Adrenal Tumors in Childhood
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John S. Fuqua, M.D.
Professor of Clinical Pediatrics
Indiana University School of Medicine

705 Riley Hospital Drive
Room 5960
Indianapolis, IN 46202
Tel: 317-944-3889
Fax: 317-944-3882
Email: jsfuqua@iu.edu

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Synopsis
Adrenal tumors are rare in children. Adrenocortical tumors often present with signs of virilization in children under 5 years old. Germline mutations may place affected children at risk for other malignancies. Treatment of adrenocortical tumors is primarily surgical. Pheochromocytomas and paragangliomas present with hypertension and associated symptoms. The evaluation requires measurement of serum or urine metanephrines and medical imaging. Surgical treatment is required following appropriate preparation with adrenergic blockade. More than 50% of affected children have underlying germline mutations, particularly in VHL and SDHx.

Key Words
Adrenocortical tumor
Virilization
Cushing syndrome
Pheochromocytoma
Paraganglioma

Key Points

- Adrenocortical tumors are rare in children and usually present with virilization before age 5 years. They may also present as Cushing syndrome or with mixed effects.
- Germline mutations in oncogenes occur in children with adrenocortical tumors, including TP53, which causes Li-Fraumeni syndrome.
- Pheochromocytoma and paraganglioma are catecholamine-secreting tumors arising from chromaffin cells and usually present with hypertension.
- More than 50% of children with pheochromocytoma and paragangliomas have mutations in oncogenes putting them at risk for other malignancies, with the most common being VHL leading to von Hippel-Lindau syndrome
- Treatment of adrenocortical tumors and pheochromocytoma/paraganglioma is surgical. Appropriate pre- and postoperative management is critical to prevent morbidity.

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Introduction

Adrenal neoplasms are rare in the pediatric population. However, they may be malignant, and they typically manifest with concerning symptoms and signs that may be life-altering. Higher stage malignant adrenal tumors carry poor prognoses. In the last decade, we have learned more about the genetic underpinnings of these lesions that should lead to improved diagnosis and management decisions. In this article, we will focus primarily on adrenocortical tumors and pheochromocytoma, with limited discussion of nodular adrenocortical disease.

Embryology and Early Development of the Adrenal Gland

The fetal adrenal cortex develops from coelomic epithelial precursors on the urogenital ridge between 4-6 weeks gestation. By 7-8 weeks gestation, the fetal adrenal cortex develops two zones: the fetal zone and the definitive zone.[1] The fetal zone represents 80-90% of the cortical volume and secretes cortisol under the influence of ACTH, but the principle product is DHEA-S, which undergoes conversion to estrogens in the placenta. By late gestation, the definitive zone has begun differentiation into the zona glomerulosa and the zona fasciculata. The adrenal medulla develops from neural crest-derived chromaffin cells that migrate ventrally to approach the cortical precursors under the influence of neuropilins.[2] Late in the first trimester, the chromaffin cells imbed into the cortical mass and become enveloped, but a structurally complete medulla does not form until after birth. At birth, the fetal adrenal is nearly as large as the kidney due to the large fetal zone. However, the fetal zone rapidly involutes as the adult cortex develops in the first few months. The zona reticularis does not develop until later in childhood.

Adrenocortical Tumors

Presentation

Pediatric adrenocortical tumors (ACTs) were first described in 1865.[3] They are rare, comprising only 0.2% of all childhood malignancies, and it is estimated that there are only 25 cases diagnosed per year in the United States.[4] The International Pediatric Adrenocortical Tumors Registry (IPACTR) is hosted by St. Jude Hospital, and based on these data the worldwide annual incidence is thought to be 0.3-0.38 cases per million children below age 15 years.[5] Interestingly, the southern region of Brazil has a 10-15-fold higher rate of disease, which may be due to a founder effect.[6] Across the lifespan, there is a bimodal distribution of cases, with a peak at about 3.8 years and a second peak occurring in the 30-50-year-old range. The majority of pediatric ACTs occur in children <5 years old. There is a female predisposition, with a female:male ratio of 1.7:1 in those <3 years old, increasing to 6.2:1 in the teenage years.[7] The reason for the young age at presentation is not fully understood but is in part related to the increased prevalence of oncogene mutations in pediatric ACT cases. Additionally, it is thought that pediatric ACTs develop in the regressing fetal adrenal zone because of the early age at first manifestation, the occasional detection of an ACT in neonates, and the predominance of androgen-secreting tumors in childhood.[1]

Pediatric adrenocortical tumors are functional in 90% of cases. An analysis of 254 patients with ACTs by the IPACTR showed that 55% presented with isolated virilization, while only 5.5% had isolated Cushing syndrome. Those with a mixed virilizing/Cushing phenotype comprised an additional 29%, and there were a few patients with elements of hyperaldosteronism. Isolated aldosterone excess (Conn syndrome) occurred in only two children.[7] Patients presenting with isolated Cushing syndrome tended to be older, with a median age of 12.6 years. Feminizing adrenal tumors are very rare.

As a result of the secretory nature of ACTs, the most common signs include rapid penile or clitoral enlargement, sexual hair growth, hirsutism, acne, and increased height velocity. (**FIGURE 1**) These may be mixed with cushingoid features, such as rapid weight gain or moon facies. (**FIGURE 2A and 2B**) In mixed presentations, the growth suppression from hypercortisolism may limit the growth acceleration from hyperandrogenism. Patients may complain of abdominal pain. The high prevalence of functioning tumors leads to a relatively short time to diagnosis, with approximately 2/3 of patients diagnosed within 6 months of the first signs.[7]

Laboratory studies are consistent with the endocrine pathophysiology.[5] Serum concentrations of testosterone, androstenedione, and particularly DHEA-S are often significantly elevated. Estradiol, 17-hydroxyprogesterone, and 11-deoxycortisol may be elevated. Measures of cortisol secretion may be abnormal, including lack of suppression in response to dexamethasone and increased 24-hour urinary cortisol and midnight salivary cortisol levels. If there is concern for adrenal medullary disease, plasma free metanephrines should be assessed (see section below on pheochromocytoma). Imaging studies are critical to establish the extent of disease, such as tumor location, size, invasion of local structures, and the presence of tumor thrombus in the inferior vena cava. The most common locations of distant metastases are the liver and lungs, so chest imaging is required in addition to abdominal imaging.[8] Kidney, brain, and bone metastases occur less often, and bone or CNS imaging is not routinely required in the absence of clinical suspicion. For abdominal imaging, the choice of CT vs. MRI may be based on local preference,[9] although MRI does not require radiation exposure. Imaging of the chest is best done by CT.

Molecular Pathogenesis and Association with Malignancy Syndromes

Adrenocortical tumors occur more commonly in inherited malignancy syndromes such as Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and familial adenomatous polyposis (FAP, Gardner syndrome), although a minority of children with ACT have one of these syndromes.[10]

Li and Fraumeni first reported an autosomal dominantly-inherited association of soft tissue sarcomas and breast carcinoma in 1969.[11] Affected families were found to carry germline mutations in the TP53 gene, encoding the tumor suppressor p53. This protein regulates genes controlling the cell cycle as well as apoptosis, DNA repair, and senescence, and somatic inactivation of p53 or members of its pathway are extremely common in malignant tumors, including ACTs. In families with Li-Fraumeni syndrome, cancers of the breast, brain, and adrenal as well as sarcomas comprise 80% of malignancies. Approximately 10% of those with germline mutations in TP53 syndrome have adrenocortical cancer.[12] Conversely, based on data from the IPACTR (in which patients from Brazil are over represented), 64-71% have germline mutations in TP53 but were not from families recognized as having Li-Fraumeni syndrome.[10,13] Findings such as this have led to the concept that the onset of cancers seen in affected families may vary depending on the specific TP53 mutation. A good example of this concept is the experience in southern Brazil, where the incidence of ACT is 10-15 times higher than in most parts of the world. Among unrelated children with ACT in this region, 78-98% carry the R337H mutation in exon 10 of TP53.[14,15] The mutation has low penetrance, however, especially in the first few decades of life. Ten to fifteen percent of individuals carrying the R337H mutation develop ACT.[15] Although the occurrence of other tumors prior to age 30 years is low in people with the R337H mutation, the lifetime risk of tumors and the tumor types are similar to those seen in classic Li-Fraumeni syndrome.[6]

Familial adenomatous polyposis (FAP) is an autosomal dominantly-inherited condition in which affected patients have hundreds to thousands of colon polyps, increased risk for colon cancer, thyroid tumors, and ACTs. Mutations in the adenomatous polyposis coli (APC) gene have been identified as the cause of FPC and adrenocortical tumorigenesis.[16] The APC gene is involved in the WNT/β-catenin pathway. In the absence of WNT binding to the frizzled receptor, β-catenin is degraded by a complex of binding proteins including APC, axin, and glycogen synthase kinase 3β. Upon WNT binding, the degradation complex is dispersed, and β-catenin accumulates, migrates to the nucleus, and activates target genes regulating the cell cycle and cell adhesion.[17] Disruption of the degradation complex by mutations in APC allow unregulated β-catenin accumulation, leading to tumorigenesis. Somatic mutations in the WNT/β-catenin pathway occur in 38% of adrenal adenomas and 85% of adrenal carcinomas and have also been implicated in numerous other cancers, including colon, gastric, and hepatocellular carcinomas.[18] MicroRNAs may also interact with the WNT/β-catenin pathway. MicroRNAs are short RNA strands that bind to mRNA and repress translation or increase degradation of mRNA. MicroRNAs play important roles in cell proliferation, differentiation, and apoptosis. MicroRNA449 has been found to play a role in nodular adrenal disease, acting through inhibition of WNT/β-catenin pathway genes. Elements of this pathway are potential therapeutic targets.[19]

Abnormalities in the insulin-like growth factor (IGF) system are also involved in ACT development. Beckwith-Wiedemann syndrome (BWS) is caused by abnormal imprinting at chromosome 11p15, a locus including the IGF2 gene, leading to IGF2 overexpression. Adrenocortical tumors have been found in 7% of individuals with BWS.[20] Additionally, in ACTs from pediatric patients without BWS, overexpression of both IGF2 and the gene for its receptor, IGF1R, have been found to be particularly prevalent.[21] Overexpression of IGF1R may be

mediated by downregulation of microRNA mir100.[22] Analysis of tumor tissue has shown that loss of heterozygosity at chromosome 11p leading to overexpression of IGF2 is an early event in tumor development,[23] and inhibition of the IGF-1 receptor may be a treatment strategy.[24]

Grading and Staging of ACTs

Differentiation between a benign adrenocortical adenoma and adrenocortical carcinoma may be difficult. In adults, pathologists frequently use the Weiss criteria to grade tumors.[25] This strategy is based on a series of histological features, including nuclear grade; mitotic rate; atypical mitoses; percentage of clear cells; microscopic necrosis; and venous, sinusoidal, and capsular invasion. The presence of three or more of these findings is highly correlated to recurrence or metastasis. However, children with ACTs have better prognoses than adults with similar histopathologic findings, with grade IV tumors per Weiss criteria correlating well with prognosis in adults but not in children.[26] This has led to the adoption of a grading system put forth by Wieneke, et al.[27] This system includes 11 items and puts more weight on tumor size and local invasion in addition to measures of cellular atypia. The scoring yielded three categories: A) Those with up to two criteria had a benign long-term clinical outcome; B) Those with three criteria were indeterminate for malignancy; and C) Tumors meeting four or more criteria were characterized as malignant and those patients had poor outcomes. Other investigators have validated this system.[28]

In general, benign adrenocortical adenomas tend to weigh <200 grams, are well defined and spherically shaped, with no invasion into local structures. Histologically, they resemble the normal zona fasciculata or reticularis. Adrenocortical carcinomas are more likely to be larger

with marked lobulation and large areas of necrosis or hemorrhage. Microscopic examination reveals larger cells that are arranged in alveolar clusters, with eosinophilic cytoplasm.[29]

The MacFarlane/Sullivan staging system was proposed in 1958, modified in 1978, and is based on series of patients ranging from neonates to age 69 years.[30] Several newer staging systems based exclusively on childhood data have been proposed in the last 25 years. These systems have variably incorporated tumor size, degree of residual tumor, normalization of hormone levels post-operatively, and the presence of distal metastases. Using the staging criteria proposed by Sandrini, et al. in 1997 and modified by others,[10,31] (**TABLE 1**) an analysis of 58 Brazilian children showed >90% long-term survival for stage 1. Survival rates for stages 2 and 3 were intermediate, but were significantly lower at 52% and 25%, respectively. Virtually none of those with stage 4 disease survived. The IPACTR, working through the Children's Oncology Group, has proposed a similar staging system that incorporates spread to retroperitoneal lymph nodes.[10]

Estimates of the overall survival rate for children with adrenocortical tumors vary widely, ranging from 46-74%.[5,29] In addition to disease stage, favorable factors important in the prognosis include age <3 years and the presence of virilization at diagnosis.[7] Factors associated with decreased survival include glucocorticoid secretion and an elevated Ki67-labeling index.[5]

Treatment

Surgical removal of the tumor is the mainstay of treatment, with the goal of a complete microscopic resection. Malignant ACTs tend to be locally invasive and adhere to surrounding structures. As a result, *en bloc* resection of kidney, liver segments, or portions of the pancreas may be needed. Selection of a laparoscopic vs. open procedure is controversial, with some

studies showing poorer prognosis with a laparoscopic approach.[32] Some authors suggest that laparoscopic adrenalectomy is acceptable if there is no local invasion noted in the staging evaluation.[5] Tumors typically have a thin capsule and are friable and easily ruptured. Intraoperative tumor spillage worsens the long-term prognosis, and having an experienced surgeon is thus important. The role of retroperitoneal lymph node dissection is not established in children, but may improve the prognosis in adults.[33] All ACTs should be considered malignant at the time of surgery.[5]

Due to the extreme rarity of ACTs in children, the role of chemotherapy is not well studied. It is recommended in children with intraoperative tumor spillage, residual disease, or in those with local or distant metastases. This differs from recommendations in adults, in whom chemotherapy is used earlier due to higher recurrence rates.[5] The most studied medication is mitotane, which inhibits steroidogenesis and is anti-proliferative and adrenolytic, leading to apoptosis of the zona fasciculata and zona reticularis. The prognosis is better when serum mitotane concentrations exceed 14 mg/L for at least six months. This can be attained by daily dosing of 4 grams/m^2 of body surface area.[34,35] Mitotane toxicity may limit dosing and commonly takes the form of abdominal pain, vomiting, and diarrhea. Neurotoxicity may lead to lethargy, ataxia, depression, and vertigo and is most often seen when serum concentrations exceed 20 mg/L.[29] Because it inhibits steroidogenesis, patients receiving mitotane require glucocorticoid and mineralocorticoid replacement. Mitotane induces hepatic cytochrome P450 3A4, which accelerates glucocorticoid clearance. Thus, patients may require higher doses to avoid symptoms of adrenal insufficiency.[36] Combination chemotherapy including cisplatin, etoposide, and doxorubicin along with mitotane has been shown to improve survival in adults, but it has not been systematically studied in children.[37] Adrenocortical tumors have been

considered to be radioresistant, so radiation therapy has not traditionally been used. However, it is useful as palliative therapy in adults with refractory disease.[34] Routine radiation therapy in children is not recommended due to the potential for secondary malignancies, especially in those with TP53 mutations.[5]

Primary Bilateral Adrenal Hyperplasias

This group of nodular adrenal diseases comprises 10% of primary adrenal causes of Cushing syndrome.[38] It is divided into micronodular forms that tend to affect children and young adults and macronodular hyperplasia, which occurs more commonly in older adults. Micronodular bilateral adrenal hyperplasia includes the subgroups of primary pigmented nodular adrenal disease (PPNAD) and isolated micronodular adrenal disease (iMAD).[39]

Primary Pigmented Nodular Adrenal Disease

PPNAD typically presents with Cushing syndrome in the 2nd, 3rd, and 4th decades and is more frequent in females. Cushing syndrome due to PPNAD tends to be relatively mild and may be cyclical.[40] Between 50-80% of those with PPNAD have Carney complex, while about 60% of those with Carney complex ultimately develop PPNAD.[41,42] Carney complex is a rare multiple neoplasia syndrome. Common features include multiple skin lentigines, blue nevi, PPNAD, myxomas of the skin and heart, large clear cell Sertoli cell tumors of the testes, thyroid nodules and carcinoma, acromegaly, and psammomatous melanotic schwannomas. Carney complex is most often caused by mutations in the PRKAR1A gene, encoding a regulatory subunit of protein kinase A. Other genes in the PKA pathway may also carry mutations, such as genes encoding the PKA catalytic subunits or phosphodiesterases.[19] Patients with Cushing syndrome associated with

Carney complex may have a paradoxical increase in cortisol production in response to dexamethasone, arising from overexpression of glucocorticoid receptors on adrenocortical cells and acting through a PKA-mediated mechanism.[43] Small adrenal nodules may be seen on high-resolution CT scans, appearing as hypodense, round, and well-delineated lesions.[42] Cushing syndrome caused by nodular adrenal disease is usually treated with bilateral adrenalectomy, although more limited surgery may be effective. Histology shows multiple 1-4 mm nodules with brown, black, yellow, or red pigmentation, with internodular adrenal atrophy.[44] Patients with Carney complex require surveillance for other manifestations. Recommendations include annual echocardiography and ultrasounds of the thyroid and testes as well as annual measurement of urinary free cortisol and IGF-1. In children and adolescents, growth and puberty should also be monitored.[42]

Isolated Micronodular Adrenocortical Disease

iMAD is a subset of micronodular bilateral adrenal hyperplasia. Like PPNAD, it leads to Cushing syndrome, but it is not associated with other non-adrenal disorders. iMAD usually presents in infancy and childhood and usually occurs earlier than PPNAD. It also tends to cause mild to moderate Cushing syndrome that may be cyclical.[40,45] Histologically, nodules are <10 mm in size and are not grossly pigmented. There is no internodular adrenal atrophy. iMAD is caused by mutations in PDE11A and PDE8B, both of which encode phosphodiesterases, leading to cellular accumulation of cAMP, aberrant signal transduction, and tumorigenesis.[45,46] As in cases of PPNAD, iMAD is usually treated with bilateral adrenalectomy.[38]

Primary Bilateral Macronodular Adrenal Hyperplasia

Primary bilateral macronodular adrenal hyperplasia (PBMAH) most commonly presents with Cushing syndrome in older adults, age 40-60 years.[45] It may develop slowly with a long period of subclinical hypercortisolism and milder Cushing syndrome that may require decades to be detected.[45,47] As with micronodular adrenal hyperplasia, patients with PBMAH may have a paradoxical increase in cortisol secretion in response to dexamethasone. Interestingly, aberrant expression of other G-protein-coupled receptors is very common and contributes to excessive cortisol secretion, including the gastric inhibitory polypeptide (GIP) receptor, adrenergic receptors, and the V1a vasopressin receptor.[48] Although mutations in FAP and MEN1 may lead to PBMAH, abnormalities in ARMC5 are the most common cause, occurring in 40% of cases.[49] PBMAH may also rarely occur in McCune-Albright syndrome, in which case it may present as early as the first year of life.[47]

Pheochromocytoma/Paraganglioma

Presentation

Pheochromocytomas and paragangliomas (collectively referred to as PPGL) are neuroendocrine tumors derived from chromaffin tissue of the adrenal medulla or extra-adrenal sympathetic ganglia in the thorax, abdomen, and pelvis. PPGL secrete catecholamines, which lead to the majority of the presenting symptoms. Paragangliomas (PGL) located in the head and neck are derived from parasympathetic nervous tissue and are usually non-functional. Although the mean age at diagnosis is 51±16 years, PPGL can occur at any age. The overall annual incidence is 0.46 per 100,000, but about 10-20% occur in the childhood population, giving an incidence rate of 0.2-0.5 per million children.[50,51] The median age at diagnosis in children is about 13 years, and about 75% of PPGL in children are pheochromocytomas (PHEO).

Symptoms of PPGL include headache, tachycardia, diaphoresis, and pallor. Less common are asthenia, weight loss, abdominal pain, fever, and seizures. Hypertension is seen in the large majority of patients. In a recent Italian cooperative study, 19/20 symptomatic patients with PHEO and 15/22 with PGL presented with hypertension.[52] Hypertension may be severe and can be associated with hypertensive cardiomyopathy. In a study of a large number of children referred for evaluation of hypertension, 1.7% had a PPGL.[53] Because there is a high prevalence of predisposing germline mutations, many patients are found to have PPGL on prospective screening studies if they have a family history of PPGL or associated syndromes. PPGL are rarely biochemically silent, and the majority of those not identified on screening present with catecholamine-related symptoms.

Evaluation

PPGL are more commonly associated with heritable germline mutations than any other cancer type.[54] Thus, genetic testing is a key component of the evaluation for any patient with a confirmed PPGL, especially children. Testing also allows for potential diagnosis in asymptomatic relatives. Patients with PPGL may have a family history consistent with a known predisposing syndrome, such as von Hippel Lindau (VHL); multiple endocrine neoplasia, type 2 (MEN2); and neurofibromatosis, type 1 (NF1). Additionally, genetic testing identifies those with mutations in the genes encoding components of succinate dehydrogenase (collectively known as SDHx), who have a high risk of metastases. The likelihood of a germline mutation is especially high in cases of multifocal tumors, extra-adrenal tumors, and when there are known metastases. Decision algorithms have been published[55] with the goal of optimizing genetic testing, but the

advancement of testing technology has made the use of gene panels faster and more cost-efficient.

The major diagnostic approach to PPGL is measurement of plasma free metanephrines or 24-hour urinary metanephrines, including both metanephrine and normetanephrine. Their measurement is preferred over catecholamines because metanephrines are specific for chromaffin tissue vs. sympathetic nervous tissue and because chromaffin tissue releases metanephrines continually, as opposed to the episodic release of catecholamines.[55] PPGL that occur in the setting of MEN2 and NF1 typically produce both metanephrine and normetanephrine, while PPGL associated with VHL or SDHx mutations lack the enzymatic machinery to produce metanephrine. Tumors caused by SDHx mutations also produce 3-methoxytyramine, a metabolite of dopamine. **(FIGURE 3)** Measurement of 3-methoxytyramine may aid in the evaluation of these tumors, but it is not widely available clinically.[56] Biochemical testing is more commonly abnormal in cases of PHEO than in PGL. In a recent retrospective study, 91% of childhood PHEO patients had abnormal biochemical testing compared to 43% of PGL patients.[52] Typically, levels are elevated at least 2-fold the upper level of normal,[57,58] and levels of either metanephrine or normetanephrine >3 times the upper limit of normal are rarely false positives. Elevation of both metabolites is also uncommonly a false positive.[55] Some PPGL are biochemically silent, particularly PGL of the head and neck. Chromogranin A may be a useful tumor marker in these cases. It is recommended to confirm PPGL biochemically before moving to imaging studies.

Numerous medications and dietary substances are well known to interfere with assays of metanephrines. Many of these are listed in **TABLE 2**. Avoiding intake of dietary interferences for three days is usually sufficient. An additional important factor to consider is patient posture.

Reference intervals for metanephrines are established following a 30-minute recumbent period. Drawing blood while the patient is seated in a chair may increase the frequency of falsely abnormal test results by 2.8 fold.[59]

After establishing the biochemical diagnosis of a PPGL, imaging is required for localization. (**FIGURE 4)** Computed tomography is recommended as the first line imaging modality due to its higher resolution (5 mm). However, MRI may be a better option in children because it avoids radiation exposure.[55] This is particularly true in this population, many of whom are at high risk for other malignancies. In children and adolescents, the great majority of PHEOs are unilateral, with 10% being bilateral at diagnosis. PGL are unifocal at diagnosis in 83% of children, and 71% are located in the abdomen. Most of the rest are roughly equally distributed between the pelvis and mediastinum, with a small number in the head and neck.[51,52] There is a high rate of metachronous development of bilateral or multifocal disease in patients with germline mutations. Malignancy in PPGL is defined by the presence of metastatic disease rather than by histological examination. While the presence of metastases at diagnosis is uncommon in children (14% in a national French database), all PPGL should be considered as potentially malignant and evaluated accordingly.[51,60] Risk factors for malignant disease include tumor size >5-6 cm, extra-adrenal locations, noradrenergic/dopaminergic biochemistry, mutation in SDHB or SDHA, multiple tumor locations, and age <20 years.[58] The most common sites of metastatic disease are bone, lung, lymph nodes, and liver.

Multiple functional imaging modalities assist in the evaluation for metastatic disease. These include ^{123}I-MIBG scintigraphy or SPECT, ^{18}F-FDG-PET/CT, ^{18}F-FDOPA-PET/CT and ^{68}Ga-DOTA-SSA scintigraphy or PET/CT, and recommendations vary on which is best. The best modality may depend on whether a germline mutation is present and which gene is mutated.[55]

Current recommendations are to use ^{68}Ga-DOTA-SSA PET/CT or scintigraphy for any PGL or for PHEO associated with SDHx mutations and ^{18}F-FDOPA PET/CT or scintigraphy for PHEO not associated with SDHx mutations.[58,61,62]

Molecular Pathogenesis

Germline mutations are extraordinarily common in patients with PPGL, and there are now >20 known susceptibility genes. (**FIGURE 3**) Mutations in SDHB, SDHC, SDHD, VHL, RET, and NF1 are particularly common. Overall, it is estimated that 40-50% of all patients with PPGL carry such a mutation. In the pediatric population, germline mutations appear to be even more common, with estimates ranging from 50-70%.[51,52,54] The most common mutated gene in children with PHEO is VHL, and the most common in PGL is SDHB.

Genetic studies have identified three clusters of genes that lead to PPGL through related mechanisms.[63] Genes involved in the pseudo-hypoxic tumorigenic pathway comprise cluster 1. These include VHL and the SDHx genes. Abnormalities in this cluster interfere with oxidative phosphorylation by Krebs cycle enzymes, leading to accumulation of metabolites that increase hypoxia inducible factor-α (HIF-α), which promotes tumor formation.[58,63] Cluster 1 mutations tend to cause aggressive and often metastatic tumors that are more often extra-adrenal in location (except for VHL-associated tumors). Cluster 1 tumors are usually dopaminergic and noradrenergic, and biochemical testing reveals normal metanephrine levels but elevations of normetanephrine and 3-methoxytyramine. The exception to this is VHL-associated tumors, which are primarily noradrenergic and do not tend to secrete dopamine. Cluster 2 genes include RET, NF1, and others. Mutations in these genes cause activation of multiple kinase signaling pathways, including PI3K/AKT, mTOR, and RAS/RAF/ERK that promote cell proliferation,

survival, and angiogenesis.[58] Cluster 2 tumors tend to be less aggressive, metastasize less frequently, and are more likely to be located in the adrenals. These tumors are adrenergic and may also be noradrenergic. Therefore, biochemical testing shows elevations of metanephrine, with or without increased normetanephrine. Cluster 3 genes are involved in the WNT signaling pathways acting through β-catenin and are associated with aggressive tumor behavior. Cluster 3 gene mutations are exclusively somatic.[62] An understanding of the molecular etiology of PPGL may lead to personalized therapies.[63]

Treatment

Surgery of localized tumors is the only curative option. Complete resection is more likely in cases of PHEO than in PGL (>90% vs. 50-75%).[51,52] Patients undergoing surgery are at high risk for hypertensive crises, and mortality is high unless adequate preoperative preparation occurs. Current recommendations are to establish α-adrenergic blockade for 10-14 days at gradually increasing doses to control blood pressure.[50] Blockade of α-adrenergic receptors leads to vasodilation with lowering of blood pressure and increased potential for orthostasis. Thus, recommendations also include increased fluid and sodium intake. Commonly used α-adrenergic blockers include phenoxybenzamine and doxazosin. After 3-4 days of α-blockade, β-adrenergic blockers can be started to control tachycardia. β-blockade should not be started before α-blockade, because unopposed β-blockade removes β_2 adrenergic receptor-mediated vasodilation and permits severe vasoconstriction from α_1 receptor stimulation.

A number of medications can cause hypertensive crises in untreated PPGL patients via a variety of mechanisms. These include a) Sympathomimetic drugs, e.g., amphetamine, methylphenidate; b) Opioids, e.g., morphine; c) Tricyclic antidepressants e.g., imipramine; d)

Serotonin reuptake inhibitors, e.g., fluoxetine; and e) Corticosteroids, e.g., hydrocortisone, dexamethasone.[50]

A laparoscopic surgical approach is preferable for small (<6 cm) and non-invasive PHEOs. Open procedures are appropriate for large PHEOs and PGLs so as to optimize tumor resection and to avoid tumor rupture.[55] Variable PGL tumor locations may necessitate multiple specialist involvement, including otolaryngology, cardiovascular surgery, and interventional radiology. Cortical-sparing partial adrenalectomy should be considered in cases of bilateral PHEO or if a PHEO develops in the contralateral gland after prior adrenalectomy, with the goal of preventing postoperative adrenal insufficiency. Partial adrenalectomy successfully prevents glucocorticoid deficiency in 80-90% of cases. However, partial adrenalectomy increases the recurrence risk when medullary remnants are left behind.[64]

Postoperatively, patients are at increased risk for both hypertension and hypotension as well as hypoglycemia. Glucocorticoids are required in patients rendered surgically adrenally insufficient. If partial adrenalectomy is performed, patients should be monitored for adrenal insufficiency.

In patients with metastases or recurrences that are not amenable to surgical resection, traditional chemotherapy has included cyclophosphamide, vincristine, and dacarbazine. Although this regimen may lead to symptomatic improvement, it is not clear if there is an increase in overall survival.[62] Alternative treatments for those with non-resectable disease include radiofrequency ablation, tumor embolization, or peptide receptor radionuclide therapy (PRRT) with ^{131}I-MIBG for those with uptake on scintigraphy or with ^{177}Lu-DOTATATE.[65] Mutation cluster-specific approaches that are under study include HIF-α, VEGF, and tyrosine

kinase inhibitors for cluster 1 mutations and mTOR inhibitors for mutations in cluster 2, as well as other novel approaches.[62,65]

Outcomes

Repeat biochemical testing for PPGL is recommended 2-4 weeks after surgery to demonstrate a biochemical cure and should be repeated annually thereafter.[55] Given the high rate of germline mutations, metachronous disease, recurrences, and metastases are common. As an example, in a group of children with PPGL after a median follow up period of 53 months, 8/81 patients had a new PPGL, 8/81 had a local relapse, and 10/81 had a metastatic relapse.[51] In a similar study conducted in children during the same time frame, 6/28 patients with PHEO had a new tumor or relapse after a mean follow up of 59 months. For those with a PGL, 4/22 had a recurrence after a mean of 52 months.[52] Thus, late recurrences are common, and the 5-year event-free survival rate has been estimated at 61%. Nevertheless, overall survival in the pediatric age range is good. In a review of nine pediatric studies published over the past 15 years, the reported mortality was 4%.[51] At this time, there are no pediatric-specific guidelines for treatment of PPGL. With the higher prevalence of germline mutations and other differences between the adult and pediatric populations, such guidelines could help improve the care of children with PPGL.

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Figure Legends

1. Genitalia of a 2-year-old girl with an ACT. Note clitoromegaly, rugation and pigmentation of the labia majora, and pubic hair.

2. A. 1-year-old boy with Cushing syndrome caused by an ACT. No virilization was present.
   B. Coronal reconstruction of CT imaging showing a right ACT measuring 5.6 cm in diameter with punctate calcifications.

3. Dopamine, norepinephrine, and epinephrine are metabolized by the enzyme catechol-O-methyltransferase to 3-methoxytyramine, normetanephrine, and metanephrine, respectively. Germline mutations in genes that lead to PPGL fall into two clusters. PPGL in patients with mutations in cluster 1 genes are noradrenergic and dopaminergic and produce normetanephrine along with 3-methoxytyramine, with the exception of PPGL in von Hippel Lindau syndrome, which only produce normetanephrine. Tumors resulting from cluster 2 mutations are adrenergic and produce metanephrine, with or without co-secretion of normetanephrine. A third cluster comprises genes that undergo somatic mutations, including MAML3 and CSDE1. ATRX, Alpha-thalassemia/mental retardation syndrome, X-linked; BRAF, BRAF protooncogene; CSDE1, Cold shock domain containing E1; EGLN1, Egl-9 prolyl hydroxylase 1; EGLN2, Egl-9 prolyl hydroxylase 2; FH, Fumarate hydratase; HIF2A, Hypoxia inducible factor 2 alpha; HRAS, HRAS protooncogene; IDH, Isocitrate dehydrogenase; KIF1B, Kinesin family member 1B; KRAS, KRAS protooncogene; MAML3, Mastermind like transcriptional coactivator 3; MAX, Myc-associated factor X; MDH2, Malate dehydrogenase; NF1, Neurofibromatosis type 1; NGFR, Nerve growth factor

receptor; RET, Rearranged during transfection; SDHA, Succinate dehydrogenase subunit A; SDHAF2, Succinate dehydrogenase complex assembly factor 2; SDHB, Succinate dehydrogenase subunit B; SDHC, Succinate dehydrogenase subunit C; SDHD, Succinate dehydrogenase subunit D; TMEM127, Transmembrane protein 127; VHL, von Hippel Lindau tumor suppressor; WNT, Wingless/Int-1

4. MRI from a 7-year-old boy with a VHL mutation showing a 1.1 cm diameter T2 hyperintense, contrast enhancing mass in the right adrenal consistent with a pheochromocytoma.

Table 1. Staging strategy for ACT in children.

Stage	Criteria
I	Completely resected, small tumors (<100 grams and <200 cm^3) with normal postoperative hormone levels
II	Completely resected large tumors (≥100 grams or ≥200 cm^3) with normal postoperative hormone levels
III	Unresectable, gross or microscopic residual disease Tumor spillage Stage I and II tumors who fail to normalize hormone levels after surgery Retroperitoneal lymph node involvement
IV	Distant metastases

From Ribeiro RC, Pinto EM, Zambetti GP, Rodriguez-Galindo C. The International Pediatric Adrenocortical Tumor Registry initiative: contributions to clinical, biological, and treatment advances in pediatric adrenocortical tumors. Mol Cell Endocrinol. 2012 Mar 31;351(1):37-43. doi: 10.1016/j.mce.2011.10.015, with permission.[10]

Table 2. Medications and dietary substances that interfere with biochemical testing for PPGL.

Dietary substances	**Medications**
Eggs	Acetaminophen
Bananas	Selective serotonin reuptake inhibitors
Cheese	Methamphetamine
Nuts	Tricyclic antidepressants
Chocolate	Buspirone
Vanilla	Sulfasalazine
Caffeine	Cocaine
Black tea	Ephedrine
Nicotine	MAO inhibitors
Alcohol	Methyldopa
	Levodopa

Figure 1

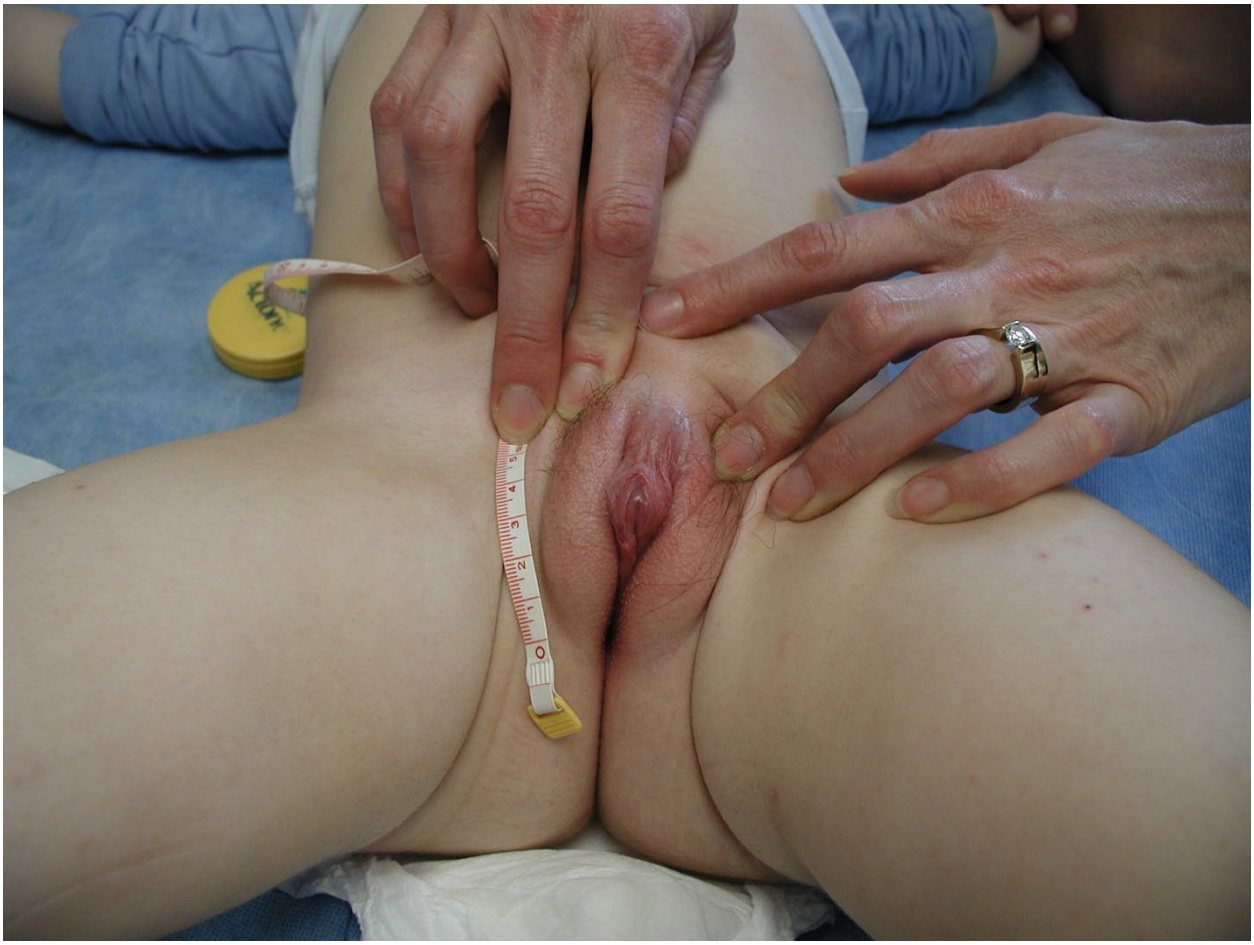

Figure 2A

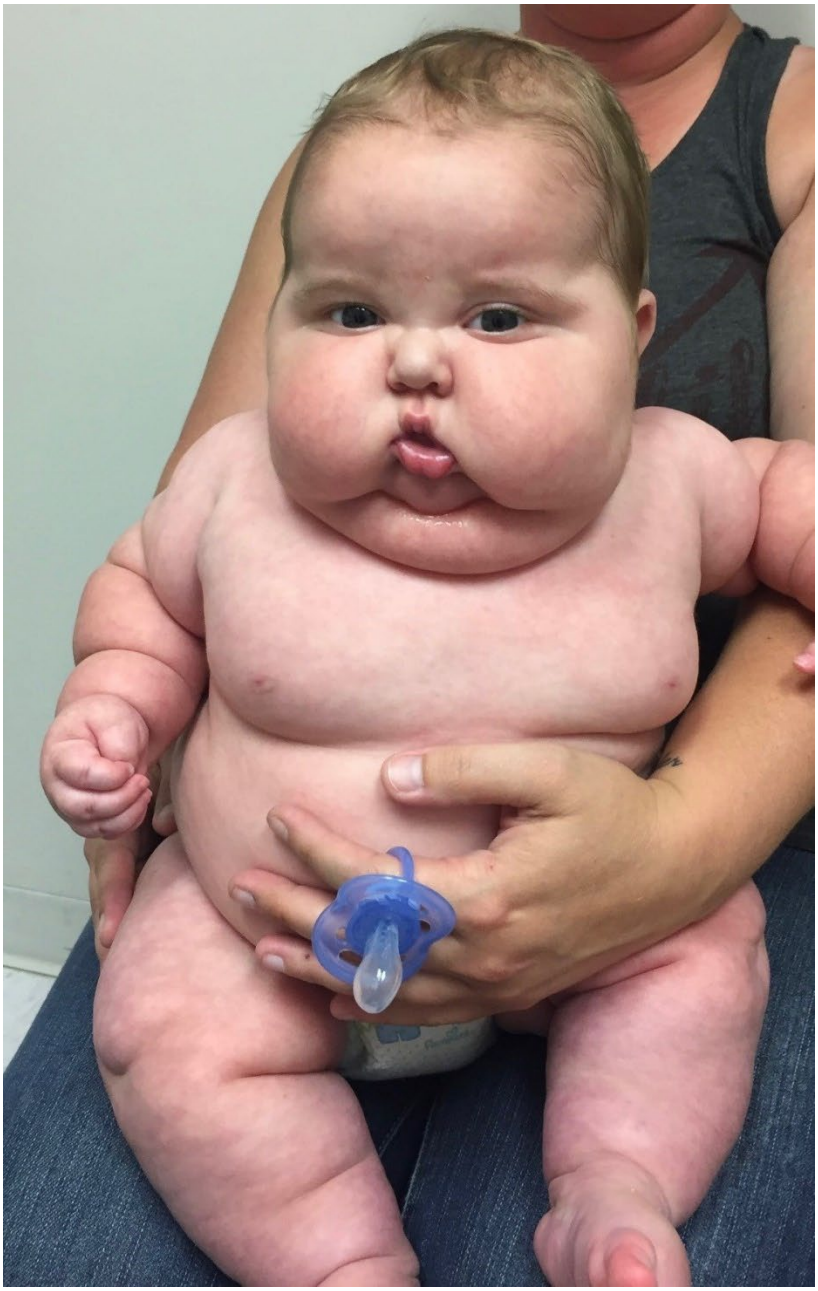

Figure 2B

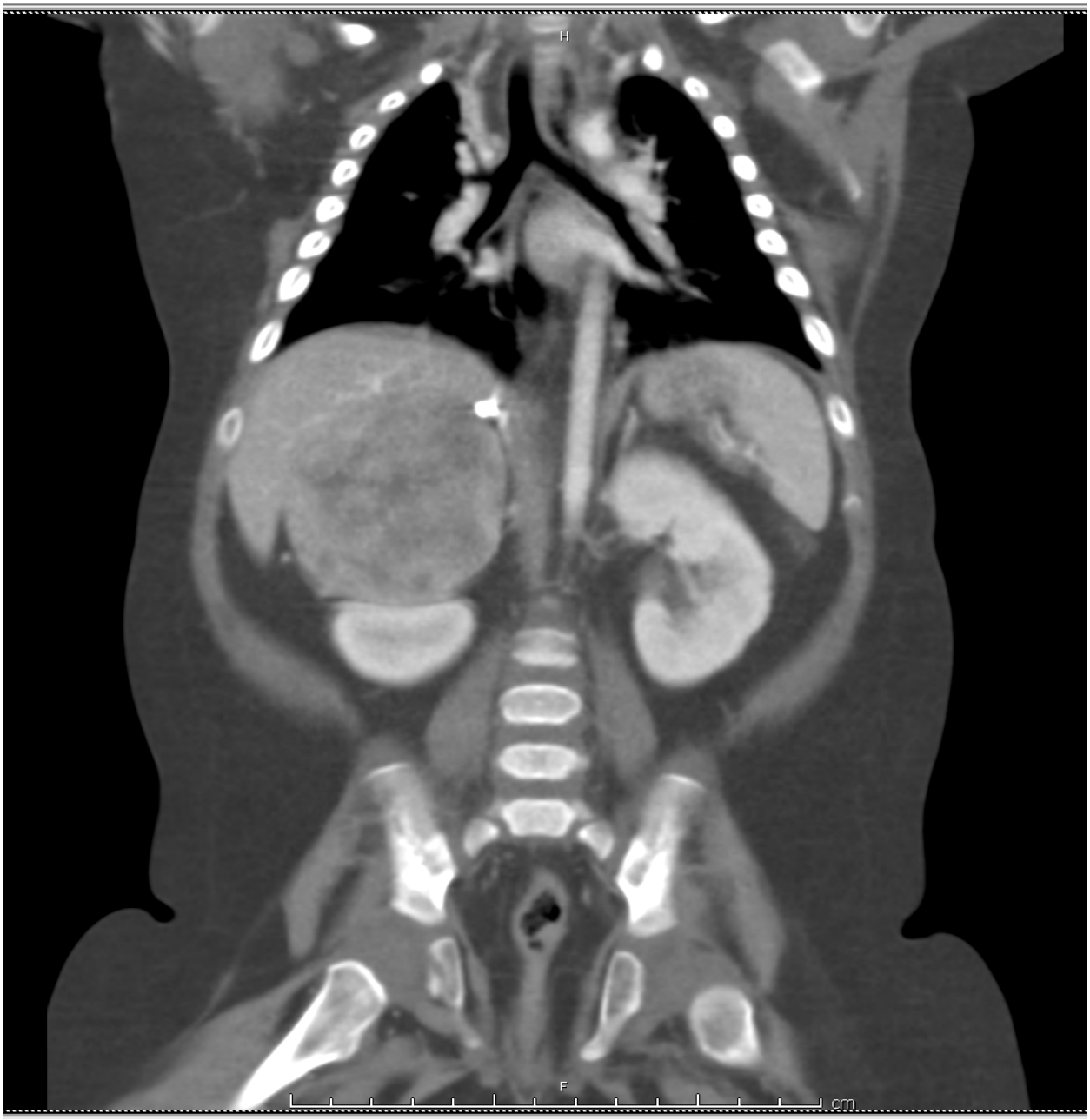

Figure 3

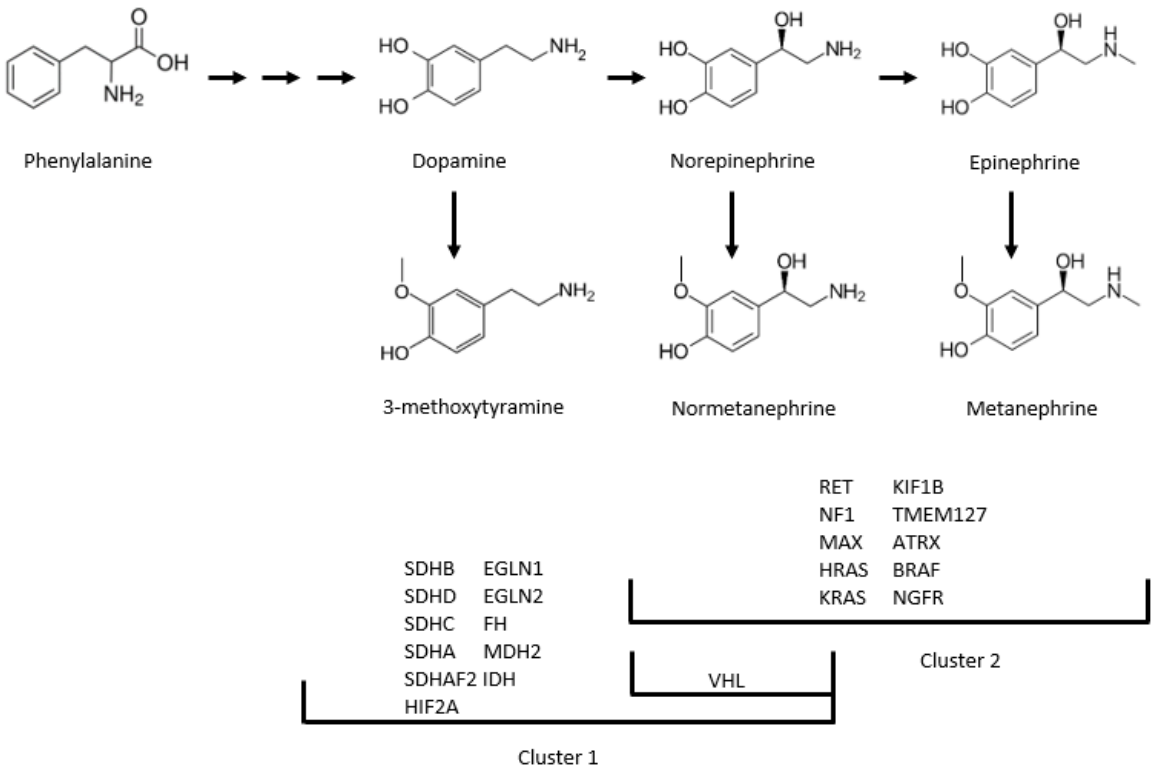
Phenylalanine
Dopamine
Norepinephrine
Epinephrine
3-methoxytyramine
Normetanephrine
Metanephrine
RET KIF1B
NF1 TMEM127
MAX ATRX
HRAS BRAF
KRAS NGFR
Cluster 2
SDHB EGLN1
SDHD EGLN2
SDHC FH
SDHA MDH2
SDHAF2 IDH
HIF2A
VHL
Cluster 1

Figure 4