lenders JWM, Reincke M. Use of steroid profiling combined with machine learning for identification and subtype classification in primary aldosteronism. JAMA Netw Open 2020; 3(9): e2016209.

33 Lu CC, Yen RF, Peng KY, Huang JY, Wu KD, Chueh JS, Lin WY. NP-59 adrenal scintigraphy as an imaging biomarker to predict KCNJ5 mutation in primary aldosteronism patients. Front Endocrinol (Lausanne) 2021; 12: 644927.

34 Wang HP (王慧萍). Analysis of pathological classifcation, somatic mutation and clinical characteristics in primary aldosteronism [D/OL]. Zhangjiakou: Hebei North University (河北北方学院), 2021 (in Chinese). https://kns.cnki.net/kcms2/article/abstract?v=Xlf5kQqXAOkjzMVNoCdutU-aaz3oinkCsdx2p3oVJC2C01jNg-QtivePL2T-BAFrFssdc_RNkihWRil587FLDSdQZgN09W7GVNda0EeavsD-H3O-0tG7dSMA==&uniplatform=NZKPT&language=gb

35 Szabo Yamashita T, Shariq OA, Foster TR, Lyden ML, Dy BM, Young WF Jr, Bancos I, McKenzie TJ. Unilateral adrenalectomy for primary aldosteronism due to bilateral adrenal disease can result in resolution of hypokalemia and amelioration of hypertension. World J Surg 2023; 47(2): 314–318.

36 Chen J, Wu J, Zhu R, Lu L, Ma XJ. Ablation versus laparoscopic adrenalectomy for the treatment of aldosterone-producing adenoma: a meta-analysis. Abdom Radiol (NY) 2021; 46(6): 2795–2804.

37 Kishimoto S, Oki K, Maruhashi T, Kajikawa M, Mizobuchi A, Harada T, Yamaji T, Hashimoto Y, Yoshimura K, Nakano Y, Goto C, Yusoff FM, Nakashima A, Higashi Y. KCNJ5 mutation is a predictor for recovery of endothelial function after adrenalectomy in patients with aldosterone-producing adenoma. Hypertens Res 2023; 46(9): 2213–2227.

38 Wang F, Ma X, Tong A, Zhang Y, Wen J, Li Y. The effects of different calcium channel blockers on aldosterone-producing adenoma cells. Front Endocrinol (Lausanne) 2020; 11: 260.

39 Zhou TT (周婷婷), Yang SW, Luo PW, Wang L, Wang T, Xing JC. Effect of verapamil on aldosterone secretion in KCNJ5-mutated human adrenocortical carcinoma H295R cells. J Contemp Urol Reprod Oncol (现代泌尿生殖肿瘤杂志) 2020; 12(5): 298–302 (in Chinese).

40 Hattangady NG, Karashima S, Yuan L, Ponce-Balbuena D, Jalife J, Gomez-Sanchez CE, Auchus RJ, Rainey WE, Else T. Mutated KCNJ5 activates the acute and chronic regulatory steps in aldosterone production. J Mol Endocrinol 2016; 57(1): 1–11.

41 Maiolino G, Ceolotto G, Battistel M, Barbiero G, Cesari M, Amar L, Caroccia B, Padrini R, Azizi M, Rossi GP. Macrolides for KCNJ5-mutated aldosterone-producing adenoma (MAPA): design of a study for personalized diagnosis of primary aldosteronism. Blood Press 2018; 27(4): 200–205.

42 Scholl UI, Abriola L, Zhang C, Reimer EN, Plummer M, Kazmierczak BI, Zhang J, Hoyer D, Merkel JS, Wang W, Lifton RP. Macrolides selectively inhibit mutant KCNJ5 potassium channels that cause aldosterone-producing adenoma. J Clin Invest 2017; 127(7): 2739–2750.

43 Yang E, Ding C, Zhu X, Zhang J, Zhang W, Zhao Y, Zhang J, Lin X. *Sfrp2* regulates the WNT/β-catenin pathway to slow the development of aldosterone-producing adenoma. Cardiovasc Diagn Ther 2023; 13(3): 523–533.

44 Fernandes-Rosa FL, Williams TA, Riester A, Steichen O, Beuschlein F, Boulkroun S, Strom TM, Monticone S, Amar L, Meatchi T, Mantero F, Cicala MV, Quinkler M, Fallo F, Allolio B, Bernini G, Maccario M, Giacchetti G, Jeunemaitre X, Mulatero P, Reincke M, Zennaro MC. Genetic spectrum and clinical correlates of somatic mutations in aldosterone-producing adenoma. Hypertension 2014; 64(2): 354–361.

45 Chen CF (陈传芳). Mechanism of genetic mutation in 7p22 region leading to hypercholesterolemia [D/OL]. Wuhan: Wuhan University (武汉大学), 2020 (in Chinese). https://kns.cnki.net/kcms2/article/abstract?v=Xlf5kQqXAOnls6HGWIa8k7WR4uT1wvpLJRhaZfB6JgCznlCJpFfRck-DXE-591DOryh5s4Nj42KDGhnLkf2d1Q8Zjec2ttWQmz-pxCo_sXo55qnGuFKmLJgg==&uniplatform=NZKPT&language=gb

46 Azizan EA, Poulsen H, Tuluc P, Zhou J, Clausen MV, Lieb A,

Maniero C, Garg S, Bochukova EG, Zhao W, Shaikh LH, Brighton CA, Teo AE, Davenport AP, Dekkers T, Tops B, Küsters B, Ceral J, Yeo GS, Neogi SG, McFarlane I, Rosenfeld N, Marass F, Hadfield J, Margas W, Chaggar K, Solar M, Deinum J, Dolphin AC, Farooqi IS, Striessnig J, Nissen P, Brown MJ. Somatic mutations in ATP1A1 and CACNA1D underlie a common subtype of adrenal hypertension. Nat Genet 2013; 45(9): 1055–1060.

47 Scholl UI, Goh G, Stölting G, de Oliveira RC, Choi M, Overton JD, Fonseca AL, Korah R, Starker LF, Kunstman JW, Prasad ML, Hartung EA, Mauras N, Benson MR, Brady T, Shapiro JR, Loring E, Nelson-Williams C, Libutti SK, Mane S, Hellman P, Westin G, Åkerström G, Björklund P, Carling T, Fahlke C, Hidalgo P, Lifton RP. Somatic and germline CACNA1D calcium channel mutations in aldosterone-producing adenomas and primary aldosteronism. Nat Genet 2013; 45(9): 1050–1054.

48 Wang LL (王力力). Association of polymorphism in the aldosterone synthase (CYP11B2) gene with cardiovascular disease events in Chinese patients with hypertension [D/OL]. Shijiazhuang: Hebei Medical University (河北医科大学), 2021 (in Chinese). https://kns.cnki.net/kcms2/article/abstract?v=Xlf5kQqXAOmD05Aq9othRxudHj5-Lga8Suo-4BeLYiorUG2xsDgxred0ufEkaVYNMk4skKGIyBdTMQmjxW0cTcVBCfdUShXUg4KeM3wmbMdDOn1Owbm-9HctSsK199Gyu_&uniplatform=NZKPT&language=gb

49 Shah WA, Jan A, Khan MA, Saeed M, Rahman N, Zakiullah, Afridi MS, Khuda F, Akbar R. Association between aldosterone synthase (*CYP11B2*) gene polymorphism and hypertension in Pashtun ethnic population of Khyber Pakhtunkwha, Pakistan. Genes (Basel) 2023; 14(6): 1184.

50 Beuschlein F, Boulkroun S, Osswald A, Wieland T, Nielsen HN, Lichtenauer UD, Penton D, Schack VR, Amar L, Fischer E, Walther A, Tauber P, Schwarzmayr T, Diener S, Graf E, Allolio B, Samson-Couterie B, Benecke A, Quinkler M, Fallo F, Plouin PF, Mantero F, Meitinger T, Mulatero P, Jeunemaitre X, Warth R, Vilsen B, Zennaro MC, Strom TM, Reincke M. Somatic mutations in ATP1A1 and ATP2B3 lead to aldosterone-producing adenomas and secondary hypertension. Nat Genet 2013; 45(4): 440–444, 444e1–e2.

51 Williams TA, Monticone S, Schack VR, Stindl J, Burrello J, Buffolo F, Annaratone L, Castellano I, Beuschlein F, Reincke M, Lucatello B, Ronconi V, Fallo F, Bernini G, Maccario M, Giacchetti G, Veglio F, Warth R, Vilsen B, Mulatero P. Somatic ATP1A1, ATP2B3, and KCNJ5 mutations in aldosterone-producing adenomas. Hypertension 2014; 63(1): 188–195.

52 Al-Salameh A, Cohen R, Desailloud R. Overview of the genetic determinants of primary aldosteronism. Appl Clin Genet 2014; 7: 67–79.