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Personalized Psychiatry and Neurology

Review

Candidate genes of empty sella

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Abstract: Empty sella (ES) is a condition characterized by arachnoid herniation into the sellar fossa which leads to flattening of the pituitary gland against the sellar floor. Besides endocrine disturbances, patients with ESS may also have neuropsychiatric symptoms such as headache, dizziness, seizures, schizophrenia. Typically, ES is not inherited. However, due to the advent of new methods of brain imaging and molecular genetics, the perspective on the genetics of ESS has been changing. The aim of this study is to analyze genome-wide association studies of candidate genes related to the development of ESS in humans. Based on the available studies which have been analyzed, all candidate genes of ESS were divided into 4 groups: group 1 – candidate genes related to ESS, group 2 – candidate genes related to pathways of ESS, group 3 – candidate genes related to cellular components of ESS, group 4 – candidate genes related to biological processes of ESS.

Keywords: *empty sella; empty sella syndrome; pituitary gland; genetics; candidate genes; personalized psychiatry; personalized neurology.*

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Introduction

Empty sella (ES) is a condition characterized by arachnoid herniation into the sellar fossa which leads to flattening of the pituitary gland against the sellar floor and stretching of the pituitary stalk [1-3]. Clinical presentation of empty sella syndrome (ESS) is usually correlated with endocrine disturbances, especially with decreased pituitary function [1-9]. Besides that, patients with ESS may also have symptoms such as headache [5,6,10,11], seizure [12], rhinorrhea [13,14], intracranial hypertension [10,15-17], visual defect from compression of optic chiasma [5,18,19], neuropsychiatric symptoms [20-23]. However, most patients with ES have no clinical presentation at all. Therefore, due to the advent of new methods of brain imaging, ES is mostly an incidental finding on MRI scans when patients are being evaluated for different reasons. Radiologically, ES is divided into partial and complete. If less than 50% of the sella turcica is filled with cerebrospinal fluid (CSF) and pituitary gland thickness is more or equal to 3 mm in diameter, it is considered to be a partial ES. If more than 50% of the sella is filled with CSF and pituitary gland thickness is less than 2 mm, it is called total (complete) ES [1-2]. Based on etiology, ES is classified into primary and secondary. Secondary empty sella (SES) occurs as a consequence of another disorder or earlier injury, such as pituitary adenomas, previous surgery, increased intracranial pressure because of cerebral tumor or hydrocephalus, cerebral radiotherapy, Sheehan's syndrome, craniocerebral trauma [2]. Primary empty sella (PES) is defined when all possible causes are excluded [3]. Typically, ES is not inherited [24]. However, there are some single descriptions of familial ESS [25]. Thus, congenital anomalies are

looked upon as a possible mechanism in the development of PES [25]. Therefore, nowadays, ESS is considered to be a multifactorial disease.

The aim of this study is to analyze genome-wide association studies of candidate genes related to the development of ESS in humans.

Methods

The systematic search in both English and Russian databases (E-library, PubMed, GoogleScholar, OxfordPress, ClinicalKeys) was carried out using keywords "empty sella", "empty sella syndrome", "pituitary gland", "genetics", "candidate genes", "personalized psychiatry", "personalized neurology" and their combinations with the period of search 2000-2021. It is also worth noting that earlier publications of historical interest were included in the review.

Results

Nowadays ES, especially PES, is considered to be a multifactorial disease, in the development of which genetic predisposition and environmental factors and exposure play a huge role. ESS has long been considered not to be inherited or to be inherited seldom [24]. However, as we progress through the 21st century, due to the advent and improvement of new methods of brain imaging and molecular genetics, the perspective on the genetics of ESS has been changing. Based on the available studies which we have analyzed, it is possible to divide all candidate genes of ESS into 4 groups [26]: group 1 – candidate genes related to ESS *(Table 1)*, group 2 – candidate genes related to pathways of ESS *(Table 2)*, group 3 – candidate genes related to cellular components of ESS *(Table 3)*, group 4 – candidate genes related to biological processes of ESS *(Table 4)*.

The most significant of all candidate genes related to the development of ESS are the *PRL* gene coding for prolactin (odd ratio (OD) = 24.29); the *GH1* gene coding for growth hormone 1 (OR = 14.39); the *POMC* gene coding for proopiomelanocortin (OR = 14.25); the *TRH* gene coding for thyrotropin releasing hormone (OR = 13.62); the *IGF1* gene coding for insulin like growth factor 1 (OR = 13.49).

The most candidate genes related to pathways of ESS are *TRH*, *PRL*, *POMC*, *NPY*, *GNRH1*, *GH1* genes coding for peptide-ligand building receptors (OR = 13.19).

Amongst all candidate genes related to cellular components of ESS, the most notenoteworthy are *PRL*, *POMC*, *NPY*, *IGFBP3*, *IGF1* genes (OR = 9.76). The proteins that encode these genes are cellular components of extracellular space.

The most significant of all candidate genes related to biological processes of ESS are affiliated genes *TRH*, *POMC*, *NPY*, *INS*, *GNRH1* (OR = 9.92) which participate in the regulation of biological processes associated with the G protein-coupled receptors signaling pathway.

Table 1. Candidate genes related to ESS [26, by authors modification].

Gene	Locus	Description	Category	Score
PRL	6p22.3	Prolactin	Protein Coding	24.29
GH1	17q23.3	Growth hormone 1	Protein Coding	14.39
POMC	2p23.3	Proopiomelanocortin	Protein Coding	14.25
TRH	3q22.1	Thyrotropin releasing hormone	Protein Coding	13.62
IGF1	12q23.2	Insulin like growth factor 1	Protein Coding	13.49
PROP1	5q35.3	PROP paired-like homeobox 1	Protein Coding	12.66
GNRH1	8p21.2	Gonadotropin releasing hormone 1	Protein Coding	12.08
INS	11p15.5	Insulin	Protein Coding	11.77
IGFBP3	7p12.3	Insulin like growth factor binding protein 3	Protein Coding	11.73
LHX3	9q34.3	LIM homeobox 3	Protein Coding	10.86
NPY	7p15.3	Neuropeptide Y	Protein Coding	10.39

Table 2. Candidate genes related to pathways of ESS [26, by authors modification].

Super pathways	Top affiliating genes	Score
Peptide ligand-binding receptors	*TRH* *PRL* *POMC* *NPY* *GNRH1* *GH1*	13.19
Regulation of lipid metabolism Insulin signaling-generic cascades	*INS* *IGFBP3* *IGF1* *GH1*	12.55
Relaxin signaling pathway	*POMC* *IGFBP3* *IGF1* *GH1*	12.22
Adipogenesis	*INS* *IGF1* *GH1*	11.66
Peptide hormone metabolism	*INS* *IGF1* *GH1*	11.52
Senescence and autophagy in cancer	*POMC* *INS* *IGF1* *GH1*	11.46
Mesenchymal stem cells and lineage-specific markers	*INS* *IGFBP3* *IGF1*	11.31
Development leptin signaling via JAK/STAT and MAPK cascades	*TRH* *POMC*	10.93
Regulation of insulin-like growth factor (IGF) transport and uptake by insulin-like growth factor binding proteins (IGFBPs)	*IGFBP3* *IGF1*	10.73
Antipsychotics pathway (metabolic side effects) pharmacodynamics	*PRL* *POMC* *NPY* *INS*	10.23

Table 3. Candidate genes related to components of ESS [26, by authors modification].

Cellular component	Top affiliating genes	Score
Extracellular space	*PRL* *POMC* *NPY* *INS* *IGFBP3* *IGF1*	9.76
Insulin-like growth factor ternary complex	*IGFBP3* *IGF1*	9.32
Extracellular region	*TRH* *PRL* *POMC* *NPY* *INS* *IGFBP3*	9.28
Insulin-like growth factor binding protein complex	*IGFBP3* *IGF1*	9.26
Endosome lumen	*PRL* *INS* *GH1*	9.13

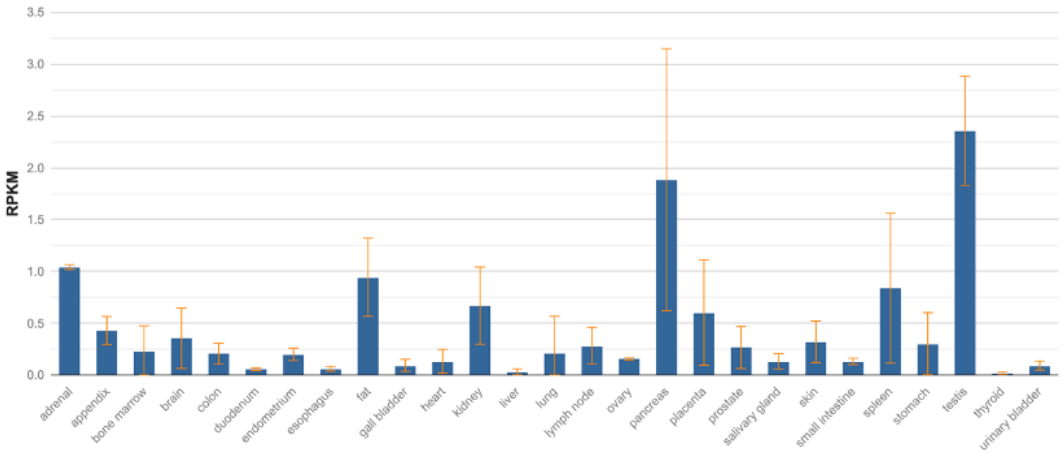

Figure 1. Broad expression of the POMC gene in the tissues of the human body [32].

It is worth mentioning that the *POMC* gene coding for proopiomelanocortin (OR = 14.25) is the most interesting one amongst all candidate genes related to ESS due to the fact that he is on top-3 of genes predisposing to the development of ESS amongst all studied groups (group 1, 2, 3 and 4).

The most significant of all candidate genes related to the development of ESS are the PRL gene coding for prolactin (odd ratio (OD) = 24.29); the *GH1* gene coding for growth hormone 1 (OR = 14.39); the *POMC* gene coding for proopiomelanocortin (OR = 14.25*);* the *TRH* gene coding for thyrotropin releasing hormone (OR = 13.62); the *IGF1* gene coding for insulin like growth factor 1 (OR = 13.49).

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The *POMC* gene is located on 2p23.3 chromosome in Homo sapiens (human) and provides instructions for making a protein called proopiomelanocortin [27]. This gene is expressed in various tissues such as testis, pancreas, adrenal, fat, kidney *(Figure 1)*.

The most studied single-nucleotide variants (SNVs) of the *POMC* gene are 3 prime UTR variant rs1042571 (G>A); synonymous variant / coding sequence variant rs2071345 (G>A,C); synonymous variant / coding sequence variant rs8192605 (G>A); inframe insertion / inframe deletion / coding sequence variant rs10654394 (CGCTGCTGC>-,CGCTGCTGCCGCTGCTGC,CGCTGCTGCCGCTGCTGCCGCTGCTGC,CGCTGCTGC CGC); coding sequence variant / synonymous variant rs28930368 (G>A); coding sequence variant / missense variant rs28932470 (T>C,G); coding sequence variant rs28932472 (G>C); coding sequence variant / synonymous variant rs34650613 (G>A); coding sequence variant / missense variant rs80326661 (T>C); stop gained / coding sequence variant / missense variant rs121918111 (C>A,G,T); stop gained / coding sequence variant rs121918112 (T>A); 5 prime UTR variant / genic upstream transcript variant / upstream transcript variant

rs139229417 (T>C); coding sequence variant / synonymous variant rs139540760 (C>T); coding sequence variant / missense variant rs141309351 (C>T); coding sequence variant / missense variant rs199636726 (G>T); coding sequence variant / missense variant rs201408477 (A>G); coding sequence variant / synonymous variant / missense variant rs201519174 (G>A,C); coding sequence variant / stop gained rs202127120 (C>A); synonymous variant / coding sequence variant / missense variant rs373721473 (C>A,T); missense variant / coding sequence variant rs746125905 (T>G). At the present moment a total of 2660 SNVs of the *POMC* gene have been described in different racial and ethnic groups of the world population [28].

Table 4. Candidate genes related to biological processes of ESS [26, by author modification].

Biological process	Top affiliating genes	Score
G protein-coupled receptors signaling pathway	*TRH* *POMC* *NPY* *INS* *GNRH1*	9.92
Signal transduction	*TRH* *PRL* *POMC* *INS* *IGF1* *GNRH1*	9.8
Negative regulation of apoptotic process	*PROP1* *IGFBP3* *IGF1*	9.78
Positive regulation of MAPK cascade	*INS* *IGF1*	9.58
Activation of protein kinase B activity	*INS* *IGF1*	9.56
Positive regulation of JAK-STAT cascade	*PRL* *GH1*	9.55
Pituitary gland development	*PROP1* *LHX3*	9.54
Positive regulation of mitotic nuclear division	*INS* *IGF1*	9.51
Positive regulation of phosphatidylinositol 3-kinase signaling	*INS* *IGF1* *GH1*	9.5
Regulation of multicellular organism growth	*PRL* *IGF1*	9.49

A search of the combination "*POMC*" and "empty sella" in National Library of Medicine gave results in 5 different databases: Bookshelf – 3 publications, PubMed – 87 publications, PubMed Central – 37 publications, GTR – 1 publication, GEO profiles – 40 publications, indicating the significance of the *POMC* gene in the development of ESS [29].

Nowadays, 2 methods of searching for SNVs mutations of the *POMC* gene in patients with ESS are used in clinical practice: deletion/duplication analysis; sequence analysis of the entire coding region. 87 publications were found in PubMed using words combination "*POMC*" and "empty sella" [30]. However, when adding the "gene" filter, only 2 publications were found [31]. It showed that the role of the proopiomelanocortin protein may be investigated better than the prognostic role of SNVs of the *POMC* gene in ESS development in humans. However, the predictive role of any of the *POMC* gene Sis are not known in patients with ESS.

Table 5. Neurological and psychiatric disorders associated with ESS (top 20) [26, by authors modification].

Related disorder	Top affiliating genes	Score
Intracranial hypertension, idiopathic	*POMC* *IGF1* *GH1*	30.5
Traumatic brain injury	*IGF1* *GH1*	30.0
Central precocious puberty	*IGF1* *GNRH1* *GH1*	30.0
Migraine with or without aura 1	*PRL* *POMC* *NPY* *INS*	29.7
Pituitary adenoma	*TRH* *PRL* *POMC* *IGF1* *GNRH1* *GH1*	29.7
Hypothyroidism, congenital, nongoitrous, 4	*PROP1* *PRL* *POMC* *GH1*	29.7
Islet cell tumor	*INS* *IGF1* *GH1*	29.7
Hydrocephalus	*PRL* *NPY* *IGFBP3* *IGF1*	29.6
Hypothalamic disease	*TRH* *PRL* *POMC* *INS* *GNRH1* *GH1*	29.0
Pituitary apoplexy	*TRH* *PRL* *POMC* *INS* *IGF1* *GNRH1*	28.8
Conn's syndrome	*TRH* *PRL* *POMC* *IGF1* *GNRH1* *GH1*	28.8
Sheehan syndrome	*PROP1* *PRL* *POMC* *INS* *IGF1*	28.6
Craniopharyngioma	*TRH* *PROP1* *PRL* *INS* *IGF1* *GNRH1*	27.7
Prader-Will syndrome	*TRH* *PRL* *POMC* *NPY* *INS* *IGFBP3*	27.2
Pituitary deficiency due to empty sella turcica syndrome	No label	12.7

Craniofacial anomalies and anterior segment dysgenesis syndrome	No label	11.7
Intracranial hypertension	No label	10.6
Headache	No label	10.5
Fibrous dysplasia / Mccune-Albright syndrome	*PRL* *GH1*	10.4
Cranial nerve palsy	*PRL* *POMC*	10.3

Discussion

Nowadays there are more than 100 neurological and psychiatric disorders associated with ESS in humans. In *Table 5* we presented the top-20 of these disorders which are very important for clinicians and scientists. Future researches are needed as they may also contribute toa better understanding of this condition.

Conclusions

Therefore, ESS is not only endocrine pathology, but it is a general interdisciplinary problem. Neurologists and psychiatrists must also be involved in the monitoring and treatment of patients with ESS.

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