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Genetic pathogenetic aspects of primary hyperaldosteronism and pheochromocytoma

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Abstract

Pheochromocytoma and primary hyperaldosteronism are the most common causes of secondary hypertension. In a group of patients with primary hyperaldosteronism the prevalence of somatic mutation has been established in patients with aldosterone-producing adenomas (APA), genetic mutations have been identified in patients with family types of the disease. The authors declare that aldosterone-producing cellular clusters, which derived from zona glomerulosa, appear as a result of somatic mutations and might be a precursor of APA. Development of bilateral adrenal hyperplasia and APA might be explained by an existence of autoantibodies and their chronic stimulation of zona glomerulosa. The assessment of somatic and germline mutations in patients with pheochromocytoma and paraganglioma facilitates early diagnostics other tumors within syndromic neoplasia. Implementation of new genetic test in practice would improve early diagnosis of adrenal pathology in hypertensive patients.

Key words: symptomatic arterial hypertension, pheochromocytoma, primary aldosteronism, aldosterone-producing adenoma, genetic mutations

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Генетические аспекты патогенеза первичного гиперальдостеронизма и феохромоцитомы

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Резюме

Наиболее частыми эндокринными причинами вторичной артериальной гипертензии (АГ) являются первичный гиперальдостеронизм и феохромоцитома (ФХ). У пациентов с гиперальдостеронизмом установлена частота соматических мутаций при альдостерон-продуцирующих аденомах (АПА), идентифицированы генетические мутации семейных форм заболевания. Исследователи сделали заключение, что область с альдостерон-продуцирующими клеточными кластерами, происходящая из клубочковой зоны, является следствием соматических мутаций и может быть представлена в качестве предшественника АПА. Наличие аутоантител и хроническая стимуляция ими клубочковой зоны, возможно, объясняет развитие двусторонней гиперплазии и АПА в надпочечниках. Выявление соматических и герминальных мутаций у пациентов с ФХ и параганглиомой способствуют ранней диагностике многих опухолей в рамках синдромальной неоплазии. Внедрение новых генетических исследований в практическую работу будет способствовать ранней диагностике заболеваний надпочечников, протекающих с АГ.

Ключевые слова: симптоматические артериальные гипертензии, феохромоцитома, первичный гипер-альдостеронизм, альдостерон-продуцирующая аденома, генетические мутации

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Secondary (symptomatic) arterial hypertension (HTN) results from the impairment of the organs involved in the regulation of blood pressure. Among adrenal diseases leading to HTN, primary hyperaldosteronism (PGA) and pheochromocytoma are the most common ones.

Based on the research data, 5–25 % of PHA patients have HTN [1]. Primary hyperaldosteronism develops as a result of aldosterone-producing adenoma (APA) or idiopathic hyperplasia of the adrenal cortex (IGA). Rare causes include hereditary forms, such as familial hyperaldosteronism of I, II or III types [2].

Data on the prevalence of IGA and APA have been revised in recent decades. According to various researchers, the incidence of IGA has significantly increased in comparison with other causes of hyperaldosteronism. Thus, in Mayo Clinic, according to the studies conducted in 1999, 120 patients were diagnosed with PGA, in 20 % of cases, the APA was confirmed, 8 % were assumed to have adenomas and 72 % — the IGA [3]. According to a screening study in 1125 patients with HTN, the prevalence of PHA caused by both APA and IGA increased significantly (from 7.2 % to 19.5 %, respectively) with an increase in the severity of hypertension [4].

At present, a large number of ongoing studies investigate genetic factors in the development of primary HA. Many studies were performed to determine somatic mutations, the genetic spectrum and the correlation of somatic mutations and the clinical picture in patients with APA [5, 6]. Analysis of the data of 474 patients showed somatic mutations in 54 % of all subjects with APA (ranging from 27.2 % to 56.8 % in different centers). To our knowledge, no data on the genetics of idiopathic hyperaldosteronism are available.

The mutation of KCNJ5 gene, representing the most common genetic breakdown in APA and detected in 38 % of APA patients [7], leads to changes in the potassium channel filter GIRK4. These changes are characterized by loss of channel selectivity, membrane depolarization, and increased intracellular calcium concentration. This, in turn, causes an increase in the synthesis of CYP11B2 and an increase in aldosterone production. KCNJ5 mutations are more common in Asian patients with a prevalence of 73 % in East Asia compared to 39 % in Europe [8].

The mutation of the CACNA1D gene is the second most common genetic breakdown and leads to the activation of potential-dependent Ca-channels, which contributes to an increase in intracellular calcium content and stimulation of aldosterone production. According to several authors, a mutation occurs in 9.3 % of patients with APA [7]. At present, ten mutations of CACNA1D were identified.

Correlation analysis of mutations in KCNJ5 and CACNA1D genes demonstrated that patients with KCNJ5 mutations were more often female and younger. All patients had a low potassium serum level [9]. A meta-analysis of 13 studies (1636 patients with APA) [10] showed high production of aldosterone and higher frequency of somatic KCNJ5 mutation in young female patients with large tumors.

CACNA1D mutations are detected in smaller adenomas. There was no correlation between these mutations and aldosterone and renin levels, aldosterone-renin ratio, as well as with postoperative outcomes and blood pressure level [9].

Some authors report mutations in the ATPase-encoding genes in APA patients: Na +/K + -ATPase1 (ATP1A1), and Ca + -ATPase3 (AT2B3). These changes were more common in men with high plasma aldosterone concentration and low potassium blood levels [11, 12]. In general, ATP1A1 and ATP2B3 gene mutations were detected in 5.3 % and 1.7 % of patients, respectively [9].

Unlike other forms, family forms of PHA are observed rarely. Back in 1992, Sutherland et al. [13] described the cause of the hereditary form of type I glucocorticoid-dependent aldosteronism. In this form, hybridization of genes from unequal cross-over occurs between CYP11B1 (encodes 11β-hydroxylase) and CYP11B (encodes aldosterone synthesis) on chromosome 8q24 [14].

Family type I hyperaldosteronism is an autosomal dominant disease and accounts for 0.5–1 % of HTN cases, 5 % among all PGA forms, found in both men and women. This is a heterogeneous disease with a wide variety of clinical and biochemical characteristics even within the same family. It is associated with severe HTN with high disability and mortality rates at young age as a result of hemorrhagic strokes. Screening should be performed in patients younger than 20 years with HTN or with a family history of HTN and hemorrhagic strokes less than 40 years of age [15]. This form is characterized by the hyperproduction of 18-hydroxycortisol (18OHF) and 18-oxocortisol (18oxoF). In most cases, bilateral hyperplasia of the adrenal cortex is found. The diagnosis of familial hyperaldosteronism of type I is usually confirmed by a long chain polymerase reaction [16].

Family type II hyperaldosteronism, occurring in 1.2–6 % of patients with PGA, is a form of hyperaldosteronism in the absence of a hybrid CYP11B1/B2 gene. It was first described in 1991. The genetic cause is still unknown, but association with the 7p22 locus has been described in some families with an autosomal dominant type of inheritance [17]. The disease has different clinical manifestations, indistinguishable from IGA and APA, so the diagnosis is based on the occurrence of PHA in two or more first degree family members.

After the initial identification of somatic mutations in aldosterone-producing adenomas, the new possibilities of genetic studies led to the discovery of germinal mutations. Family type III hyperaldosteronism was first described in 2008 in the father and two daughters with severe hypokalemic juvenile HTN [18]. Glucocorticoidependent HA was accompanied by high levels of 18OHF and 18oxoF. Bilateral adrenal hyperplasia was found in most patients. Recently, familial hyperplasia of the adrenal type III was shown to be related to a heterozygous mutation in the GIRK4 gene (encoded by KCNJ5). In addition, the Thr158Ala mutation was observed in the examined families [19]. U.I. Scoll et al. [23] described four families with PHA. Two of them had a severe course of the disease and a germinal mutation Gly151Arg KCNJ5. In two other families with a mild course of PGA, germinal mutations Gly151-Glu KCNJ5 were detected. Similar changes were detected in 21 European families [20]. Ile157Seru mutations were found in the mother and daughter with severe hyperaldosteronism, massive adrenal hyperplasia, and refractory juvenile HTN [21]. Thus, various germinal mutations of KCNJ5 in family type III type have an autosomal dominant type of inheritance. Patients have different clinical manifestations and severity.

Mendel's syndrome, including PGA and neuromuscular changes, was described in two cases caused by the germinal mutations of CACNA1D [22]. Recently, five independent cases of identical germinal mutations in the CACNA1H gene were described among 40 patients with juvenile PHA, which is a new family form of hyperaldosteronism, since these mutations were not previously described in PHA. CACNA1H encodes potential-dependent calcium channels [23]. The mutation helps to reduce inactivation of the channel and increase the level of intracellular calcium, stimulating aldosterone production.

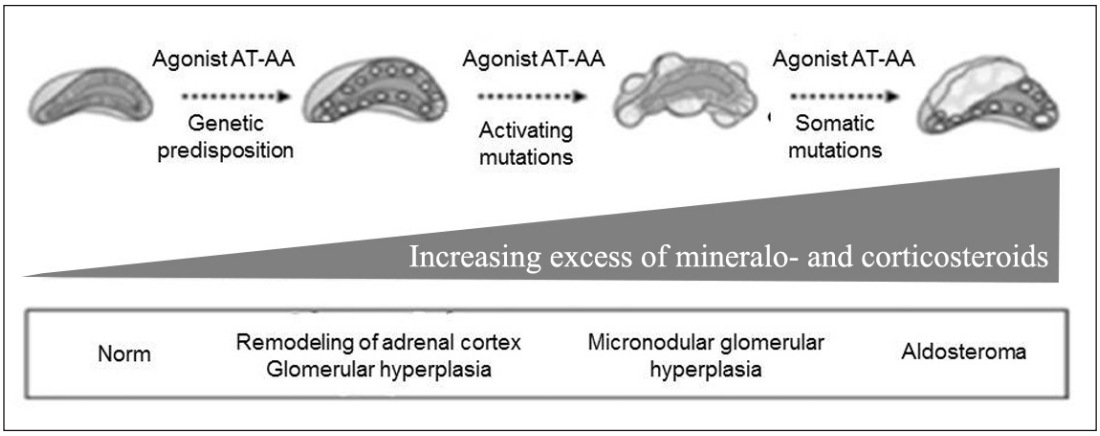
Immunohistochemistry studies showed aldosterone-producing clusters of cells with a high degree of CYP11B2 expression both in healthy adrenal glands and in APA [24]. The number of aldosterone-producing cell clusters (ARCC) was greater in women than in men. These cell groups are located in the layer of cortisol-producing cells negative for CYP11B2. Thus, the production of aldosterone comes from aldosterone-producing cell clusters of the beam zone and stimulates the glomerulus zone. A microarray study showed that these cell clusters are similar in structure to the glomerular zone and have the ability to enhance aldosterone production [25]. In addition, new generation sequestration demonstrated that APCC-cells are found in APA with somatic mutations (CACNA1D and ATP1A1), which leads to renin-independent hyperaldosteronism. The spectrum of identified genetic mutations in APCC-cells differed from that in APA. There was no mutation in KCNJ5. As a result, the researchers concluded that aldosterone-producing cell clusters originate from the glomerular zone of the adrenal cortex due to somatic mutations and may precede the aldosterone-producing adenoma.

Autoantibodies against angiotensin II receptor type 1, bound to G-protein (AT1-AA), have recently been associated with such conditions as preeclampsia, renal transplant rejection, HTN [26]. D.C. Kem et al. [27] investigated the pathogenic role of these autoantibodies and concluded that they contribute to the development of PHA and HTN [27]. The authors showed that the antibodies AT1-AA isolated from 13 patients activate losartan- and candesartan-sensitive AT1 (AT1R) receptor. The effect of these antibodies leads to a decrease in resistance to arterial shrinkage and stimulation of aldosterone production in adrenocortical carcinoma (HAC15 cell line). Antibodies AT1-AA can alter the allosteric configuration of the AT1R receptor and enhance the binding of angiotensin II. The authors suggested that the autoantibodies might contribute to the post-adrenalectomy maintenance of HTN in 50% of patients with APA [27]. A similar group of patients with PGA showed a large prevalence of AT1-AA antibodies in idiopathic adrenal hyperplasia (75%) compared with adenomas (46%) [28]. Thus, the chronic stimulation of the glomerular zone by autoantibodies AT1-AA with predisposition to somatic mutations may explain the development of bilateral hyperplasia and aldosterone-producing adenoma in the adrenal glands (Fig. 1).

The pheochromocytoma (FH) develops from the chromaffin cells of the adrenal medulla. Paragangliomas (PGL) are tumors that produce catecholamines emanating from paraganglia of different locations (near the solar, renal, adrenal, aortic, hypogastric plexuses, anterior to the abdominal aorta and above the mesenteric artery). In HTN, PX and PGL occur in 0.2–0.6% of patients [29, 30]. In the general population, the incidence of PX is 1: 100 000–200 000 cases per year, and the incidence of PGL is 1: 500 000 per year [31, 32].

The hereditary cause of chromaffin tumors is detected in more than 30% [32, 33]. FH is associated with the following hereditary diseases: syndrome of

Figure 1. Adrenocortical remodeling with primary hyperaldosteronism



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multiple endocrine neoplasia type 2, type 1 neurofibromatosis (NF-1), von Hippel-Lindau disease (VHL syndrome). FH and PGL result from mixed genetic mutations and epigenetic changes. These mutations are responsible for the phenotype of FH. Considering novel concept of the epidemiology of genetic PC, the study of the phenotypic and laboratory features of its various family forms is relevant: the time of manifestation, the frequency of metastatic lesion, the tumor secretion. Genotyping is a reliable method of diagnosing hereditary diseases and is required to choose therapeutic strategy [34, 35].

Genetic mutations, depending on the gene expression, are classified into two main clusters [33, 36]. The pseudohypoxic pathway cluster (cluster 1) includes mutations of the genes HIF2A, PHD2, VHL, SDHX, IDH, MDH2 and FH. Cluster 2 comprises mutations which are associated with impaired activation of the kinase-signaling pathway. This cluster includes mutations of the genes RET, NF1, KIF1Bβ, MAX and TMEM127. In recent years, gene mutations responsible for predisposition to PX and PGL have been identified. These genes include GDNF, H-ras, K-ras, GNAS, CDKN2A, p53, BAP1 and BRCA 1 and 2 [33, 36, 37].

The detection of germinal mutations in patients with PX or PGL contributes to the early diagnosis of many tumors as part of neoplasia syndrome. The germinal mutations were detected in the SDHA, SDHC, SDHAF2, FH, KIF1β and TMEM127 genes [33, 37], while somatic mutations were found only in the HRAS gene [36]. Mutations in the TMEM127 gene have been recently described in PGL. Earlier, mutations were detected only in patients with tumors located in the adrenal gland. Recently, genetic mutations of genes have been described in tumors located outside the adrenal glands [33, 37]. These were somatic and germinal mutations in the genes SDHB, SDHD, NF1, RET, VHL, MAX. Mutations of other genes, such as MEN1, EGLN1, EGLN2, MDH2, IDH1, and BAP1 were detected in isolated cases in patients with PX and PGL [33, 35, 38].

In 2002, H. P. H. Neumann et al. [39] performed genotyping of the main genes associated with PX and PGL (SDHB, SDHD, VHL, RET) in more than 3,600 patients. They found hereditary mutations in 33.8%. The most common mutations were found in the SDHB (10.3%), SDHD (8.9%), VHL (7.3%), RET (6.3%) and NF1 (3.3%) genes. The rate of hereditary mutations SDHC, SDHA, MAX and TMEM127 was less than 2%. In a survey of 315 patients with sporadic cases of PX and PGL, no single SDHAF2 mutation was detected [39].

The discovery of mutations in the succinate dehydrogenase gene (SDH) demonstrated a much more frequent identification of hereditary variants [33]. SDH is an integrated membrane-protein complex that participates both in the oxidative phosphorylation and in critical reactions of the tricarboxylic acid cycle (Krebs cycle) [40]. The SDH complex is bound to the inner mitochondrial membrane, has a complex structure and consists of 4 subunits: 2 hydrophilic subunits — SDHA and SDHB and 2 hydrophobic subunits — SDHC and SDHD [41].

The first identified SDHA mutation was the heterozygous germinal mutation p.Arg589Trp associated with catecholamine-producing abdominal paraganglioma [42]. In vivo and in vitro mutations of SDHA lead to loss of SDH-enzymatic activity in tumor tissues [42]. The germinal mutations of the SDHB gene are considered to determine the malignancies developed from the chromaffin tissue, and

are predictors of poor prognosis [33, 43, 44]. Mutant alleles of SDHD lead to loss of functional activity of complex II of the electron transport chain [33]. To date, a large number of SDHB mutations associated with neuroendocrine neoplasias have been described. In the study of malignant PX and PGL (malignancy was assessed by the presence of metastases and histologically confirmed invasion of the lymph nodes), germinal mutations of SDHB were detected in 42 % of cases [45, 46]. F. Brouwers et al. [46] demonstrated SDHB mutation in 13 patients out of 44 examined subjects with malignant PGL. The average time till metastases occurrence in patients with SDHB mutations is 4 months, compared to 20 months for patients without such mutations [45, 46]. In the review by B. Pasini and C.A. Stratakis [47], the prevalence of a SDHB gene mutation is estimated as 36 % among patients with malignant PX and PGL. Germinal mutations of SDHB are considered as predictors of subsequent rapid metastatic process.

The germinal mutations of SDHC and SDHD genes are found in patients with hereditary paragangliomas ("paranglion-pheochromocytoma syndrome"). Variant SDH mutations are described in tumors of the gastrointestinal tract [49], kidneys, including familial renal cell carcinoma [33, 49], which confirms the association between variant germinal mutations of SDH and various neuroendocrine tumors.

The germinal mutations of the RET-protooncogene, which lead to uncontrolled cell proliferation, result in multiple endocrine neoplasia type 2 (MEN 2) [50]. The RET gene, located on the chromosome 10q11.2, encodes a receptor protein responsible for the cell growth, differentiation and survival. At present, typical mutations of the RET gene are determined in 8 exons [50, 51]. Patients with MEN-2a have missense mutations in exon 10 (C609, C610, C611, C618, C620) and exone 11 (C634) [52]. These mutations damage one of the six-cysteine residues in the RET-extracellular domain [53]. Mutations in these cysteine residues lead to homodimerization of the receptor through the formation of disulfide bridges. Up to 98 % of patients with MEN-I2a have a mutation in one of the cysteine codons of the extracellular domain of the RET protein: 609, 611, 618, 629 (exon 10) and 634 (exon 11) [52, 54]. More than 80 % of the cases of MEN-2a are due to a codon 634 mutation. In rare cases, the cysteine domain mutations may be in 610, 620, 630-m and other codons [53, 54].

With MEN-2b, more than 95 % of patients have a mutation in exon 16 (C918). This mutation localization provides the tyrosine kinase receptor the ability to activate in the monomeric state, which leads to increased phosphorylation of intracellular tyrosine residues (local kinase catalytic activity increases). In addition, more rare non-cysteine mutations located within the intracellular catalytic domain of RET are described [53, 54].

The specific location of the mutating residue within the RET protein correlates with the phenotypic features of the patients. For the first time diagnosed, 30 % of the FH are bilateral. In 50 % of patients with newly diagnosed unilateral PX, on average, the FH of the other adrenal gland is detected within a decade. The secretion of predominantly adrenaline occurs in the paroxysmal regimen. Compared with tumors with von Hippel-Lindau disease, PH at MEN 2 have a greater supply of catecholamines and a slower intracellular metabolism [54]. The development of new generation sequencing methods, family occurrence of these genetic mutations and syndromes can contribute to early diagnosis.

Thus, secondary arterial hypertension of the endocrine etiology often requires specific diagnostic tests and treatment beyond the use of typical antihypertensive drugs. An incorrectly established diagnosis can lead to catastrophic complications or irreversible damage to target organs. In this regard, the introduction of genetic methods to examine patients with HTN will contribute to the early diagnosis of adrenal diseases and the selection of the right treatment tactics.

Conflict of interest
The authors declare no conflict of interest.

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