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A bioinformatics-based approach and expression assay for identification of dysregulated genes in pituitary adenoma

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Abstract

Non-functioning pituitary adenomas (NFPAs) are a group of pituitary [neuroendocrine tumors](#) that are associated with morbidity. The exact pathophysiological process leading to this pathology is not known. [Nerve growth factor](#) (NGF) is a [neurotropic factor](#) that might be involved in this process. We used bioinformatics tools to analyze expression of genes in [NFPA](#) samples. Our analyses led to identification of NGF-related genes, namely [ARC](#), [ID1](#), and [SH3GL3](#) - as well as one long non-coding RNA (lncRNA) called myocardial infarction associated transcript (MIAT). Then, we assessed their expression in NFPAs and their adjacent non-cancerous samples. While expression levels of [SH3GL3](#) and [MIAT](#) were different between [NFPA](#) samples and control samples, expressions of [ARC](#) and [ID1](#) were not meaningfully different between these two groups of specimens. [SH3GL3](#) was over-expressed in NFPA samples compared with control samples (expression ratio (95% CI)= 8.22 (1.51–44.6), P value= 0.03). Similarly, expression of [MIAT](#) was higher in NFPAs compared with controls (expression ratio (95% CI)= 7.7 (1.7–33.6), P value= 0.009). Taken together, we validated the bioinformatics results regarding the expression of [SH3GL3](#) and [MIAT](#). This study provides a deeper understanding of the involvement of these genes in the pituitary tumorigenesis.

Introduction

Pituitary neuroendocrine tumors (PitNETs) are classified as a type of intracranial tumors [2]. Patients affected by these kinds of tumors require regular check-ups by both neurosurgeons and endocrinologists [2]. PitNETs undergo different classifications, and one the most important ones is based on their size. If the tumors are larger than 10 millimeters, they are called macroadenoma, and if they are smaller than 10 millimeters, they are referred to as microadenoma [11]. In severe cases, tumors can grow up to 40 millimeters, and this type of tumor is called “Giant tumor” [4]. Another important type of classification of PitNETs is based on their effect on hormonal levels. If the tumor affects different hormonal levels, it is called a functioning tumor. Based on the cellular origin, this type can be called “prolactinoma”, “somatotropin” or other types [21]. On the other hand, if the tumor does not cause hormonal imbalances, it is called non-functioning. The most prevalent form of pituitary tumors is prolactinoma, followed by non-functioning ones [6], [10]. Most cases of PitNETs are sporadic and due to acquired mutations, but they are also seen in the inherited familial syndromes like Multiple endocrine neoplasia type 1 (MEN1), MEN4 and Carney complex (CNC) [23]. The prevalence of PitNETs has been estimated to be 17% in general population [16]. However, since it has a silent nature, most of the times it remains undiagnosed or diagnosed as incidental findings through annual MRI check-ups [16]. Symptoms of pituitary adenoma vary based on their size and effect on hormonal levels. For instance, in functioning tumors, different manifestations like infertility, decreased libido and osteoporosis are seen in prolactinomas, and acromegaly is a basic feature of growth hormone secreting tumors. In non-functioning tumors, different symptoms like headaches, impaired vision and apoplexy are reported [17]. Therapeutic interventions are usually not necessary, but in severe cases, hormone replacement therapy or surgical removal through transsphenoidal approach is performed [15]. Nerve growth factor (NGF) is a neurotropic factor which was firstly discovered in 1950 s [1], [9]. NGF secretion has nourishing and maintaining effects and it contributes to the maintenance of peripheral nerves system (PNS) cells, in addition to central nervous system (CNS) stability [1]. NGF exerts its functions through binding to [trkANGFR](#) and [p75NTR](#) receptors [22]. Upon binding, different cellular pathways like MAPK, ERK and PI3K signaling are activated [22]. Transcription of a variety of genes is affected by NGF, and this has led to introduction of a new signaling pathway called “NGF stimulated transcription” in Reactome database [19]. In this study, firstly, GSE51618 data series, which contains gene expression data of non-functioning pituitary tumors (invasive and non-invasive) was download from NCBI GEO, in order to analyze differentially expressed gene (DEGs). In order to find the related molecular pathway, top candidates were uploaded in Reactome database, which led to identification of NGF stimulated transcription pathway. To confirm bioinformatics results and better understand their role in the pituitary tumor development, we selected four genes for further analysis by Real-time PCR. These genes included three protein coding genes - [ARC](#), [ID1](#), and [SH3GL3](#) - as well as a long non-coding RNA (lncRNA) called myocardial infarction associated transcript ([MIAT](#)). [ARC](#), also known as Activity-Regulated Cytoskeleton-Associated Protein, has a crucial role in the synaptic plasticity and RNA-mediated cell-cell communication. Studies have shown that [ARC](#) expression is associated with increased chemoresistance [24]. [ID1](#) encodes a helix-loop-helix protein that prevents various transcription factors from binding to DNA. Overexpression of [ID1](#) has been linked to several types of cancer, and this gene is crucial for cell cycle regulation, proliferation, and tumorigenesis [25]. [SH3GL3](#), or [SH3 Domain Containing GRB2 Like 3](#), is believed to play a role in synaptic vesicle uncoating and is primarily expressed in the brain and testes [7]. Its expression has been associated with glioma invasion. [SH3GL3](#) silencing has been shown to restore normal cellular features [7]. Finally, we selected [MIAT](#) for expression analysis because previous studies have demonstrated that silencing of this lncRNA leads to decreased levels of NGF in diabetic retinas [12], [20]. Overall, by analyzing the expression of these four genes, we aim to validate our bioinformatics results and gain a deeper understanding of their involvement in the pituitary tumorigenesis, particularly in relation to NGF.

Section snippets

Data collection

Gene Expression Omnibus (GEO); <http://www.ncbi.nlm.nih.gov/geo/>

) was used to get expression profile of GSE51618, which contains expression data of non-functioning pituitary adenoma (NFPA) patients (platform: Agilent-014850 Whole Human Genome Microarray 4×44K G4112F). From this data series, four non-invasive non-functioning pituitary tumors and three normal pituitary glands were selected for DEG and pathway analysis.

Data processing

Processing the data was performed via R statistical programming language. Raw

General information

General information about NFPA patients is shown in Table S2. Age (Mean ± standard deviation) of study participants was 50.65 ± 12.46. Totally, 34 patients had macroadenoma, 7 had giant tumors and 2 patients had microadenoma.

Expression assays

While expression levels of SH3GL3 and MIAT were different between NFPA samples and control samples, expressions of ARC and ID1 were not considerably different between these two groups of specimens (Fig. 2). SH3GL3 was over-expressed in NFPA samples compared with control

Discussion

NGF has been known to affect physiological process in the pituitary gland. This factor is a stimulator of differentiation and proliferation of lactotrope cells. In addition, as a systemic neurohormone, it is secreted along with prolactin into the circulation [18]. The bioinformatics steps used in the current study potentiated four genes, namely ARC, ID1, SH3GL3 and MIAT as possible contributors in the pathology of NFPA in relation with NGF. Real time PCR assays confirmed up-regulation of SH3GL3

Ethics approval and consent to participant

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent forms were obtained from all study participants. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences.

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Author contributions

SGF wrote the draft and revised it. EJ and GS designed and supervised the study. SE analyzed the data. AA, HS, MAH, AB and NAD performed the experiment and data collection. All the authors read and approved the submitted version.

CRedit authorship contribution statement

Elena Jamali: Investigation, Methodology. **Arian Askari:** Conceptualization, Investigation. **Solat Eslami:** Formal analysis. **Nader Akbari Dilmaghani:** Investigation, Methodology. **Mohammad Amin Hashemnejad:** Data curation. **Hanieh Shomali:** Data curation. **Soudeh Ghafouri-Fard:** Supervision, Writing – original draft, Writing – review & editing. **Arefe Bahranian:** Data curation, Investigation. **Guive Sharifi:** Data curation.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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Consent of publication

Not applicable.

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