ORIGINAL ARTICLE

Arvand Journal of Health & Medical Sciences

Gene ontology analysis of obsessive-compulsive disorder related expressed genes

Mona Zamanian Azodi, Majid Rezaei Tavirani

Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

✉ **Reprint or Correspondence**: Majid Rezaei-Tavirani; MD Proteomics Research Center, Shahid Beheshti University of Medical sciences, Tehran, Iran
@✉ tavirani_m@yahoo.com.

ABSTRACT

Obsessive-Compulsive Disorder is one of the complex mental disorders that combination of genetic components and environmental factors influence its phenotype. In this study, data from microarray findings has been evaluated from gene ontology perspective. The raw data from GEO was at first analyzed by the use of GEO2R Software as two groups of samples (Normal/OCD and Normal/ OCD with comorbidity); and then enrichment analysis of 50 significant differentially expressed genes of each group of samples was handled. The data indicates that enrichment findings in two groups are relatively similar. Furthermore, regulation of transcription, plasma membrane, and nucleotide and ion bindings are the most involved processes, parts and functions, respectively. In conclusion, these terms can be introduced as potential representations in OCD risk; however, clinical validations are required and suggested. Thus, for this aim, systematic molecular studies, particularly in the field of proteomics and metabolomics are fundamental.

Keywords: Obsessive-Compulsive Disorder, Gene ontology, Gene expression.

***Received*: 16 November 2015 *Accepted*: 9 January 2016**

Introduction

Obsessive-compulsive disorder is a complex neuropsychiatric disorder that is typical with intrusive thoughts and repetitive acts. It was previously categorized as anxiety disorders, but in 2013, it was moved to a new section as "Obsessive and Compulsive and Related Disorders" by American Physiatrist Association (1). lifetime prevalence of OCD is estimated about 1 to 3% around the world (2). Many different studies indicated that etiopathology of OCD is related to the various factors (3). Genetic and environmental factors combine and manifest different subtypes of OCD (2). The main subtypes of OCD comprise of contamination/cleaning, checking, hoarding and rumination (4). Most of the OCD molecular studies are related to genetic basis of this disorder. Genetic foundation of OCD is very complicated as many genes with their polymorphism are linked to OCD risk (2, 5, 6). Numerous susceptibility parts of the genome are relevant to this familial disorder (7). This fact purpose OCD as a polygenic disease with many subtypes. Pathways of serotonin, dopamine, glutamate, and their communications are important in cortico-striatal circuits. In fact,

Please cite as: **Zamanian Azodi M, Rezaei Tavirani M. Gene ontology analysis of obsessive-compulsive disorder related expressed genes. Arvand J Health Med Sci 2016;1(1):27-34.**

dysfunction in cortico-striatal-thalamo-cortical (CSTC) circuitry is the main incident in OCD pathophysiology (8). These include the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus and striatum (9). However, more research is needed to find out other implicated processes of this disorder for providing other treatment strategies. Many treatment options are available for OCD (10). One of the popular medicines is serotonin reuptake inhibitors (SRIs) family. However, not all the patients with OCD response to this type of drug family (11). The etiology of OCD has remained challenging over the past years since the manifest of this heterogenic disease is accompanied with different phenotypes that include overlap between OCD and other types of anxiety disorders including tic, phobia, and bipolarity (12). Molecular studies can be helpful to examine other potential agents in OCD nature and therefore can provide better treatment options. Bioinformatics is one of the new disciplines in today modern world (20). Its application is very wide that engaged with large dataset analysis. Gene ontology analysis showed promising role in presenting fundamental knowledge of massive molecular data (13). It comprises of three important features of biological process, molecular function and cellular component (14). The aim of this study is to provide characteristic information of the mRNA expression profiles of significant associated genes with OCD. In a way that, by the annotation analysis of the related gene products, a better insight in treatment options for OCD patients can be provided.

Materials and Methods

The study of *"Genetic Neuropathology of Obsessive Psychiatric Syndromes"* by *Jaffe AE et al*(15), in 2014 was selected for gene ontology evaluations. In this study, gene expression levels of different kinds of obsessions are studied from postmortem human brain dorsolateral prefrontal cortex (DLPFC) tissue. For this research, the gene expression data of OCD human samples and control ones from Gene Expression Omnibus (GEO) with series number of GSE60190 was extracted. The first analysis step was to compare the expression levels between control and OCD male samples. In this regard, GEO2R as a dataSet analysis tool was applied for differentially expressed genes analysis. By applying GEOquery and limma R packages from the Bioconductor project, GEO2R analyses the selected datasets (GDS) by using multiple-testing corrections based on P-values. In fact, it performs R statistical analysis independent of operator. The *Benjamini & Hochberg* (false discovery rate) is the applied P-value adjusted method. GEO2R provides statistical information including adjusted P. value, Raw P-value, B-statistic, Log 2-fold, moderated t-statistic and moderated F-statistic. Here the top genes are selected for further evaluations with p-value <0.05. Uniprot accession numbers for each gene were retrieved from Uniprot.org. The codes were applied for enrichment analysis using DAVID bioinformatics resources 6.7 (http://david.abcc.ncifcrf.gov.) (16). Annotation cluster analysis by DAVID software can be helpful in retrieving genes related information based on different annotation aspects such as (GO) function category. In each clusters, the count numbers signify the number of annotated proteins for each mentioned term in DAVID output. Similar related biological features are grouped in individual clusters.

Results

Comparison of gene expression profiles was performed between two samples of normal

(without psychiatric disorder) and OCD patients. For this purpose, two groups are defined as normal/OCD (group 1) and normal/OCD with comorbidity (group 2) and their gene expression profiles were analyzed with GEO2R (See tables1 and 2). The two groups were examined for gene ontology (BP, CC, MF) analysis. For each group, 50 top differentially expressed genes were selected.

Table1. Gene expression profiles of group1 (4 normal and 4 OCD patients) analyzed with GEO2R. The result is presented as a table of genes ordered by significant amounts (adj. P-Val <0.05 and P-value <0.05)

GEO2R | Value distribution | Options | Profile graph | R script

▸ Quick start

Recalculate if you changed any options. Save all results Select columns

ID	adj.P.Val	P.Value	t	B	logFC	Gene.symbol	Gene.title
ILMN_1707958	0.99	0.00024	-7.11	1.1304	-0.0846	AES	amino-terminal enha...
ILMN_1860518	0.99	0.000275	-6.95	0.9934	-0.0997		
ILMN_1792607	0.99	0.000417	6.47	0.569	0.0677	OBP2A	odorant binding prot...
ILMN_1750940	0.99	0.000422	-6.46	0.5575	-0.0855	SLITRK1	SLIT and NTRK-like...
ILMN_1684704	0.99	0.000678	5.95	0.0704	0.0369		
ILMN_2370772	0.99	0.000832	5.74	-0.1419	0.4795	EIF4G1	eukaryotic translatio...
ILMN_1876703	0.99	0.001073	5.49	-0.4055	0.2678		
ILMN_2329958	0.99	0.001454	-5.2	-0.7219	-0.3782	ABI1	abl-interactor 1
ILMN_1914034	0.99	0.001501	-5.17	-0.755	-0.0398		
ILMN_2234515	0.99	0.001511	5.16	-0.762	0.3343	SLC7A5P2	solute carrier family ...
ILMN_1767184	0.99	0.001748	5.03	-0.9138	0.0577		
ILMN_1730796	0.99	0.002056	4.88	-1.0837	0.0367	NPHP1	nephronophthisis 1 (...
ILMN_1756220	0.99	0.002209	-4.81	-1.1585	-0.3646	DDX18	DEAD (Asp-Glu-Ala-...
ILMN_1712031	0.99	0.002328	-4.77	-1.2134	-0.1472	SPDYE6	speedy/RINGO cell c...
ILMN_1779185	0.99	0.002528	4.69	-1.2999	0.3862	SPECC1L	sperm antigen with c...

Table 2. Gene expression profiles of group 2 (10 normal and 10 OCD patients with comorbidity) analyzed by GEO2R. The finding is presented as a table of genes ordered by significance (adj. P value <0.05 and P-value <0.05).

▸ Quick start

Recalculate if you changed any options. Save all results Select columns

ID	adj.P.Val	P.Value	t	B	logFC	Gene.symbol	Gene.title
ILMN_1760089	0.0066	1.36e-07	-8.15	7.75578	-0.2289		
ILMN_1739154	0.0102	6.08e-07	7.35	6.27251	1.1186	LSAMP	limbic system-assoc...
ILMN_1802780	0.0102	7.01e-07	-7.28	6.13218	-0.3647	CD163L1	CD163 molecule-like 1
ILMN_2102515	0.0102	8.40e-07	-7.18	5.9528	-0.2829	PGAM4	phosphoglycerate m...
ILMN_1698406	0.0109	1.12e-06	7.04	5.67052	0.5418	ORMDL1	ORMDL sphingolipi...
ILMN_1860288	0.0198	2.44e-06	-6.65	4.89594	-0.5041	MBTPS2	membrane-bound tr...
ILMN_1904111	0.0274	3.94e-06	6.41	4.41899	0.1837		
ILMN_1685985	0.0275	4.55e-06	-6.34	4.27798	-0.1942		
ILMN_1813573	0.0275	5.37e-06	-6.26	4.11253	-0.1471	SETD1B	SET domain contai...
ILMN_2261784	0.0275	5.65e-06	-6.24	4.06281	-0.8431	CCNY	cyclin Y
ILMN_1696702	0.0316	7.13e-06	6.13	3.83034	0.4441	NEO1	neogenin 1
ILMN_1768558	0.0317	7.82e-06	-6.08	3.73946	-0.13		
ILMN_1690295	0.0352	9.40e-06	-6	3.55598	-0.3294		
ILMN_1729515	0.0382	1.10e-05	-5.92	3.40179	-0.291	PIN4	protein (peptidylprol...
ILMN_1848226	0.0397	1.22e-05	-5.87	3.29525	-0.0895		
ILMN_1781225	0.0495	1.74e-05	-5.71	2.94319	-0.3421		
ILMN_1678707	0.0495	1.80e-05	5.69	2.91033	0.7526	TAF15	TAF15 RNA polyme...
ILMN_1803742	0.0495	1.83e-05	-5.68	2.89376	-0.1964	CAPZA1	capping protein (acti...
ILMN_1810324	0.0504	2.10e-05	5.62	2.75624	0.1667	SGCB	sarcoglycan, beta (4...

Table 3. Clustering based on biological process (BP) for 50 significant differentially expressed genes in A. Group 1 and B. Group 2, by the use of David Bioinformatics V.6.7.

2 Cluster(s) Download File

Annotation Cluster 1	Enrichment Score: 0.48			Count	P_Value	Benjamini
GOTERM_BP_FAT	protein amino acid phosphorylation	RT		4	2.2E-1	1.0E0
GOTERM_BP_FAT	phosphorylation	RT		4	3.1E-1	1.0E0
GOTERM_BP_FAT	phosphorus metabolic process	RT		4	4.3E-1	1.0E0
GOTERM_BP_FAT	phosphate metabolic process	RT		4	4.3E-1	1.0E0
Annotation Cluster 2	**Enrichment Score: 0.26**			**Count**	**P_Value**	**Benjamini**
GOTERM_BP_FAT	regulation of transcription, DNA-dependent	RT		6	4.4E-1	1.0E0
GOTERM_BP_FAT	regulation of RNA metabolic process	RT		6	4.6E-1	1.0E0
GOTERM_BP_FAT	response to organic substance	RT		3	5.3E-1	1.0E0
GOTERM_BP_FAT	regulation of transcription from RNA polymerase II promoter	RT		3	5.4E-1	1.0E0
GOTERM_BP_FAT	regulation of transcription	RT		7	6.3E-1	1.0E0
GOTERM_BP_FAT	transcription	RT		5	7.8E-1	1.0E0

A

4 Cluster(s) Download File

Annotation Cluster 1	Enrichment Score: 1.11			Count	P_Value	Benjamini
GOTERM_BP_FAT	cytoskeleton organization	RT		5	2.8E-2	1.0E0
GOTERM_BP_FAT	actin cytoskeleton organization	RT		3	1.2E-1	1.0E0
GOTERM_BP_FAT	actin filament-based process	RT		3	1.3E-1	1.0E0
Annotation Cluster 2	**Enrichment Score: 0.48**			**Count**	**P_Value**	**Benjamini**
GOTERM_BP_FAT	macromolecular complex assembly	RT		4	2.6E-1	1.0E0
GOTERM_BP_FAT	macromolecular complex subunit organization	RT		4	2.9E-1	1.0E0
GOTERM_BP_FAT	protein complex assembly	RT		3	3.9E-1	1.0E0
GOTERM_BP_FAT	protein complex biogenesis	RT		3	3.9E-1	1.0E0
Annotation Cluster 3	**Enrichment Score: 0.19**			**Count**	**P_Value**	**Benjamini**
GOTERM_BP_FAT	regulation of apoptosis	RT		3	6.4E-1	1.0E0
GOTERM_BP_FAT	regulation of programmed cell death	RT		3	6.5E-1	1.0E0
GOTERM_BP_FAT	regulation of cell death	RT		3	6.5E-1	1.0E0
Annotation Cluster 4	**Enrichment Score: 0.14**			**Count**	**P_Value**	**Benjamini**
GOTERM_BP_FAT	regulation of transcription from RNA polymerase II promoter	RT		3	5.8E-1	1.0E0
GOTERM_BP_FAT	regulation of transcription, DNA-dependent	RT		5	7.1E-1	1.0E0
GOTERM_BP_FAT	regulation of transcription	RT		7	7.2E-1	1.0E0
GOTERM_BP_FAT	regulation of RNA metabolic process	RT		5	7.3E-1	1.0E0
GOTERM_BP_FAT	transcription	RT		4	9.3E-1	1.0E0

B

IDs with gene symbols are chosen for the enrichments (See tables 3, 4, 5).

Discussion

Obsessive-compulsive Disorder as one of the complex mental disorders is prominent to study from molecular aspect. Many OCD molecular studies are focused on genetic basis of the disorder. In this study, a research conducted by *Jaffe AE et al* (15) in 2014 was chosen for the gene ontology analysis. That is, GO perspective of the most significantly altered genes expression is examined. Two groups of normal/OCD and normal/OCD with comorbidity are defined in this research. The first group consists of normal people with no mental disorder and OCD samples that were not reported with any kinds of comorbidity. The second group is the normal people and OCD patients with different kinds of comorbidity. The related comorbidity are bipolar, tic and MDD. As it is shown in table1, none of the

Table 4. Clustering cell component (CC) for 50 significant differentially expressed genes in A. Group1 and B. Group2, by the use of David Bioinformatics V.6.7.

3 Cluster(s) Download File

Annotation Cluster 1	Enrichment Score: 0.43				Count	P_Value	Benjamini
GOTERM_CC_FAT	plasma membrane part	RT			10	6.0E-2	1.0E0
GOTERM_CC_FAT	cell junction	RT			4	1.2E-1	1.0E0
GOTERM_CC_FAT	integral to plasma membrane	RT			4	5.4E-1	1.0E0
GOTERM_CC_FAT	plasma membrane	RT			10	5.5E-1	1.0E0
GOTERM_CC_FAT	intrinsic to plasma membrane	RT			4	5.5E-1	1.0E0
GOTERM_CC_FAT	integral to membrane	RT			10	9.3E-1	1.0E0
GOTERM_CC_FAT	intrinsic to membrane	RT			10	9.5E-1	1.0E0
Annotation Cluster 2	Enrichment Score: 0.2				Count	P_Value	Benjamini
GOTERM_CC_FAT	membrane fraction	RT			3	5.7E-1	1.0E0
GOTERM_CC_FAT	insoluble fraction	RT			3	5.9E-1	1.0E0
GOTERM_CC_FAT	cell fraction	RT			3	7.4E-1	1.0E0
Annotation Cluster 3	Enrichment Score: 0.1				Count	P_Value	Benjamini
GOTERM_CC_FAT	nucleolus	RT			3	4.9E-1	1.0E0
GOTERM_CC_FAT	intracellular non-membrane-bounded organelle	RT			6	7.6E-1	1.0E0
GOTERM_CC_FAT	non-membrane-bounded organelle	RT			6	7.6E-1	1.0E0
GOTERM_CC_FAT	membrane-enclosed lumen	RT			4	8.3E-1	1.0E0
GOTERM_CC_FAT	cytoskeleton	RT			3	8.5E-1	1.0E0
GOTERM_CC_FAT	nuclear lumen	RT			3	8.7E-1	1.0E0
GOTERM_CC_FAT	intracellular organelle lumen	RT			3	9.3E-1	1.0E0
GOTERM_CC_FAT	organelle lumen	RT			3	9.4E-1	1.0E0

A

3 Cluster(s) Download File

Annotation Cluster 1	Enrichment Score: 0.93				Count	P_Value	Benjamini
GOTERM_CC_FAT	non-membrane-bounded organelle	RT			11	8.1E-2	1.0E0
GOTERM_CC_FAT	intracellular non-membrane-bounded organelle	RT			11	8.1E-2	1.0E0
GOTERM_CC_FAT	cytoskeleton	RT			6	2.4E-1	1.0E0
Annotation Cluster 2	Enrichment Score: 0.3				Count	P_Value	Benjamini
GOTERM_CC_FAT	nucleolus	RT			4	2.4E-1	1.0E0
GOTERM_CC_FAT	nuclear lumen	RT			5	4.7E-1	1.0E0
GOTERM_CC_FAT	intracellular organelle lumen	RT			5	6.4E-1	1.0E0
GOTERM_CC_FAT	organelle lumen	RT			5	6.6E-1	1.0E0
GOTERM_CC_FAT	membrane-enclosed lumen	RT			5	6.8E-1	1.0E0
Annotation Cluster 3	Enrichment Score: 0.06				Count	P_Value	Benjamini
GOTERM_CC_FAT	intrinsic to membrane	RT			12	8.5E-1	1.0E0
GOTERM_CC_FAT	plasma membrane	RT			8	8.5E-1	1.0E0
GOTERM_CC_FAT	integral to membrane	RT			11	8.9E-1	1.0E0

B

genes confirmed significant expression changes based on adjusted P-Value while in table2, about 19 genes are significant in this manner. The top 50 ranked genes with significant expression changes (Raw P-Value) were targeted for gene ontology evaluations. However, the genes that posses gene symbol were chosen for the analysis and the rest of the them were discarded due to not providing identity for the evaluation. In other words, the top 50 IDs with gene symbols were the finalized selections. David Bioinformatics analysis indicates that the differentially expressed genes in postmortem human brain dorsolateral prefrontal cortex (DLPFC) tissue are related to many cell parts, processes and functions in OCD. The most known biological processes in OCD pathophysiology are serotonergic, dopamine, glutamatergic pathways based on SNP studies (17, 18). Conversely, here, other involved processes are introduced. This is also confirmed by the Jaffe AE et al, that the

Table 5. Clustering molecular function (MF) for 50 significant differentially expressed genes in **A**. Group1 and **B.** Group2, by the use of David Bioinformatics V.6.7.

2 Cluster(s) — Download File

						Count	P_Value	Benjamini
Annotation Cluster 1		Enrichment Score: 0.13						
	GOTERM_MF_FAT	nucleotide binding	RT			6	7.0E-1	1.0E0
	GOTERM_MF_FAT	ribonucleotide binding	RT			5	7.1E-1	1.0E0
	GOTERM_MF_FAT	purine ribonucleotide binding	RT			5	7.1E-1	1.0E0
	GOTERM_MF_FAT	purine nucleotide binding	RT			5	7.4E-1	1.0E0
	GOTERM_MF_FAT	ATP binding	RT			4	7.4E-1	1.0E0
	GOTERM_MF_FAT	adenyl ribonucleotide binding	RT			4	7.5E-1	1.0E0
	GOTERM_MF_FAT	adenyl nucleotide binding	RT			4	7.8E-1	1.0E0
	GOTERM_MF_FAT	purine nucleoside binding	RT			4	7.9E-1	1.0E0
	GOTERM_MF_FAT	nucleoside binding	RT			4	8.0E-1	1.0E0
Annotation Cluster 2		Enrichment Score: 0.02				Count	P_Value	Benjamini
	GOTERM_MF_FAT	cation binding	RT			8	9.4E-1	1.0E0
	GOTERM_MF_FAT	ion binding	RT			8	9.5E-1	1.0E0
	GOTERM_MF_FAT	zinc ion binding	RT			4	9.5E-1	1.0E0
	GOTERM_MF_FAT	metal ion binding	RT			7	9.8E-1	1.0E0
	GOTERM_MF_FAT	transition metal ion binding	RT			4	9.8E-1	1.0E0

A

3 Cluster(s) — Download File

						Count	P_Value	Benjamini
Annotation Cluster 1		Enrichment Score: 0.93						
	GOTERM_MF_FAT	GTPase regulator activity	RT			4	9.4E-2	1.0E0
	GOTERM_MF_FAT	nucleoside-triphosphatase regulator activity	RT			4	9.9E-2	1.0E0
	GOTERM_MF_FAT	small GTPase regulator activity	RT			3	1.7E-1	1.0E0
Annotation Cluster 2		Enrichment Score: 0.41				Count	P_Value	Benjamini
	GOTERM_MF_FAT	zinc ion binding	RT			9	2.8E-1	1.0E0
	GOTERM_MF_FAT	transition metal ion binding	RT			10	3.3E-1	1.0E0
	GOTERM_MF_FAT	metal ion binding	RT			13	4.4E-1	1.0E0
	GOTERM_MF_FAT	cation binding	RT			13	4.6E-1	1.0E0
	GOTERM_MF_FAT	ion binding	RT			13	4.8E-1	1.0E0
Annotation Cluster 3		Enrichment Score: 0.26				Count	P_Value	Benjamini
	GOTERM_MF_FAT	nucleotide binding	RT			9	2.5E-1	1.0E0
	GOTERM_MF_FAT	purine ribonucleotide binding	RT			6	5.6E-1	1.0E0
	GOTERM_MF_FAT	ribonucleotide binding	RT			6	5.6E-1	1.0E0
	GOTERM_MF_FAT	ATP binding	RT			5	5.7E-1	1.0E0
	GOTERM_MF_FAT	adenyl ribonucleotide binding	RT			5	5.9E-1	1.0E0
	GOTERM_MF_FAT	purine nucleotide binding	RT			6	6.1E-1	1.0E0
	GOTERM_MF_FAT	adenyl nucleotide binding	RT			5	6.3E-1	1.0E0
	GOTERM_MF_FAT	purine nucleoside binding	RT			5	6.4E-1	1.0E0
	GOTERM_MF_FAT	nucleoside binding	RT			5	6.5E-1	1.0E0

B

involved expressed genes are totally different from previous introduced SNPs (15). The biological process (BP) enrichments of the 50 genes in samples of groups1and 2 show that the involved genes in group2 are clustered in four groups, while in group1, genes are organized in two groups. The adjusted P-Value for clustering task is not significant, but the top processes are selected. The second finding indicates that, the related BP for the two groups is different. For example, phosphorylation process is the most important process for the group1, but cytoskeletal organization is major one in group2. However, there are common processes such as transcription processes in the two groups. The analysis for CC terms shows more similarity for the two groups. The genes are clustered in the similar manner and the components are nearly a like. As it is depicted in table 5, despite,

difference between two groups from clustering aspects, it seems that the MF is very close for two groups.

In addition, regulation of transcription, plasma membrane, and nucleotide and ion bindings are the most involved processes, parts and functions, respectively. That is, these terms can be representing as the targets for investigating OCD treatment approaches. On the other hand, the different enrichment annotations between groups imply on the fact the possible differences are associated to the presence of comorbidity phenotypes. Our finding are consist with the previous reported data that the clustering is useful tool for gene enrichment analysis (19). In the most bioinformatics researches, it is indicated that clinical studies are final and prominent approach for validating the theoretical assessments (20). Therefore, it is suggested that, the finding should be examined by other high-throughput screening tools.

Conclusion

David bioinformatics analysis showed fine differences between OCD patients and the OCD patients with comorbidity in the gene expression level. In addition, this analysis provided additional molecular details for OCD phenotype and difference between OCD and OCD with comorbidity.

Acknowledgement

This research has been supported by Proteomics Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. It is derived from Miss Mona Zamanian Azodi Ph.D. thesis and "*Comparative evaluation of Proteome Profile of obsessive-Compulsive Disorder and Its Genes Expression Profile and Related SNPs via Bioinformatics and Orthogonal Tests*" project.

Conflict of Interest

Not Declared.

References

1. Hallion LS, Sockol LE, Wilhelm S. Obsessive-Compulsive Disorder. Anxiety Disorders and Gender: Springer; 2015. p. 69-87.

2. Zamanian-Azodi M, Rezaei-Tavirani M, Kermani-Ranjbar T, Arefi Oskouie A, Rezaei-Tavirani M, RahmatiRad S, et al. Pathophysiology, genetics, types, and treatments in obsessive compulsive disorder. Koomesh. 2015;16:475-87.[In Persian]

3. Stein DJ. Neurobiology of the obsessive–compulsive spectrum disorders. Biol Psychiatry. 2000;47:296-304.

4. McKay D, Abramowitz JS, Calamari JE, Kyrios M, Radomsky A, Sookman D, et al. A critical evaluation of obsessive–compulsive disorder subtypes: symptoms versus mechanisms. Clin Psychol Rev. 2004;24:283-313.

5. Stewart SE, Yu D, Scharf JM, Neale BM, Fagerness JA, Mathews CA, et al. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry. 2013;18:788-98.

6. Zamanian-Azodi M, Rezaei-Tavirani M. Evaluation Of Obsessive Compulsive Disorder Related Genes From Gene Ontology Perspective. International Journal of Analytical, Pharmaceutical and Biomedical Sciences. 2015;4:1-14.

7. Nestadt G, Grados M, Samuels JF. Genetics of obsessive-compulsive disorder. Psychiatr Clin North Am. 2010;33:141-58.

8. Brennan BP, Rauch SL, Jensen JE, Pope HG. A critical review of magnetic resonance spectroscopy studies of obsessive-compulsive disorder. Biol Psychiatry. 2013;73:24-31.

9. Piras F, Piras F, Chiapponi C, Girardi P, Caltagirone C, Spalletta G. Widespread structural brain changes in OCD: A systematic review of voxel-based morphometry studies. Cortex. 2015;62:89-108.

10. Baxter Jr LR, Ackermann RF, Swerdlow NR, Brody A, Saxena S, Schwartz JM, et al. Specific brain system mediation of obsessive-compulsive disorder

responsive to either medication or behavior therapy. 2000.

11. Qin H, Samuels J, Wang Y, Zhu Y, Grados M, Riddle M, et al. Whole-genome association analysis of treatment response in obsessive-compulsive disorder. Mol Psychiatry. 2015.

12. Angelakis I, Gooding P, Tarrier N, Panagioti M. Suicidality in obsessive compulsive disorder (OCD): a systematic review and meta-analysis. Clin Psychol Rev. 2015;39:1-15.

13. Rezaei-Tavirani M, Zamanian-Azodi M, Rajabi S, Masoudi-Nejad A, Rostami-Nejad M, Rahmatirad S. Protein Clustering and Interactome Analysis in Parkinson and Alzheimer's Diseases. Arch Iran Med. 2016;19:101-109.

14. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene Ontology: tool for the unification of biology. Nat Genet. 2000;25:25-9.

15. Jaffe A, Deep-Soboslay A, Tao R, Hauptman D, Kaye W, Arango V, et al. Genetic neuropathology of obsessive psychiatric syndromes. Translational psychiatry. 2014;4:e432.

16. Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protocols. 2008;4:44-57.

17. Taylor S. Molecular genetics of obsessive–compulsive disorder: a comprehensive meta-analysis of genetic association studies. Mol Psychiatry. 2013;18:799-805.

18. Gassó P, Ortiz AE, Mas S, Morer A, Calvo A, Bargalló N, et al. Association between genetic variants related to glutamatergic, dopaminergic and neurodevelopment pathways and white matter microstructure in child and adolescent patients with obsessive–compulsive disorder. J Affect Disord. 2015;186:284-92.

19. Zali H, Rezaei-Tavirani M, Vafaee R, Rezaei-Tavirani M. Gastric cardia adenocarcinoma pathway analysis. Gastroenterol Hepatol Bed Bench. 2013;6:S8-S11.

20. Nobakht M. Gh BF, Aliannejad R, Rezaei-Tavirani M, Taheri S, Oskouie AA. The metabolomics of airway diseases, including COPD, asthma and cystic fibrosis. Biomarkers. 2015;20:5-16.