Abstract

**Background:** Posttraumatic stress disorder (PTSD) is known by a number of mental disorders, including recurring memories of trauma, mental appalling, and escaping of sign that make them recall the trauma in question. Clinical interviews serve as the main diagnostic tool for PTSD. With respect to treatment, either pharmacotherapy or psychotherapy or a combination of both is used as a therapeutic method for PTSD. In this study, a number of crucial genes related to PTSD, which can be considered as biomarker candidates, were represented.

**Materials and Methods:** The genes related to PTSD were extracted from the STRING database and organized in a protein-protein interaction network with the help of Cytoscape software version 3.6.0. The network was analyzed, and the important genes were introduced based on central indices. The biological processes related to the crucial genes were enriched via gene ontology using ClueGO.

**Results:** From a total of 100 genes, 63 genes were extracted that formed the main connected component, and of these, 12 crucial genes—POMC, BDNF, FOS, NR3C1, CRH, IL6, NPS, HTR1A, NPY, CREB1, CRHR1, and TAC1—were introduced. Biological processes were classified into the regulation of corticosterone, regulation of behavior, response to fungus, multicellular organism response to stress, and associative learning.

**Conclusion:** The introduced 12 crucial genes can be used as a biomarker panel related to PTSD and can be considered as a diagnostic reagent or drug target; however, more investigations are needed to use these genes as biomarkers.

**Keywords:** Posttraumatic Stress Disorder; Protein-Protein Interaction Network; Cytoscape; ClueGO; Biomarker Panel

Introduction

Posttraumatic stress disorder (PTSD) is a condition that results from trauma. However, not all individuals exposed to a traumatic event develop PTSD [1]. A number of manifestations of PTSD, which include recurring remembrances of trauma, mental shocking, and escaping from the signs that make the people recall the trauma in question, have been reported [2]. Clinical interviews serve as the main diagnostic tool to determine PTSD [3].

**Correspondence to:**
Mostafa Rezaei-Tavirani, Proteomics Research Center, Faculty of Paramedical Sciences, Darband Street, Tad-jrish, Tehran, Iran
Telephone Number: +98-21-22439787
Email Address: tavirany@yahoo.com
Drug therapy or psychotherapy and a combination of both are used as therapeutic methods for PTSD [4]. Different molecular and cellular aspects of the disorder have been studied and discussed in detail [5-7]. The significant role of several hormones, such as cortisol, in PTSD is introduced and emphasized [8-10]. Genome-wide studies about PTSD have provided valuable information about the mechanism of the disease [11, 12]. In protein-protein interaction (PPI) network analysis, the genes, the production of genes and proteins or metabolites that are related to a condition are organized in an interactome unit based on graph theory [13, 14]. The elements (nodes) of the constructed network play various role in the network. The nodes that connect to a higher number of other elements of the network are known as hub nodes. These central nodes play a crucial role in the network. The absence of hub nodes leads to gross alteration in the topological properties of the network [15, 16]. Since there is a correlation between the network properties and the studied condition, the critical nodes of the network play a significant role in the pathology of diseases or disorders. The other important nodes in the network are known as the bottleneck nodes. These nodes control the other nodes of the network [17, 18]. Scientists had introduced more properties of the nodes such as closeness centrality and stress that identify the nodes as the more important nodes relative to other nodes [19]. Finally, network analysis can represent limited nodes among a large number of query nodes as the highlighted ones [20, 21]. Investigations show that these painted nodes are the main players related to the studied condition [22, 23]. It is possible to determine biological processes, molecular functions, and cellular components related to the critical genes (nodes) by enriching them through gene ontology (GO). The identified terms improve the understanding of the mechanism of condition or disease [24, 25]. A large number of diseases are studied via PPI network analysis, and the related crucial genes or proteins are identified and represented in a unique panel [26-30]. The findings can facilitate the introduction of efficient disease biomarkers. The discovered biomarkers are useful in treatment, diagnosis (especially in early diagnosis), and follow-up of patients [31-33].

**Materials and Methods**

The genes related to PTSD were extracted from the STRING database. STRING (http://string-db.org/) as an efficient interaction source is a plug-in of Cytoscape software. Cytoscape software and its applications such as STRING database are free sources that can be used to provide related proteins to diseases. This software is compatible with different sources. It is a useful tool for data collection and analysis using the PPI network. The PPI network was constructed using Cytoscape software version 3.6.0. The main connected component of PTSD PPI network was analyzed by the network analyzer plug-in of Cytoscape. Since centrality parameters are the most important topological properties of the nodes of the PPI network, the 4 well-known central indices, including degree, betweenness, closeness, and stress of nodes, were considered to rank the nodes of the network. The numbers of top 20% of the genes base of degree values were selected as hub genes and 20% of genes based on betweenness were identified as bottleneck nodes. The third group of highlighted genes were the top 20% of high-score nodes based on closeness. Similar groups were chosen by stress values. The genes were classified into 5 categories on the basis of the following criteria and introduced as important nodes of the PPI network of PTSD:

1. The common genes between hub and bottleneck nodes (as hub-bottleneck genes)
2. The hub-bottleneck nodes that were painted in the high-score nodes based on closeness and stress
3. The common hub nodes with the selected genes via closeness and stress
4. The bottleneck genes with high scores of closeness and stress
5. The hub and bottleneck genes with high scores of closeness or stress

Connections between the important elements
of the PPI network of PTSD were recognized by a subnetwork that was constructed by the critical nodes. The subnetwork was used as a screening tool to determine crucial genes. The regulatory pattern of the crucial genes was investigated via the literature survey for the validation of the findings. Finally, the crucial genes were enriched via GO by using ClueGO (http://apps.cytoscape.org/apps/cluego). The biological processes were classified and discussed in detail. The P-value of ≤0.01 was considered as the statistic index.

**Results**

The genes related to a disease are required for constructing a PPI network. The data may be provided through an experimental study, literature survey, or database. In this study, the genes related to PTSD were extracted from the STRING database. As shown in Figure-1, a total of 63 genes were included in the main connected component. The network was analyzed, and the nodes were ranked on the basis of centrality parameters. Top 20% of nodes based on the degree value, betweenness centrality, closeness centrality, and stress were selected and organized in 4 groups (see Table-1). As described in the Materials and Methods section, 18 important genes were introduced; these are presented in Table-2. In Figure-2, connections between the important genes are highlighted via an integrative subnetwork. As shown in Figure-2, several important genes interact with almost all other nodes; however, a few genes have limited connections. As shown in Table-2, these few genes are bottleneck nodes that are common with the selected genes based on the stress value. Therefore, these nodes were excluded, and the remaining 12 nodes were introduced as the crucial genes related to PTSD (Table-3). Expression change of the crucial genes in PTSD patients and animal models was investigated via the literature survey, and the findings are presented in Table-3. Because the attribution of a gene in biological processes is an important feature of the role of gene in the investigated disease, 12 crucial genes were enriched through GO, and the significant processes were determined as shown in Figure-3. Important roles of these biological processes in relation to PTSD are discussed in detail in the following section.
Table-1. The Top 20% Nodes Related to the Main Component of PTDS PPI Network, Based On Degree Value, Betweenness Centrality, Closeness Centrality, and Stress Value

| Name | Betweenness centrality | Closeness centrality | Stress | Disease score |
|------|------------------------|----------------------|--------|--------------|
| POMC | BDNF                   | BDNF                 |        |              |
| BDNF | IL6                    | FOS                  | IL6    |              |
| FOS  | FOS                    | POMC                 | FOS    |              |
| CRH  | FKBP5                  | CRH                  | POMC   |              |
| NPS  | ADCYAP1                | NPS                  | NR3C1  |              |
| HTR1A| POMC                   | CREB1                | FKBP5  |              |
| NPY  | PIN1                   | TAC1                 | C1orf56|              |
| DRD2 | C1orf56                | NPY                  | PIN1   |              |
| NR3C1| NR3C1                  | NR3C1                | ADCYAP1|              |
| CREB1| OGN                    | CRHR1               | CRH    |              |
| CRHR1| PTGIS                  | IL6                  | OGN    |              |
| TAC1 | CCAR1                  | HTR1A                | CCAR1  |              |

Table-2. The Most 18 Important Genes Related to PTDS

| Name | Description | Degree | Betweenness centrality | Closeness centrality | Stress | Disease score |
|------|-------------|--------|------------------------|----------------------|--------|--------------|
| POMC | Proopiomelanocortin | 32     | 0.10                   | 0.56                 | 1908   | 2.1          |
| BDNF | Brain-derived neurotrophic factor | 31     | 0.13                   | 0.58                 | 2120   | 2.6          |
| FOS  | FBJ murine osteosarcoma viral oncogene homolog | 31     | 0.11                   | 0.56                 | 2060   | 2.0          |
| NR3C1| Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor) | 21     | 0.08                   | 0.51                 | 1806   | 2.5          |
| CRH  | Corticotropin releasing hormone | 27     | 0.04                   | 0.53                 | 1124   | 2.7          |
| IL6  | Interleukin 6 (interferon, beta 2) | 20     | 0.12                   | 0.50                 | 2068   | 1.5          |
| NPS  | Neuropeptide S | 27     | 0.03                   | 0.53                 | 880    | 1.6          |
| HTR1A| 5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled | 25     | 0.02                   | 0.50                 | 746    | 2.0          |
| NPY  | Neuropeptide Y | 24     | 0.02                   | 0.52                 | 682    | 2.3          |
| CREB1| Campresponsiveelementbindingprotein1 | 21     | 0.05                   | 0.52                 | 976    | 1.4          |
| CRHR1| Corticotropinreleasinghormonereceptor1 | 21     | 0.04                   | 0.51                 | 934    | 2.5          |
| TAC1 | Tachykinin, precursor 1 | 21     | 0.03                   | 0.52                 | 890    | 1.2          |
| FKBP5| FK506 binding protein 5 | 6      | 0.10                   | 0.42                 | 1748   | 3.0          |
| ADCYAP1| Adenylate cyclase activating polypeptide 1 (pituitary) | 15     | 0.10                   | 0.48                 | 1376   | 1.8          |
| PIN1 | Peptidylprolyl cis/trans isomerase, NIMA-interacting 1 | 3      | 0.09                   | 0.32                 | 1606   | 1.7          |
| C1orf56 | Chromosome 1 open reading frame 56 | 7      | 0.09                   | 0.41                 | 1638   | 1.8          |
| OGN  | Osteoglycin | 3      | 0.07                   | 0.25                 | 1112   | 3.8          |
| CCAR1| Cell division cycle and apoptosis regulator 1 | 2      | 0.06                   | 0.31                 | 1074   | 1.8          |
Table-3. Regulation Pattern for Elements of Displayed Sub-Network. Green and Red Colors Refer to Down and Up Regulation.

| Name  | Down regulated | Up regulated | Reference        |
|-------|----------------|--------------|------------------|
| POMC  |                | Meyerhoff JL et al [34] |
| BDNF  |                | Dell’Osso L et al [35] |
| FOS   |                | Segman RH et al [36] |
| NR3C1 |                | Vukojevic V et al [37] |
| CRH   |                | Asalgoo S et al [38] |
| IL6   |                | Gill J et al [39] |
| NPS   |                | Ionescu IA et al [40] |
| HTR1A |                | Sullivan et al (41) |
| NPY   |                | Cohen H et al [42] |
| CREB1 |                | Segman RH et al [36] |
| CRHR1 |                | Mehta D, Binder EB [43] |
| TAC1  |                | Lindberg J [44] |

Figure-2. A sub-network including 18 top nodes of the main component of PTDS PPI network is presented.
Discussion

The PPI networks of diseases have different sizes, for example, esophageal adenocarcinoma has a small network compared with the pancreatic adenocarcinoma PPI network. The size of a network is in proportion to the number of the introduced genes. The more number of high-quality investigations provides more information and documents about a considered disorder. It seems that more investigations can explore more genes related to PTSD. Based on defined confidence, the genes are partly included in the network. In this study, by using the confidence value of 0.4 (default of software), 63% of the extracted nodes were included in the main connected component of the network. Analysis revealed that 18 genes play an important role in the PTSD PPI network. It is expected that these central genes be connected to each other and be organized in the integrated subnetwork. As shown in Figure-2, the numbers of nodes including FKBP5, PIN1, C1ORF56, OGN, and CCAR1 (the bottleneck nodes that are characterized with a high score of stress) have poor connections with the neighboring nodes. Corresponding with this finding, the mentioned group including 6 nodes is excluded, and the 12 remaining nodes were introduced as crucial nodes. In the following paragraphs, the role of these 12 crucial genes in the pathology of PTSD will be discussed briefly.

Proopiomelanocortin (POMC) is the first crucial gene related to PTSD. It is a hub-bottleneck node that is highlighted by high scores of closeness and stress. As is shown in Table-3, POMC gene is upregulated in PTSD. It can be processed to adrenocorticotropic hormone (ACTH) and melanocortin peptides [45]. Investigations indicate that an increase in ACTH concentration is accompanied by an increased value in cortisol concentration [46]. Cortisol, which is known as the “stress hormone,” is affected by inflammation, food intake, and obesity [47, 48]. It seems that POMC may be a suitable biomarker for PTSD. The second crucial gene is BDNF, and its situation in the PPI network is similar to that of POMC. It is reported that brain-derived
neurotrophic factor concentration decreases due to exposure to stress. This neurotrophic factor decrement is associated with physiological effects. Learning and memory are the two affected behavioral aspects related to BDNF. There are pieces of evidence that correspond to the role of BDNF in Alzheimer disease [49]. It can be concluded that the downregulation of BDNF in PTSD (see Table-3) is accompanied by the decrement of learning and memory. Cognitive aspects of PTSD were investigated. The finding indicates a decrease in sustained attention, working memory, and initial learning [50]. Similar to POMC and BDNF, the third gene, FOS, is a hub-bottleneck gene with high-scores of closeness and stress. FOS is known as a metabolite marker of tracing neuroanatomical connections and sites of action of neuroactive drugs [51]. This property of FOS is used to determine the involved brain nuclei in PTSD [52]. As shown in Table-3, FOS was upregulated in PTSD. It seems that FOS concentration is a suitable marker for the follow-up of patients. The fourth crucial gene is NR3C1 that is upregulated, and its topological situation in the network is similar to the 3 aforementioned genes, which we have already discussed. Glucocorticoid hormones belong to a group of hormones that are secreted by the adrenal cortex and bind to glucocorticoid receptors in response to the stress via the circadian pattern. Hypothalamic corticotropin-releasing hormone (CRH) in response to the internal or external signals affects the secretion of pituitary hormone ACTH [53]. Cortisol is major human glucocorticoid [54]. The roles of ACTH and cortisol in PTSD were discussed in the initial part of the Discussion section. CRH is a hub node that is not a bottleneck gene, but it is highlighted by high values of closeness and stress (see Table-2). The closed relationship between CRH, ACTH, and cortisol refers to the critical role of each of them in PTSD. CRHR1, the familiarized gene in row 11 of Table-3, is another gene related to CRH, which encodes the R1 receptor of CRH. It is a hub node with a high closeness value (see Table-2). Its upregulation is consistent with the other related genes in Table-3. The relationship between a high level of interleukin (IL)-6, IL1β, interferon γ, and tumor necrosis factor (TNF α; inflammatory markers), and PTSD was reported by Passos et al. via a systematic review, meta-analysis, and meta-regression study [55]. As is represented in Table-3, IL6 is a unique bottleneck node that is achieved through high scores of closeness and stress. The roles of neuropeptide S (NPS) and neuropeptide Y (NPY) in alcohol use disorder are reported by Rodriguez and Covenas. These neuropeptides and corticotropin-releasing factors are responsible for the malfunction of brain in the patients [56]. The decrement of the NPY level in PTSD is reported, and it is suggested as a protector agent for PTSD [57]. Growing pieces of evidence indicate that NPY is a protective neurochemical reagent that is related to stress resilience [58]. These 2 hub nodes are tinted by high closeness values (Table-2). Evidence indicates that HTR1A in PTSD patients than in the healthy people. The patients were selected without comorbidity or major depressive disorder (MDD) [41]. The crucial roles of serotonin malfunction in MDD, anxiety disorders, and the overlap of these diseases with PTSD correspond to the important role of serotonin in PTSD [59]. The increased level of the serotonin receptor after the malfunction of serotonin can be interpreted in this regard. HTR1A is announced as a hub node with high closeness value (Table-2). cAMP-responsive element binding (CREB) protein 1 is a member of transcription factors that are involved in several neural processes such as stress response, learning, and neural plasticity. Investigation indicates that PTSD patients have less number of this protein relative to the healthy individuals [60]. As is reported, the significant role of CREB is neuronal caloric restriction [61]. Evidence indicates that TAC1 plays a main role in narcolepsy and the low level of this protein is recorded [44]. Association between PTSD and narcolepsy is reported and emphasized [62]. Biological processes related to the 12 crucial genes of the PPI network of PTSD correspond with the discussed roles of the nodes. As depicted in Figure-3, the regulation
of corticosterone is an important process that is related to the nodes. A total of 11 terms are grouped in this cluster, including the regulation of the endocrine process, steroid hormone secretion, corticosteroid hormone secretion, and glucocorticoid secretion. The second main cluster is the regulation of behavior that includes the number of terms that are correlated with the crucial nodes and have been discussed in detail. It seems that the analysis of the PPI network led to the finding critical opinions of PTSD. The introduced critical nodes can be used for the therapeutic method and diagnosis of PTSD and also for the follow-up of patients. The impact of the findings is to introduce a possible molecular-based method for the diagnosis of PTSD and also for the potential drug targets.

**Conclusion**

In this study, at least 12 proteins among a large number of introduced proteins were identified, which can be used as a biomarker panel related to PTSD. The highlighted genes can be considered as the diagnostic reagents or drug targets; however, more investigation is needed to reduce this number to an economic quantity.

**Acknowledgments**

This project is supported by Shahid Beheshti University of Medical Sciences.

**Conflict of Interest**

None declared

---

**References**

1. Smith A, Ratanatharathorn A, Boks M, Logue M, Maihofer A, Kilaru V, et al. 86-Epigenetic signatures of PTSD: results from the psychiatric genomics consortium PTSD epigenetics workgroup. Biol Psychiatry. 2017; 81(10): S36.
2. Busbee PB, Nagarkatti M, Nagarkatti P. Alterations in p53 expression in PMBCs of PTSD patients leads to dysregulation in miRNA biogenesis which promotes an inflammatory Th17 immune cell phenotype. Am Assoc Immnol. 2017; 198 (Suppl 1): 223.12.
3. Marx BP, Engel- Rebitzer E, Bovin MJ, Parker-Guilbert KS, Mosher S, Barretto K, et al. The influence of veteran race and psychometric testing on veterans affairs posttraumatic stress disorder (PTSD) disability exam outcomes. Psychol Assess. 2017; 29(6):710-9.
4. Lokshina Y, Liberon I. Enhancing efficacy of PTSD treatment: role of circuits, genetics, and optimal timing. Clin Psychol (New York). 2017; 24(3): 298-301.
5. Girgenti MJ, Hare BD, Ghosal S, Duman RS. Molecular and cellular effects of traumatic stress: Implications for PTSD. Curr psychiatry rep. 2017; 19(11): 85.
6. Chakraborty N, Meyerhoff J, Jett M, Hammamieh R. Genome to phenome: a systems biology approach to PTSD using an animal model. Methods Mol Biol. 2017; 1598: 117-54.
7. Muhie S, Gautam A, Chakraborty N, Hoke A, Meyerhoff J, Hammamieh R, et al. Molecular indicators of stress-induced neuroinflammation in a mouse model simulating features of post-traumatic stress disorder. Transl Psychiatry. 2017; 7(5): e1135.
8. Matosin N, Cruceanu C. Stress-related memory impairments are modulated by the synergistic action of stress hormones: implications for PTSD. J Neurosci. 2017; 37(16): 4225-7.
9. Rhind S, Rakesh J, Richardson D, Di Battista A, Lanius R. Dysregulation of hypothalamic-pituitary-adrenal axis and sympathoadrenergic system is associated with posttraumatic stress disorder in combat veterans. Biolo Psychiatry. 2017; 81(10 Suppl): S394.
10. Dias BG. Hormonal influences on memory dimensions of post-traumatic stress disorder. Psychoneuroendocrinology. 2017; 83(Suppl):82-3.
11. Chen C-Y, Stein M, Ursano R, Cai T, Gelernter J, Heeringa S, et al. 223. Genomewide association study of post traumatic stress disorder symptom domains in two cohorts of United States army soldiers. Biol Psychiatry. 2017;81(10):S91-S2.

12. Liberzon I, Duncan L, Nievergelt C, Ressler K, Koenen K. First wave genome wide study In PTSD: genetic overlap and sex differences in heritability. Eur Neuropsychopharmacol. 2017;27(Suppl 3): S415-6.

13. Mason O, Verwoerd M. Graph theory and networks in biology. IET Syst Biol. 2007; 1(2): 89-119.

14. Lesne A. Complex networks: from graph theory to biology. Lett Math Phys. 2006; 78(3): 235-62.

15. Safari-Alighiarloo N, Taghizadeh M, Rezaei-Tavirani M, Goliaei B, Peyvandi AA. Protein-protein interaction networks (PPI) and complex diseases. Gastroenterol Hepatol bed bench. 2014; 7(1): 17-31.

16. Maghvan PV, Rezaei–Tavirani M, Zali H, Nikzamir A, Abdi S, Khodadoostan M, et al. Network analysis of common genes related to esophageal, gastric, and colon cancers. Gastroenterol Hepatol bed bench. 2017; 10(4): 295-302.

17. Akbari S, Hosseini M, Rezaei Tavirani M, Rezaei Tavirani MR, Salehi SH, Alamrajabi M, et al. Common and differential genetically pathways between ulcerative colitis and colon adenocarcinoma. Gastroenterol Hepatol bed bench. 2017; 10(Suppl 1): S93-101.

18. Safari-Alighiarloo N, Taghizadeh M, Tabatabaei SM, Shahsavari S, Namaki S, Khodakarim S, et al. Identification of new key genes for type 1 diabetes through construction and analysis of protein–protein interaction networks based on blood and pancreatic islet transcriptomes. J diabetes. 2017; 9(8): 764-77.

19. Safari-Alighiarloo N, Rezaei Tavirani M, Taghizadeh M, Tabatabaei SM, Namaki S. Network-based analysis of differentially expressed genes in cerebrospinal fluid (CSF) and blood reveals new candidate genes for multiple sclerosis. PeerJ. 2016; 4: e2775.

20. Zali H, Rezaei Tavirani M. Meningioma protein-protein interaction network. Arch Iran Med. 2014; 17(4): 262-72.

21. Abbaszadeh HA, Peyvandi AA, Sadeghi Y, Safaei A, Zamanian-Azodi M, Khoramgah MS, et al. Er: YAG laser and cyclosporin A effect on cell cycle regulation of human gingival fibroblast cells. J lasers Med Sci. 2017; 8(3): 143-9.

22. Zamanian-Azodi M, Rezaei-Tavirani M, Rahmati Rad S, Hasanzadeh H, Rezaei Tavirani M, Seyyedi SS. Protein-protein interaction network could reveal the relationship between the breast and colon cancer. Gastroenterol Hepatol bed bench. 2015; 8(3): 215-24.

23. Rezaei-Tavirani M, Zamanian-Azodi M, Rajabi S, Masoudi Nejad A, Rostami Nejad M, Rahmatiad S. Protein clustering and interactome analysis in parkinson and Alzheimer's diseases. Arch Iran Med. 2016; 19(2): 101-9.

24. Rezaei Tavirani M, Okhovatian F, Zamanian-Azodi M, Rezaei Tavirani M. Duchenne muscular dystrophy (DMD) protein–protein interaction mapping. Iran J child neurol. 2017; 11(4): 7-14.

25. Karbalaei R, Piran M, Rezaei-Tavirani M, Asadzadeh-Aghdaei H, Heidari MH. A systems biology analysis protein–protein interaction of NASH and IBD based on comprehensive gene information. Gastroenterol Hepatol bed bench. 2017; 10(3): 194-201.

26. Su J, Yoon B-J, Dougherty ER. Identification of diagnostic subnetwork markers for cancer in human protein-protein interaction network. BMC bioinformatics. 2010;11(Suppl 6): S8.

27. eng J, He W, Song Y, Wang Y, Simpson RJ, Zhang X, et al. Platelet-derived growth factor receptor beta: a novel urinary biomarker for recurrence of non-muscle-invasive bladder cancer. PLoS One. 2014; 9(5): e96671.

28. Safaei A, Oskouie AA, Mohebbi SR, Rezaei-Tavirani M, Mahboubi M, Peyvandi M, et al. Metabolomic analysis of human cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis diseases. Gastroenterol Hepatol bed bench. 2016; 9(3): 158-73.

29. Zamanian-Azodi M, Peyvandi H, Rostami-Nejad M, Safaei A, Rostami K, Vafaei R, et al. Protein–protein interaction network of cicelic disease. Gastroenterol Hepatol bed bench. 2016; 9(4): 268-77.
30. Khayer N, Zamanian-Azodi M, Mansouri V, Ghassemi-Broumand M, Rezaei-Tavirani M, Heidari MH, et al. Oral squamous cell cancer protein-protein interaction network interpretation in comparison to esophageal adenocarcinoma. Gastroenterol Hepatol bed bench. 2017; 10(2): 118-24.

31. Doecke JD, Laws SM, Faux NG, Wilson W, Burnham SC, Lam C-P, et al. Blood-based protein biomarkers for diagnosis of Alzheimer disease. Arch neurol. 2012; 69(10): 1318-25.

32. Paczesny S, Krijanovski OI, Braun TM, Choi SW, Clouthier SG, Kuick R, et al. A biomarker panel for acute graft-versus-host disease. Blood. 2009; 113(2): 273-8.

33. Younossi ZM, Jarrar M, Nugent C, Randhawa M, Afendy M, Stepanova M, et al. A novel diagnostic biomarker panel for obesity-related nonalcoholic steatohepatitis (NASH). Obes Surg. 2008; 18(11): 1430-7.

34. Meyerhoff J, Oleshansky M, Mougey E. Psychologic stress increases plasma levels of prolactin, cortisol, and POMC-derived peptides in man. Psychosom Med. 1988; 50(3): 295-303.

35. Dell’Osso L, Carmassi C, Del Debbio A, Dell’Osso MC, Bianchi C, da Pozzo E, et al. Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2009; 33(5): 899-902.

36. Segman R, Shefi N, Golser-Dubner T, Friedman N, Kaminski N, Shalev A. Peripheral blood mononuclear cell gene expression profiles identify emergent post-traumatic stress disorder among trauma survivors. Mol psychiatry. 2005; 10(5): 500-13.

37. Yukojevic V, Kolassa I-T, Fastenrath M, Gschwind L, Spalek K, Milnik A, et al. Epigenetic modification of the glucocorticoid receptor gene is linked to traumatic memory and post-traumatic stress disorder risk in genocide survivors. J Neurosci. 2014; 34(31):10274-84.

38. Asalgoo S, Jahromi G, Meftahi G, Sahraei H. Posttraumatic stress disorder (PTSD): Mechanisms and possible treatments. Neurophysiol. 2015; 47(6): 482-489.

39. Gill J, Vythilingam M, Page GG. Low cortisol, high DHEA, and high levels of stimulated TNF-α, and IL-6 in women with PTSD. J Trauma Stress. 2008; 21(6): 530-9.
50. Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain Jr AN, Sutker PB. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology. 2002; 16(1): 5-14.

51. Dragunow M, Faull R. The use of c-fos as a metabolic marker in neuronal pathway tracing. J Neurosci Methods. 1989;29(3):261-5.

52. Kung J-C, Chen T-C, Shyu B-C, Hsiao S, Huang ACW. Anxiety-and depressive-like responses and c-fos activity in preproenkephalin knockout mice: oversensitivity hypothesis of enkephalin deficit-induced posttraumatic stress disorder. J Biomed Sci. 2010; 17(1): 29.

53. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol. 2013; 132(5): 1033-44.

54. Lu NZ, Wardell SE, Burnstein KL, Defranco D, Fuller PJ, Giguere V, et al. International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progestrone, and androgen receptors. Pharmacol Rev. 2006; 58(4): 782-97.

55. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015; 2(11): 1002-12.

56. Rodriguez FD, Covenas R. Targeting NPY, CRF/UCNs and NPS neuropeptide systems to treat Alcohol Use Disorder (AUD). Curr Med Chem. 2017; 24(23): 2528-58.

57. Rasmusson AM, Hauger RL, Morgan CA, Brenner JD, Charney DS, Southwick SM. Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. Biol psychiatry. 2000; 47(6): 526-39.

58. Enman NM, Sabban EL, McGonigle P, Van Bockstaele EJ. Targeting the neuropeptide Y system in stress-related psychiatric disorders. Neurobiol Stress. 2015; 1: 33-43.

59. Davis LL, Suris A, Lambert MT, Heimberg C, Petty F. Post-traumatic stress disorder and serotonin: new directions for research and treatment. J Psychiatry Neurosci. 1997; 22(5): 318-26.

60. Martini C, Da Pozzo E, Carmassi C, Cuboni S, Trincavelli ML, Massimetti G, et al. Cyclic adenosine monophosphate responsive element binding protein in post-traumatic stress disorder. World J Biol Psychiatry. 2013; 14(5): 396-402.

61. Fusco S, Ripoli C, Podda MV, Ranieri SC, Leone L, Toietta G, et al. A role for neuronal cAMP responsive-element binding protein (CREB)-1 in brain responses to calorie restriction. Proc Natl Acad Sci USA. 2012;109(2):621-6.

62. Mellman TA, Ramsay RE, Fitzgerald SG. Divergence of PTSD and narcolepsy associated with military trauma. J Anxiety Disord. 1991; 5(3): 267-72.