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THE RELEVANCE OF PITUITARY TUMORS: MOLECULAR AND GENETIC ASPECTS

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ABSTRACT

Our understanding of the interplay between genetics and pituitary adenomas has seen a tectonic shift over the past two decades. It is an evolving narrative that is changing the face of clinical endocrinology. Previously, our knowledge was limited to the familial predisposition in the context of Multiple Endocrine Neoplasia type 1 syndrome (MEN1), where pituitary adenomas were noted to emerge sporadically, albeit with inconsistent expression. Now, we stand on the threshold of a new era where the expansive list of genetic conditions that can lead to pituitary adenoma is both astonishing and enlightening. The Main Focus: Although the majority of pituitary tumors appear sporadically, an intriguing 5% are borne out of hereditary diseases. We now recognize the potential for pituitary tumors to emerge within familial lineages, either in isolation such as Familial Isolated Pituitary Adenoma (FIPA), linked to the AHR protein, or in association with X-linked acrohygantism (X-LAG). Furthermore, pituitary adenomas can manifest as part of a syndromic cluster, as observed in MEN1, MEN4, Carney Complex, McCune-Albright Syndrome (MAS), the trinity of Pheochromocytoma/Paraganglioma with Pituitary Adenoma (3P Association or 3Pa), DICER1 Syndrome, and USP8-related syndrome. Several other conditions with unclear associations to pituitary adenomas have also been identified, their intricate relationships awaiting further scientific dissection. Potential and Implications of Genetic Testing: Genetic testing has rapidly evolved from being a mere diagnostic tool to becoming an instrument of proactive healthcare. Recognition of a syndromic disease can stimulate prompt detection of other disease facets, leading to a more holistic disease management approach.

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Introduction

Pituitary adenomas now make up a considerable 15% of all primary brain tumors, moving up to the position of second most common. Their categorization stems from the makeup of the hormones they emit in excess [1]. Each hormone secretion correlates with unique clinical symptoms linked to particular kinds of pituitary cells [2]. For instance, adenomas that secrete corticotropin, growth hormone, or both lead to Cushing's disease, hyperprolactinemia from lactotropic adenomas that overproduce prolactin, and hyperthyroidism from adenomas that secrete thyrotropin. Hypogonadism is frequently a side effect of adenomas that defy categorization, including null cell, silent gonadotroph, silent corticotroph, and silent somatotroph adenomas [3]. These adenomas are typically characterized by random cell forms.

Treatment Modalities

Among these adenomas, lactotrophic adenomas exclusively receive dopamine agonists as a primary line of treatment. With a dearth of effective pharmacological options, most pituitary adenomas are managed using transsphenoidal surgery as a first-

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line therapeutic intervention [4,5]. Nevertheless, it is believed that medication and stereotactic radiosurgery are necessary for the best tumor control or biochemical remission due to the inherent invasiveness and inoperability of many adenomas or the tiny size of some Cushing's disease tumors that evade detection or complete removal during surgery. Despite employing cutting-edge treatment techniques, the ten-year recurrence rates—which fall between 7 and 12%—remain alarmingly high [6,7].

Significance of Molecular Biology in Therapeutics

The need for a thorough understanding of the diverse molecular and biological traits present in distinct forms of pituitary adenomas is underlined by this stark clinical problem. Understanding the intricate relationships between gene mutations, DNA methylation patterns, microRNA (miRNA) controls, and other multi-level modulations may help us develop individualized and targeted treatment approaches that will improve prognosis outcomes [8].

Our Contribution

In this study, we endeavor to distill the known variations across different types of pituitary adenomas and explore promising molecular targets for future clinical applicability. We will dissect familial pituitary adenomas into two distinct categories: isolated and syndromic, adding another layer of complexity to our understanding and approach to these elusive tumors.

Materials and Methods

Using the PubMed database, we looked for English-language papers in the literature. The following search phrases were used in various combinations: "acromegaly," "growth hormone," "genetic predisposition," and "pituitary tumor." Additionally, we searched the same database specifically for papers on pituitary adenomas' diagnostic and treatment options. Original research papers, reviews, points of view, opinions, comments, case studies, and case reports that are pertinent to our goal have been included. The relevant papers' titles and abstracts were first confirmed using the search method, and if necessary, the complete text was retrieved to assess appropriateness. The relevancy of the received articles' connections and pertinent citations was also examined. Finally, a logical order was created from the information.

Results and Discussion

The hallmark sign of the MEN1 syndrome is the co-existence of neuroendocrine tumors, pituitary adenomas, and parathyroid adenomas (30–40% of the time) [5,9]. Pituitary tumors that manifest in MEN1 syndrome include corticotropic tumors (3%), silent pituitary tumors (42%), somatotropic tumors (9%), and lactotropic tumors (46%).

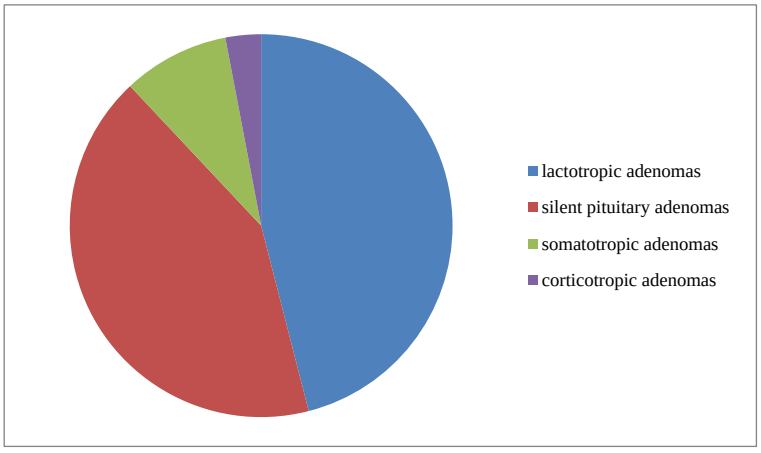

Figure 1. Pituitary adenomas in MEN1 syndrome

Somatic mutations in the MEN1 gene, which is located on chromosome 11q13.1, are present in both spontaneous and MEN1-associated pituitary adenomas (PAs) [10-12]. The regulation of G1/S control points depends on this gene, which encodes a cofactor for cyclin transcription. Notably, de novo mutations account for around one in ten PAs associated with MEN1, occasionally manifesting in the proband as mosaicism [13]. Yet, MEN1 mutations are conspicuously absent in some patients, who instead show mutations in the CDKN1B inhibitor—a trait defining MEN4 syndrome. These patients have an increased risk of developing somatotropic adenomas, among other Pas [14]. The change from the G1 to the S phase in cell mitosis is greatly influenced by CDKN1B, a cyclin-dependent kinase inhibitor. The Carney Complex, which affects a large number of people, is characterized by cardiac and cutaneous myxomas, endocrine and neuroendocrine tumors, and patchy skin pigmentation [15]. The pituitary hyperplasia in more than two thirds of individuals causes asymptomatic increases in prolactin, GH, and IGF-1. Adenomas with symptomatic acromegaly are present in about 10% of individuals. This complex is frequently brought on by a PRKAR1A gene inactivating mutation or a PRKACB gene function-enhancing mutation. X-LAG syndrome,

which has just recently been discovered, affects people with PA or pituitary gigantism who have microduplications on chromosome Xq26.3. Managing excess growth hormone in these people is difficult and frequently necessitates many therapies due to the aggressive nature of the condition [16]. Given that the G-protein-coupled receptor 101 (GPR101) is located on chromosome Xq26.3, this condition most likely results from an overexpression of this receptor. The DICER1 syndrome, which results from heterozygous germline mutations in the DICER1 gene, has been linked to a number of uncommon pediatric pituitary blastomas and recently discovered corticotropic adenomas [17]. A cytoplasmic endoribonuclease called DICER1 converts hairpin precursor microRNAs into functional short microRNAs that silence target mRNAs, hence regulating cellular protein synthesis. Germline mutations in genes involved in DNA mismatch repair are the cause of Lynch syndrome, a cancer-predisposing disease. Due to germline mutations in MLH1 and MSH2, this disease has been associated with aggressive corticotropin-secreting adenomas. Additionally, missense mutations in four mismatch repair genes (MH5, MH6, MLH1, and MLT3) have been discovered in certain unclassified adenomas. The pathogenesis of pituitary adenomas is deeply intertwined with the genetic mutations underpinning these syndromes. By understanding these links, we can forge ahead in developing more effective treatments for these conditions.

Conclusion

We discussed new findings about the molecular variances of somatotropic, corticotropic, lactotropic, unclassifying, and thyroid-stimulating adenomas. To identify the physiological pathways of adenomas, it will be helpful to generalize genetic and epigenetic markers of different forms of pituitary adenomas and to elucidate their intricate molecular processes. These findings will improve our comprehension of the occurrence of pituitary adenomas and pave the way for the creation of novel therapeutic approaches.

Patients who have a family history of pituitary tumors, who are in the early stages of developing a pituitary tumor, and who have additional clinical characteristics that contribute to the development of pituitary tumors may consider genetic testing. In conclusion, genetic testing not only enables early diagnosis and improved therapy outcomes by identifying people at a higher risk of developing pituitary gland or other cancers, but it also advances our understanding of the development of pituitary tumors.

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References

1. Tatsi C, Stratakis CA. The Genetics of Pituitary Adenomas. J Clin Med. 2020;9(1):30. doi:10.3390/jcm9010030
2. Melmed S. Pituitary-Tumor Endocrinopathies. N Engl J Med. 2020;382(10):937-50. doi:10.1056/NEJMra1810772
3. Salomon MP, Wang X, Marzese DM, Hsu SC, Nelson N, Zhang X, et al. The Epigenomic Landscape of Pituitary Adenomas Reveals Specific Alterations and Differentiates Among Acromegaly, Cushing's Disease and Endocrine-Inactive Subtypes. Clin Cancer Res. 2018;24(17):4126-36. doi:10.1158/1078-0432.ccr-17-2206
4. Caimari F, Korbonits M. Novel Genetic Causes of Pituitary Adenomas. Clin Cancer Res. 2016;22(20):5030-42. doi:10.1158/1078-0432.Ccr-16-0452
5. Maxwell JE, Sherman SK, Howe JR. Translational Diagnostics and Therapeutics in Pancreatic Neuroendocrine Tumors. Clin Cancer Res. 2016;22(20):5022-9. doi:10.1158/1078-0432.ccr-16-0435
6. Chang M, Yang C, Bao X, Wang R. Genetic and Epigenetic Causes of Pituitary Adenomas. Front Endocrinol. 2021;11:596554. doi:10.3389/fendo.2020.596554
7. Othoum G, Maher CA. CrypticProteinDB: an integrated database of proteome and immunopeptidome derived non-canonical cancer proteins. NAR Cancer. 2023;5(2):zcad024. doi:10.1093/narcan/zcad024
8. Stratakis CA. An update on, and genetics of refractory adenomas of childhood. Pituitary. 2023;26(3):281-7. doi:10.1007/s11102-023-01327-2
9. Ryczek N, Łyś A, Makałowska I. The Functional Meaning of 5'UTR in Protein-Coding Genes. Int J Mol Sci. 2023;24(3):2976. doi:10.3390/ijms24032976
10. Filatova A, Reveguk I, Piatkova M, Bessonova D, Kuziakova O, Demakova V, et al. Annotation of uORFs in the OMIM genes allows to reveal pathogenic variants in 5'UTRs. Nucleic Acids Res. 2023;51(3):1229-44. doi:10.1093/nar/gkac1247
11. Jürgens L, Wethmar K. The Emerging Role of uORF-Encoded uPeptides and HLA uLigands in Cellular and Tumor Biology. Cancers (Basel). 2022;14(24):6031. doi:10.3390/cancers14246031

12. Singeisen H, Renzulli MM, Pavlicek V, Probst P, Hauswirth F, Muller MK, et al. Multiple endocrine neoplasia type 4: a new member of the MEN family. Endocr Connect. 2023;12(2):e220411. doi:10.1530/EC-22-0411
13. Mazarico-Altisent I, Capel I, Baena N, Bella-Cueto MR, Barcons S, Guirao X, et al. Novel germline variants of CDKN1B and CDKN2C identified during screening for familial primary hyperparathyroidism. J Endocrinol Invest. 2023;46(4):829-40. doi:10.1007/s40618-022-01948-7
14. Bengtsson D, Joost P, Aravidis C, Askmalm Stenmark M, Backman AS, Melin B, et al. Corticotroph Pituitary Carcinoma in a Patient With Lynch Syndrome (LS) and Pituitary Tumors in a Nationwide LS Cohort. J Clin Endocrinol Metab. 2018;102(11):3928-32. doi:10.1210/jc.2017-01401
15. Lavezzi E, Brunetti A, Smiroldo V, Nappo G, Pedicini V, Vitali E, et al. Case Report: New CDKN1B Mutation in Multiple Endocrine Neoplasia Type 4 and Brief Literature Review on Clinical Management. Front Endocrinol (Lausanne). 2022;13:773143. doi:10.3389/fendo.2022.773143
16. Moshina B, Ghose S. Preoperative analysis of risk of malignancy indices in the distinction of malignant ovarian tumors. Clin Cancer Investig J. 2020;9(6):238-43. doi:10.4103/ccij.ccij_102_20
17. Chen L, Shuai J, Liu T. Germinal Center-Derived Diffuse Large B-cell Lymphomas with Aberrant Co-expression of MUM1 in Adults and Children. Clin Cancer Investig J. 2022;11(5):1-6. doi:10.51847/3FRFymkUPW