AAMS Internal Medicine & Therapeutics
ISSN: 2834-7102 (Print) | eISSN: 2834-7103 (Online)
Volume 07, Issue 04, Pages 1-15
DOI: 10.4103/aams.0498
ORIGINAL ARTICLE

Pathogenesis of Prolactin-Secreting Pituitary Adenomas: Genetic, Molecular, and Hormonal Mechanisms (Literature Review)

D.B. Abdumurodova[1], T.T. Atoev[2], G.Sh. Negmatova[3],

2nd-Year Master's Student, Department of Endocrinology Samarkand State Medical University Samarkand, Uzbekistan[1], Assistant of the Department of Endocrinology Samarkand State Medical University Samarkand, Uzbekistan[2], Head of the Department of Endocrinology Samarkand State Medical University Samarkand, Uzbekistan[3],

Received: 2026-02-20 · Accepted: 2026-03-30

Abstract

The article examines the mechanisms of development of prolactin-secreting pituitary adenomas from the perspective of the interaction between genetic, molecular, and hormonal factors. It highlights that disturbances in the embryonic development stages of the pituitary gland, alterations in transcriptional regulatory systems, and clonal transformation of lactotroph cells play a crucial role in the pathogenesis of prolactinoma. The effects of key transcription factors such as Pit-1, Prop-1, and Hesx1, as well as mutations in genes including MEN1, PRKAR1A, and SF3B1, on cell proliferation and hormonal activity are analyzed. In addition, estrogen-dependent mechanisms, aromatase enzyme activity, and disruptions in signaling pathways are considered in the development of prolactinomas, while also substantiating the sex-related clinical features of the disease.

Keywords: prolactinoma, pituitary adenoma, pathogenesis, transcription factors, genetic mutations, estrogens, aromatase, Pit-1, MEN1, SF3B1, hormonal regulation.

1. Introduction

Relevance of the problem and prevalence of prolactin-secreting pituitary adenomas.
Prolactin-secreting pituitary adenomas (prolactinomas) are among the most frequently detected pituitary tumors, and they are diagnosed significantly more often in women than in men. According to modern studies, the use of oral contraceptives, estrogen replacement therapy, and multiple pregnancies are not considered proven risk factors for the development of prolactinoma. Despite isolated reports of tumor occurrence after prolonged use of high-dose estrogens in transgender women, large retrospective cohort studies have not confirmed a significant increase in risk [16]. Of particular clinical importance is the direct relationship between the level of hormonal secretion of prolactinoma and the severity of reproductive disorders in patients [12].
The high significance of this issue is due to the widespread prevalence of pituitary tumors in the population. According to Ho KKY, Kaiser UB et al. (2023), pituitary adenomas are detected in approximately 10% of the population based on autopsy studies and neuroimaging methods. However, clinically significant forms associated with health disorders are much less common—about 70–100

cases per 100,000 population, while the annual incidence is 1–5 new cases per 100,000 people. About two-thirds of such conditions are associated with hormonal hypersecretion syndromes [11].
Most pituitary microadenomas remain stable in size for a long time and are localized within the sella turcica. They are often detected during examination of patients for endocrine disorders or symptoms of compression of surrounding structures. Only a small proportion of neoplasms are characterized by aggressive behavior, resistance to therapy, and a tendency to recur. Malignant forms are extremely rare and account for less than 0.1% of all clinically diagnosed pituitary tumors [11].
Special attention is given to this pathology in children and adolescents. According to Korbonits M., Blair J.C. et al. (2024), adenohypophyseal tumors account for about 1% of all intracranial neoplasms in patients younger than 15 years, but they can lead to significant morbidity and serious endocrine disorders. At the same time, the evidence base regarding treatment of this patient category remains limited [13].
Additional scientific interest is represented by multiple pituitary tumors. According to Reese J.C. et al. (2024), cases with two or more independent, clearly separated tumor foci occur in 0.2–2.6% of surgical observations and in 7.0–10.5% of pathological studies of adenomatously altered pituitary glands [18].
Thus, the high prevalence of prolactinomas, the diversity of clinical manifestations, the peculiarities of their course in different age groups, as well as the possibility of rare and complex forms of the disease determine the considerable relevance of further study of this problem.
The aim of this review is to define and study modern concepts of the probability theory of occurrence, as well as the pathogenetic mechanisms of development of prolactin-secreting pituitary adenomas.

2. Materials and Methods

This article was prepared as a narrative literature review based on the analysis of modern domestic and international scientific publications devoted to prolactin-secreting pituitary adenomas. Sources indexed in PubMed, Scopus, Web of Science, and Google Scholar were studied. The search included the terms: prolactinoma, pituitary adenoma, MEN1, PRKAR1A, SF3B1, Pit-1, estrogen receptor α, aromatase, pathogenesis, genetic mutations, and hormonal regulation.
Priority was given to peer-reviewed studies, systematic reviews, clinical guidelines, and experimental works published in recent years, as well as classical studies of pathogenetic significance. The selected publications were analyzed according to the following criteria: genetic mechanisms, transcription factor disturbances, signaling pathways, estrogen-dependent effects, sex-related differences, tumor aggressiveness, and therapeutic implications.
Mechanisms of Development of Prolactin-Secreting Pituitary Adenomas
According to Shutova A.S. et al. (2023), prolactinomas are considered monoclonal tumors whose development is associated with the gradual accumulation of genetic and epigenetic disturbances at various stages of pituitary formation—from embryogenesis and organ primordium formation, through differentiation of cell lineages, up to the functioning of mature tissue [15]. The formation of modern concepts regarding the molecular mechanisms of prolactinomas is impossible without considering the peculiarities of pituitary embryonic development and the sequence of its morphogenesis.
Pituitary development is strictly controlled by a network of transcription factors ensuring stepwise regulation of organogenesis. In the early stages, the key role is played by the genes Nkx2.1, Sox3, and Lhx2, which promote interaction between neuroectoderm and the epithelium of the primitive oral cavity. Formation of Rathke's pouch is regulated by expression of the factors Pitx1, Pitx2, and Lhx3/4, responsible for coordination of adenohypophysis and neurohypophysis development. The final stage of embryogenesis is controlled by the genes Hesx1 and Prop-1, which ensure separation of the adenohypophysis from the primary ectoderm and initiate cell differentiation programs.
Disturbances in the expression of these regulatory factors—including mutations, deficiency, or discoordination of their temporal activity—may lead to the formation of a cascade of molecular defects. These changes are accompanied by activation of proto-oncogenes, inactivation of tumor suppressor genes, and disruption of cell-cycle control. As a result, a clonal tumor population of lactotrophs is formed with subsequent development of prolactinoma.
It is important to note that clonal transformation may occur both during embryogenesis and in the mature pituitary under the influence of endogenous and exogenous mutagenic factors. Despite their tumor nature, prolactinomas retain dependence on transcriptional regulatory systems. The key factors are Pit-1 and estrogen receptor α (ERα), which determine the hormonal activity of lactotroph

adenomas. Similar mechanisms are involved in the regulation of somatotropin and thyrotropin, explaining the possibility of mixed hormonally active adenomas [2].

Certain genetic syndromes also play an important role in the pathogenesis of prolactinomas. Thus, mutation of the MEN1 (MENIN) gene disrupts cell-cycle control due to decreased expression of proliferation inhibitors (CDKN1B, CDKN2C), promoting tumor transformation. However, the reasons for tissue specificity of pituitary involvement in this syndrome remain unclear. It is assumed that MENIN may interact with the transcription factor PIT1, affecting hormone-dependent expression in somato-, lacto-, and thyrotrophic cells.

Another significant molecular mechanism is disruption of the PKA signaling pathway due to mutation of PRKAR1A, which leads to constitutive activation of protein kinase A and increased proliferation of hormonally active cells. However, such changes are more often associated with hyperplasia rather than aggressive tumors.

In sporadic cases of prolactinomas, somatic mutations and splicing disorders have been actively studied in recent years. Although driver mutations have already been identified for many pituitary adenomas (for example, USP8 in corticotropinomas or GNAS in somatotropinomas), such changes long remained uncharacteristic for prolactinomas. At the same time, SF3B1 mutations have been identified, leading to abnormal RNA splicing and formation of altered protein products that enhance PIT1-dependent prolactin transcription and contribute to invasive tumor growth [14]. In addition, decreased expression of the tumor suppressor DLG1 further enhances the proliferative potential of cells [1].

These data confirm that the pathogenesis of prolactinomas without SF3B1 mutation remains multifactorial and incompletely understood. Estrogen-dependent regulation plays a substantial role in tumor growth through VEGF, PTTG, and other signaling molecules. Gender differences in clinical course, including more aggressive tumor behavior in men, are associated with peculiarities of ERα signaling and genomic instability [21].

In men, an important source of estrogens is aromatase (CYP19A1), which ensures local synthesis of estradiol in pituitary tissues. Experimental studies confirm its role in maintaining the lactotroph population and regulating endocrine functions [4,8,15]. However, the role of aromatase in progression and adenoma subtypes remains a subject of further study [9,10,20].

Mechanisms of estrogen influence on the pituitary include several levels: stimulation of proliferation of mature lactotrophs, transdifferentiation of precursor cells, and effects on pituitary stem cells. In addition, estrogens alter the tumor microenvironment by enhancing angiogenesis and cytokine production, and also modify hypothalamic regulation of prolactin secretion [7].

Experimental models show that prolonged estrogen exposure causes lactotroph hyperplasia and increased pituitary mass, as well as enhanced VEGFA expression and vascular density of tumor tissue [22]. Men demonstrate a higher frequency of macroprolactinomas and a more aggressive disease course, which may be related to peculiarities of hormonal regulation and accumulation of genetic disturbances [19].

3. Results

The reviewed literature demonstrates that prolactinoma development is based on a combination of embryological, molecular, genetic, and endocrine mechanisms.

Genetic abnormalities involving MEN1, PRKAR1A, and SF3B1 genes were repeatedly associated with abnormal proliferation and hormone hypersecretion. Disturbances in transcription factors such as Pit-1, Prop-1, and Hesx1 were linked with altered differentiation of pituitary cells and tumor formation.

Hormonal stimulation, especially estrogen-dependent signaling through ERα and aromatase-mediated estradiol synthesis, was strongly associated with lactotroph hyperplasia and tumor progression [4,8,15].

Clinical observations also indicate sex-related differences: women are more frequently diagnosed earlier due to reproductive symptoms, whereas men more commonly present with macroadenomas and invasive forms [19,21].

Thus, current evidence supports a multifactorial model in which genetic predisposition interacts with hormonal and molecular triggers.

4. Discussion

The findings confirm that prolactinomas cannot be explained solely by hyperprolactinemia or isolated endocrine dysregulation. Contemporary evidence indicates a complex interplay between genetic susceptibility, transcriptional imbalance, and hormonal stimulation.
Particular attention should be given to the role of transcription factors, since they link embryonic pituitary development with adult neoplastic transformation. Disturbances of Pit-1-dependent pathways may explain both excessive prolactin secretion and mixed pituitary adenoma phenotypes [2].
The discovery of SF3B1 mutations has expanded understanding of sporadic prolactinomas and may become clinically useful for identifying invasive tumors and predicting treatment resistance [14].
Sex-related differences remain incompletely understood. More aggressive disease in men may result from delayed diagnosis, lower estrogen receptor sensitivity, or distinct genomic alterations [19,21].
Further studies integrating genomics, transcriptomics, endocrine biomarkers, and long-term clinical outcomes are required to improve personalized treatment strategies.

5. Conclusion

Modern data indicate the key role of disturbances in transcriptional regulation, signaling pathway mutations, and the influence of estrogen-dependent stimulation in the initiation and progression of tumor growth. Despite significant progress in studying the molecular basis of prolactinomas, many aspects of their pathogenesis remain insufficiently investigated, including the causes of tissue specificity and differences in clinical course. Of particular importance are gender characteristics, the level of hormonal activity of the tumor, and variability of genetic changes determining the aggressiveness of the process.
Thus, further in-depth study of the molecular and endocrine mechanisms of prolactinoma development is of great importance for improving diagnosis, predicting disease course, and developing personalized approaches to treatment.

References

1. Го Цз., Ли С., Фан К., Лю Ю., Ван Д., Чэнь И., Се В., Чжан И. Мутация SF3B1(R625H) способствует прогрессированию опухоли пролактиномы посредством аномрантного сплайсинга DLG1. J. Exp. Clin. Cancer Res. 2022;41:26. DOI: 10.1186/s13046-022-02245-0.
2. Шутова А.С., Дзеранова Л.К., Воротникова С.Ю. и др. Современные представления о генетических и иммуногистохимических особенностях пролактин-секретирующих аденом гипофиза // Проблемы эндокринологии. 2023. Т. 69, №3. С. 44–50. DOI: 10.14341/probl13222.
3. Vazquez-Borrego M.C., Fuentes-Fayos A.C., Venegas-Moreno E., Rivero-Cortes E., Dios E., Moreno-Moreno P., Madrazo-Atutxa A., Remon P., Solivera J., Wildemberg L.E. et al. Splicing machinery is dysregulated in pituitary neuroendocrine tumors and associated with aggressive features. Cancers. 2019;11:1439. DOI: 10.3390/cancers11101439.
4. Cooke P.S., Nanjappa M.K., Ko C., Prins G.S., Hess R.A. Estrogens in Male Physiology. Physiol Rev. 2017;97:995–1043. doi: 10.1152/physrev.00018.2016.
5. Cristina C., Luque G.M., Demarchi G., Lopez Vicchi F., Zubeldia-Brenner L., Perez Millan M.I., Perrone S., Ornstein A.M., Lacau-Mengido I.M., Berner S.I. et al. Angiogenesis in pituitary adenomas: Human studies and new mutant mouse models. Int J Endocrinol. 2014;2014:608497. doi: 10.1155/2014/608497.
6. Delgrange E., Vasiljevic A., Wierinckx A., Francois P., Jouanneau E., Raverot G., Trouillas J. Expression of estrogen receptor alpha is associated with prolactin pituitary tumor prognosis and supports the sex-related difference in tumor growth. Eur J Endocrinol. 2015;172:791–801. doi: 10.1530/EJE-14-0990.
7. Fröhlich E., Wahl R. The forgotten effects of thyrotropin-releasing hormone: Metabolic functions and medical applications. Front Neuroendocrinol. 2019;52:29–43. doi: 10.1016/j.yfrne.2018.06.006.
8. García-Barrado M.J., Blanco E.J., Catalano-Iniesta L., Sanchez-Robledo V., Iglesias-Osma M.C., Carretero-Hernández M., Rodríguez-Cobos J., Burks D.J., Carretero J. Relevance of pituitary aromatase and estradiol on the maintenance of the population of prolactin-positive cells in male mice. Steroids. 2016;111:121–126. doi: 10.1016/j.steroids.2016.03.020.
9. García-Barrado M.J., Blanco E.J., Iglesias-Osma M.C., Carretero-Hernández M., Catalano-Iniesta L., Sanchez-Robledo V., Carretero M., Herrero J.J., Carrero S., Carretero J. Relation among Aromatase P450

and Tumoral Growth in Human Prolactinomas. Int J Mol Sci. 2017;18:E2299. doi: 10.3390/ijms18112299.
10. Gonzales P.H., Mezzomo L.C., Ferreira N.P., Roehe A.V., Kohek M.B., Oliveira M.C. Aromatase P450 expression in human pituitary adenomas. Neuropathology. 2015;35:16–23. doi: 10.1111/neup.12145.
11. Ho KKY, Kaiser UB, Chanson P, Gadelha M, Wass J, Nieman L, Little A, Aghi MK, Raetzman L, Post K, Raverot G, Borowsky AD, Erickson D, Castaño JP, Laws ER, Zatelli MC, Sisco J, Esserman L, Yuen KCJ, Reincke M, Melmed S. Pituitary adenoma or neuroendocrine tumour: the need for an integrated prognostic classification. Nat Rev Endocrinol. 2023;19(11):671-678. doi: 10.1038/s41574-023-00883-8.
12. Khalimova Z.Y., Uralova D.U., Safarova M.S. et al. Diagnostic aspects of hyperprolactinemia syndrome. The American Journal of Medical Sciences and Pharmaceutical Research. 2020;2(12):78–86. doi: 10.37547/TAJMSPR/Volume02Issue12-13.
13. Korbonits M., Blair J.C., Boguslawska A., Ayuk J., Davies J.H., Druce M.R., Evanson J., Flanagan D., Glynn N., Higham C.E. et al. Consensus guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: Part 1, general recommendations. Nat Rev Endocrinol. 2024;20(5):278-289. doi: 10.1038/s41574-023-00948-8.
14. Li C., Xie W., Rosenblum J.S., Zhou J., Guo J., Miao Y., Shen Y., Wang H., Gong L., Li M. et al. Somatic hotspot mutation of SF3B1 in prolactinomas. Nat Commun. 2020;11:2506. doi: 10.1038/s41467-020-16052-8.
15. Lindzey J., Wetsel W.C., Couse J.F., Stoker T., Cooper R., Korach K.S. Effects of castration and chronic steroid treatments on hypothalamic gonadotropin-releasing hormone content and pituitary gonadotropins in male wild-type and estrogen receptor-alpha knockout mice. Endocrinology. 1998;139:4092–4101. doi: 10.1210/endo.139.10.6253.
16. Melmed S., Kaiser U.B., Lopes M.B., Bertherat J., Syro L.V., Raverot G., Reincke M., Johannsson G., Beckers A., Fleseriu M. et al. Clinical Biology of the Pituitary Adenoma. Endocr Rev. 2022;43(6):1003-1037. doi: 10.1210/endrev/bnac010.
17. Mitsui T., Ishida M., Izawa M., Arita J. Differences between rat strains in the development of PRL-secreting pituitary tumors with long-term estrogen treatment. Endocr J. 2013;60:1251–1259. doi: 10.1507/endocrj.ej13-0245.
18. Reese J.C., Zervos T.M., Rock J. et al. A rare case of double pituitary prolactinomas: the diagnostic application of intraoperative ultrasonography and DNA methylation markers. Arch Endocrinol Metab. 2024;68(Suppl 1):e230506. doi:10.20945/2359-4292-2023-0506.
19. Song Y.J., Chen M.T., Lian W., Xing B., Yao Y., Feng M., Wang R.Z. Surgical treatment for male prolactinoma: A retrospective study of 184 cases. Medicine (Baltimore). 2017;96:e5833. doi: 10.1097/MD.0000000000005833.
20. Su Y.X., Du G.L., Shen H.L., Wang W., Bao J.L., Aierken A., Wang B.W., Jiang S., Zhu J., Gao X.M. Increased expression of aromatase cytochrome P450 enzyme is associated with prolactinoma invasiveness in post-menopausal women. J Int Med Res. 2019;47:3115–3126. doi: 10.1177/0300060519848916.
21. Šošić-Jurjević B., Ajdžanović V., Miljić D., Trifunović S., Filipović B., Stanković S., Bolevich S., Jakovljević V., Milošević V. Pituitary Hyperplasia, Hormonal Changes and Prolactinoma Development in Males Exposed to Estrogens—An Insight From Translational Studies. Int J Mol Sci. 2020;21(6):2024. doi: 10.3390/ijms21062024.
22. Šošić-Jurjević B., Filipović B., Renko K., Miler M., Trifunović S., Ajdžanovič V., Köhrle J., Milošević V. Testosterone and estradiol treatments differently affect pituitary-thyroid axis and liver deiodinase 1 activity in orchidectomized middle-aged rats. Exp Gerontol. 2015;72:85–98. doi: 10.1016/j.exger.2015.09.010.
23. Yin C., Kang L., Lai C., Zhou J., Shi B., Zhang L., Chen H. Effects of 17β-estradiol on leptin signaling in anterior pituitary of ovariectomized rats. Exp Anim. 2017;66:159–166. doi: 10.1538/expanim.16-0087.

Indexed & Abstracted In

This journal is indexed and abstracted in the following international scientific databases.

Google Scholar

ISSN

ORCID

CiteFactor

ResearchBib

DOI

Zenodo

Crossref

Grammarly

Article Verification

Scan the QR code to verify the authenticity of this article

DOI: 10.4103/aams.0498