Clinics in Surgery

Review Article
Published: 24 Oct, 2022

Genetic Aspects of Acromegaly

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Abstract

The prevalence of acromegaly is 40 to 70 cases per million with an annual incidence of 3 to 4 new cases per million of population. Patients with pituitary tumors usually do not have a family history of the pituitary gland diseases, and in most cases, embryo or mosaic changes cannot be detected, while recurrent somatic mutations are common in ubiquitin specific peptidase 8, in corticotropinomas and guanine nucleotide binding protein, alpha stimulating complex locus in somatotropinomas genes. The hereditary pituitary tumors are rare (~5%), but are currently well known and represented as a family disease or manifested sporadic cases. Sporadic cases can have mutations of the germline *de novo* (for example, most cases of X-linked acrogigantism due to duplication of GPR, mosaic mutations (McCune-Albright syndrome [GNAS mutations] or XLAG) whereas family history is masked as low penetrance (aryl hydrocarbon receptor-interacting protein, AIP) or imprinting.

Introduction

The pituitary tumors are the most common intracranial neoplasms, affecting 1/1000 population of the world [1]. Although, they are usually benign, the adenomas of the anterior pituitary gland cause excess or deficiency of hormones, tumor growth and the need for neurosurgical, radiological and/or long-term medical therapy to control the disease. Adenomas that secrete Growth Hormone (GH), also known as somatotropinomas, make up about 20% of all the pituitary tumors and are the second most common pituitary tumor, securing the hormone, after tumors securing Prolactin (PRL), which accounts for 40% to 45% of all pituitary tumors [2,3]. The prevalence of acromegaly is 40 to 70 cases per million with an annual incidence of 3 to 4 new cases per million of population [4-6]. Patients with pituitary tumors usually do not have a family history of the pituitary gland diseases, and in most cases, embryo or mosaic changes cannot be detected, while recurrent somatic mutations are common in Ubiquitin Specific Peptidase 8 (USP8), in corticotropinomas [7-14] and guanine nucleotide binding protein, alpha stimulating complex locus (GNAS) in somatotropinomas genes. The hereditary pituitary tumors are rare (~5%), but are currently well known and represented as a family disease or manifested sporadic cases. Sporadic cases can have mutations of the germline *de novo* (for example, most cases of X-Linked Acrogigantism (XLAG) due to duplication of GPR101, mosaic mutations (McCune-Albright syndrome [GNAS mutations] or XLAG) whereas family history is masked as low penetrance (Aryl hydrocarbon receptor-Interacting Protein, AIP) or imprinting (SDHD) (Table 1). Genetic defects can predispose to the development of a pituitary tumor either as an isolated disease (AIP, GPR101), or as part of the syndrome predisposing to the tumor: Multiple Endocrine Neoplasia type 1 (MEN1), type 4 (CDKN 1B) or other Cyclin-Dependent Kinase Inhibitor (CDKN 1A, CDKN 2B or CDKN 2C), type 5 (MAX) [15,16], pituitary tumors, pheochromocytomas or paraganglioma (SDHx), Carney complex (PRKAR1A) and the potential risk of the pituitary adenoma development with Lynch syndrome (MSH2 and PMS2) [17,18]. Genes with germline mutations that predispose the syndrome to tumors can also contribute to the tumor pathogenesis of sporadic tumors through somatic changes. However, this rarely happens to the genes associated with the pituitary tumor. GNAS is often found in the form of a somatic mutation in tumor tissue and in the form of a mosaic mutation in McCune-Albright syndrome. GPR101 is considered as an embryo or mosaic mutation. Understanding the genetic background of the pituitary tumors can lead to an early diagnosis of the disease. Moreover, an understanding of their molecular mechanism can also open opportunities for targeted medical therapy even for sporadic tumors.

Embryo or Mosaic Mutations

Patients with mutations of the germline associated with the pituitary tumors are classified as isolated pituitary tumors. The first group includes relatives with AIP and GPR101 germs and,

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Received Date: *13 Sep 2022*
Accepted Date: *20 Oct 2022*
Published Date: *24 Oct 2022*

Citation:
Djumaniyazovna NG, Madrimovna AA, Saydullaevna IS, Miltikbaevich AA. Genetic Aspects of Acromegaly. Clin Surg. 2022; 7: 3579.

possibly, recently described by changes in Cdk5 and Abl Enzyme Substrate 1 (CABLES1), in addition to a large number of Familial Isolated Pituitary Adenomas (FIPA) without identified genetic anomalies, while the last group includes MEN1, MEN4 and recently discovered MEN5, the Carney complex, paragangliomas, diseases associated with related genes (SDHx), DICER1, Lynch and McCune-Albright syndromes. The general term "Familial Isolated Pituitary Adenomas (FIPA)" refers to a family consisting of at least two family members with pituitary tumors in the absence of other associated tumors [19,20]. In most families with FIPA (90%) there is no genetic mutation can be identified among major genes predisposing to pituitary adenoma. On the other hand, mutations of the embryo line can also be identified in sporadic cases (so-called simple cases) due to *de novo* mutations, as is often the case with XLAG syndrome, or due to low penetrance and, therefore, an inconspicuous family history, as is usually observed in cases with AIP mutation, or simply the lack of information among family members about the disease. FIPA is a heterogeneous state with significant differences in the phenotype. While homogeneous (the same type of tumor for all family members) and heterogeneous (different types of tumors for family members) cases can be distinguished, this differentiation complicated with the common somatomammotroph and other multihormonal or clinically asymptomatic hormones producing phenotypes.

Aryl Hydrocarbon Receptor-Interacting Protein

Embrious heterozygous inactivating mutations in AIP gene are present in about 10% of FIPA families [19] and demonstrate an autosomal-dominant type of inheritance with incomplete penetrance. About half of the families with isolated GH-producing tumors have mutations in this gene [21]. The AIP gene encodes a koseperon of 330 amino acids involved in many processes, including subcellular transfer, stability of nuclear receptors and transactivation potential [19-23]. It is assumed that in the AIP pituitary gland acts as a tumor suppressor, which is confirmed by the fact that mutations are represented with the function failure and the presence of a normal copy of the gene (Loss of Heterozygosity, LOH, usually due to the loss of part of the chromosome area 11q [13] in pituitary tumors with AIP mutation. In patients with sporadic pituitary macroadenomas younger than 18 years-old AIP germline mutations can be found in 20% of cases (only 3% in cases of unremarkable sporadic pituitary tumors). Patients with AIP mutation usually have somatotropinomas mixed with somatomammotropinoma or prolactinomas (10%), rarely with clinically asymptomatic somatotropinomas and a single case of thyrotropinoma. There are also several cases of somatotrophic hyperplasia with or without associated tumors. During prospective screening, patients with clinically non-functioning microadenomas were identified, in which pathology is unknown. The presence of AIP mutations in patients is usually associated with macroadenomas in young age, usually with invasive pattern and a predisposition to apoplexy and poor response to the first-generation somatostatin analogues, while second-generation somatostatin analogues showed a good response in some cases [21,24]. Thus, there is a spectrum of manifestations of patients with positive AIP mutations, ranging from disease manifestation period up to five years to cases when the disease is not diagnosed up to an older age, while an aggressive disease in adolescence is the most typical clinical manifestation of penetrant cases. AIP, as a chaperon, has several interacting partners. While the aryl hydrocarbon receptor (AIP) gave the name to the protein, and their interaction was studied in relation to the pituitary oncogenesis, the causal association has not yet been shown. AIP is a transcription factor activated by a ligand, whose client proteins include Phosphodiesterase type 4 (PDE4), which switches off the cAMP path. AIP is expressed in somatotropinomas and NFPA, and AIP polymorphism was associated with aggressive tumor behavior with transformation into sporadic somatotropinomas [25,26]. Molecular factors causing a decrease in the response to the first-generation somatostatin analogues were widely discussed [27-29]: Low level of type 2 Somatostatin Receptor (SSRT2), [30] high level of expression of 5TMD4 depression [31] and low ratio of SSRT2/SSRT5 [32] or the absence of ZAC1 [33,34]. On plasma membrane, AIP plays an important role in the initial stages of the RET-apoptosis path in cells expressing PIT1. The absence of AIP or pathogenic mutations blocks this path, contributing to the RET-survival characteristic of the pituitary tumors [35]. This mechanism can also explain the unique tissue and cellular specificity of tumors associated with AIP, since PIT1 and RET are usually expressed only in somato- and lactotrophic cells. It was found that in tumors with a positive AIP, microRNA-34a (miR-34a) is activated, which correlates with prooncogenic characteristics, high levels of cAMP and a wrong response to first-generation somatostatin analogues [36-39].

Family FIPA without Common Mutations

Most (90%) family FIPA do not have known genetic mutations [21]. Although the type of inheritance can be compatible with monogenic autosomal dominant variant with very low penetrance, an oligogenic inheritance model is more likely. In the cohort of FIPA International Consortium of 318 AIP-negative (and GPR101) FIPA 21% have homogeneous acromegaly (which is 46% of 146 homogeneous AIP-negative families), and 32% have heterogeneous FIPA, at least in one family with acromegaly (54% of 172 heterogeneous families with the absence of AIP mutations) [21]. Although, somatotropinoma is not as common as in patients with a positive AIP mutation, somatotropinoma is the most common subtype in patients with a negative AIP mutation. Among heterogeneous groups (172 kinds), 29% have acromegaly and prolactinoma, 26% have acromegaly and NFPA, 4% have acromegaly and Cushing's disease [21]. In these families, only two or three patients with this disease are usually identified. The disease very rarely begins in childhood (≤ 18 years), but more often in adulthood (the average age at the time of diagnosis in the cohort of patients with AIP-negative FIPA is 38 years) [40]. It is impossible to establish accurate penetrance among AIP-negative FIPA. When comparing the AIP-positive and AIP-negative FIPA, the number of affected cases is much lower in AIP-negative persons, which implies lower penetrance [41].

XLAG (GPR101)

X-Linked Acrogigantism Syndrome (XLAG) is a rare condition performed with acrogigantism, manifested in early childhood. Hypophyseal gigantism and clinical signs of acromegaly occur in children during the first few years of life due to excessively high levels of GH and IGF-1 [40-42]. This disease has 100% penetrance and is considered one of two confirmed genetic causes of FIPA [42]. XLAG is caused by the germinal or somatic mosaic duplication of the GPR101 gene, leading to the effect of accelerating the function [43-46] GPR101 (located on the XQ26.3) codes the receptor associated with the G-protein, and is a strong activator for cAMP path [42-49]. GPR101 duplications are more common in women (80% of cases, this is more expected 66% due to the gene located in the X-chromosome) as a mutation of the germline *de novo*. Most men with highest height

Table 1: Genetic conditions with GH secretin pituitary adenomas.

Gene name	Mutation of the embryo line	Mosaic mutation	Somatic mutations in pituitary	Embryo line: isolated or syndromal	Notice
AIP	Yes	?	No	isolated	Penetrance 20%–23%
ATRXa	No	?	Yes	somatic	The bialel embryo line causes a neurological disorder. Somatic changes in aggressive pituitary tumors. Somatic mutations are also present in other neuroendocrine tumors.
CABLES1a	Yes	?	?	Isolated	Corticotrophic tumors, all mutations were Missense and not one of them was shortened. There are no family cases
CDH23a	Yes	?	?	Isolated	CDH23 homozygous mutations are associated with the deafness and Asher syndrome. There are no reports of patients with the pituitary adenoma in these families.
CDKN1Aa	Yes	?	?	syndromal	MEN1/4-like syndrome
CDKN1Ba	Yes	?	Yes (rare)	syndromal	Some cases of corticotrophic tumor in children without well -known other syndromic manifestations
CDKN2Ba	Yes	?	?	syndromal	MEN1- like syndrome
CDKN2Ca	Yes	?	Yes (rare)	syndromal	MEN1- like syndrome
DICER1	Yes	Yes	Yes	Syndromal	The blastoma of the pituitary gland with the early beginning, usually secreting ACTH, one teenage case
GNAS	No	Yes	Yes	Syndromal	Mosaic (McCune-Albright syndrome) or somatic (30–40% of somatotroph adenomas)
GPR101	Yes	Yes	No	Isolated	Data refers to genes duplication
MAXa	Yes	?	?	Syndromal	Several cases with MAX large deletions
MEN1	Yes	Yes	Yes	syndromal	Penetrance 40%
MLH1a	Yes	?	?	syndromal	Lynch syndrome, one case of pituitary carcinoma
MSH2a	Yes	?	?	syndromal	Lynch syndrome, aggressive corticotroph and lactotroph pituitary tumors
MSH6a	Yes	?	?	syndromal	Lynch syndrome, mainly corticotroph pituitary tumors
NF1b	Yes	?	?	syndromal	Excess growth hormone in 10% of patients with optic nerve glioma not related to pituitary tumors
NR3C1a	No	?	Yes	syndromal	The mutation of the embryo line usually causes resistance syndrome to glucocorticoids
PMS2a	Yes	?	?	syndromal	Lynch syndrome, mainly corticotroph pituitary tumors.
PRKAR1A	Yes	Yes	No	syndromal	Large deletions of PRKAR1A lead to a more severe phenotype of the disease
PRKACAa	Yes	?	?	syndromal	Single case
SDHx	Yes	?	Yes (rare)	syndromal	SDHX mutations can be associated with the tumors of the pituitary gland, but the penetrance is very low

[50] have somatic mosaicism, while in three described families the transfer was from mother to son. The pituitary tumors (95%) with significant co-secretion of prolactin, are not as aggressive as in patients with AIP mutations, and in 25% of cases the cause of the disease is the pituitary hyperplasia, not a tumor [42,46-50].

Multiple Endocrine Neoplasia Type 1 (MEN1)

MEN1 is a tumor disease affecting multiple organs with three main manifestations: Neoplasms of parathyroid glands that cause primary hyperparathyroidism, neuroendocrine pancreatic tumors and approximately 30% to 40% of the pituitary tumors, also, thymus, skin and adrenal tumors [51-54]. MEN1 is diagnosed clinically if (1) the patient has two or more tumors associated with MEN1; (2) a patient has a relative of the first degree of kinship with MEN1 and one tumor associated with MEN1, or; (3) the carrier of the mutant gene with the MEN1 mutation, but without clinical, biochemical or anatomical features of MEN1 [55]. The main genetic defect is inherited by an autosomal-dominant type of mutation with a loss of function in MEN1 gene, usually accompanied by a second change in another allele at a somatic level [56]. Most cases develop either in families (up to 90%) or as *de novo* mutations (10% of cases) [57,58] and although in general, the syndrome demonstrates complete penetrance with biochemical changes present by the fifth decade of lifetime in more than 95% of patients [59], the pituitary aspect has ~40% penetrance. Gene MEN1 (11Q13) encodes menin, a tumor-protein, which plays an important role in the regulation of transcription, genome stability, cellular division and control of the cell cycle. The pituitary tumors are the first feature of approximately 15% to 20% of cases of family MEN1 patients who are usually found in women with an average age of 40 years. There is a small inconsistency in the types of pituitary tumors associated with MEN1, depending on how the data was collected. In a cohort with clinical manifestations, prolactinomas are the most common lesions (60%), usually developing in childhood, whereas acromegaly contributes 25%, NFPAs (15%), corticotropes (5%). In prospective cohort prolactinomas make up to 42%, 42% of NFAPs (many of them have only a few millimeters size and are difficult to differentiate from incidentaloma), 7% of acromegaly and mixed tumors and corticotropes [60-65]. The sporadic tumors of the pituitary gland with the somatic mutation of MEN1 are rare (3.5%), but menin levels were decreased in most pituitary tumors and were absent in metastatic pituitary carcinoma [60].

MEN4

MEN4 [66,67] have a MEN1-like phenotype with primary hyperparathyroidism and pituitary tumors (prolactinomas, somatotropinomas, corticotropinomas and NFPAs) found in approximately 40% of patients, but with functionally intact genome of MEN1 [68,69]. In carriers of MEN4 mutations found during family

screening, the NFPAs was described as the most common pituitary tumor [69-71]. Due to the rarity of the disease, the penetrance and correlation of the genotype-phenotype evaluation chance is poor. These pituitary tumors have an average age when diagnosed from 30 to 79 years, are usually not aggressive and are treated well [69]. While MEN4 was first observed in rats with MEN1- and MEN2-like tumors [72,73] due to the mutation in the inhibitor of the P27 cell cycle (codes CDKN1b), other mutations of the cell cycle inhibitor (CDKN2B (P15), CDKN2C (P18) and CDKN1A (P21) [74]. CDKN1B also found in several cases with corticotropinomas in children [74,75].

Carney Complex

The Carney complex is a rare heterozygous autosomal dominant disease with multiple endocrine and non-endocrine symptoms, including pituitary hyperplasia or tumor with complete penetrance [76,77]. The disorder can be diagnosed clinically if there are two or more basic criteria or one large criterion and there is a patient relative of the first degree of kinship or a well-known inactivating mutation of PRKAR1A. The main criteria are spotted skin hyperpigmentation, skin and cardiac myxomas, Primary Pigmented Nodular Adrenocortical Disease (PPNAD), acromegaly, large cell calcifying Sertoli cell tumor of testis, thyroid carcinoma or multiple nodules, mammary gland adenoma, psammomatous melanotic schwannoma, blue naevus and osteochondromyxoma) [78,79]. Large deletions lead to a more serious illness, and *de novo* mutations are present in a significant minority of simple cases [80,81]. The PRKAR1A gene (17Q23-24) encodes the PKA regulatory protein of subunit of type 1α and functions as a tumor suppressor gene [82]. Although most (~70%) patients have an abnormal dynamic of the GH axis and an increased IGF-1 level, only 10% has active acromegaly, often with hyperprolactinemia, usually manifested for the third decade of life [79,83]. Corticotrophic adenomas are rarely described [84,85] and are a diagnostic problem, since the adrenal gland Cushing's syndrome is a common manifestation [86-91].

McCune-Albright Syndrome

McCune-Albright syndrome is a rare genetic disease manifested by fibrous dysplasia, "café-au-lait" skin pigmentation and premature puberty [92-96]. Other endocrine problems include an excess of GH, hypercortisolemia due to nodular adrenal hyperplasia and thyrotoxicosis, but recently pancreatic and hepatic tumors are also described [97-100]. Hypersecretion of GH is observed in 20% of patients with McCune-Albright syndrome, but only about 50% of patients have a pituitary tumor or pituitary hyperplasia discovered on imaging studies. The disorder is caused by somatic activating mutations in the GNAS gene, which occur at the early postzygotic stage, which leads to the somatic mosaicism of this mutation. GNAS encodes guanine-nucleotide-binding protein, α-stimulating polypeptide, and a mutation leads to an increase in the function with constantly increased levels of adenylate cycles, cAMP and PKA activity, which leads to persistent hypersecretion of GH and cell proliferation. Due to the variable level of mosaicism, the degree of phenotype covers a wide range of severity.

Conclusion

Although there was significant progress in the characterization of the molecular basis of the pituitary oncogenesis, current data indicate that any of these changes are hardly responsible for sporadic tumors that most cases account for. In conclusion, genetic testing in the treatment of pituitary diseases is recommended in rare cases. Understanding the genetic basis of the disease helps to identify patients and family members at risk, facilitates early diagnosis and, therefore, improves the long-term outcomes, and also leads to a better understanding of its oncogenesis.

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