Biomedical Research 2018; 29 (18): 3415-3428 *ISSN 0970-938X*
www.biomedres.info

Complex networks of interaction of genes located in the critical region of Down syndrome expressed in the normal human brain.

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Abstract

The quantification and analysis of the human transcriptome allows expanding the knowledge of the genomic functioning, especially in body's parts as complex and important as the human brain. In this way, in silico studies offer the possibility to extract and analyse information contained in databases, at the level of gene expression along the different brain structures. This study aimed to correlate the transcription levels of 38 genes located in the critical region of the chromosome 21 associated with Down syndrome with the cerebral localization and its intervention in the correct operation of different brain substructures. To carry out this, the expression profiles of these genes along 24 substructures of the brain cores and 18 of the Limbic lobe were done, from gene expression data of microarray experiments of DNA, available in the database of the Atlas of the brain of the "Allen Institute for Brain Sciences". It was determined a differential expression of these genes along the analysed structures, in addition to register higher levels of overall transcription in certain areas of the brain, which appear to be associated with different processes of learning and memory. The differential transcription was correlated with the cerebral localization and its potential functional role.

Keywords: Basal ganglia, Limbic lobe, DNA microarrays, Critical region of Down syndrome, *PCP4*, *KCNJ6*, *DYRK1A*.

Accepted on July 12, 2018

Introduction

The human brain has a wide variety of cells, each of those ones has a single morphophysiology, functionality and connectivity [1,2]. These properties are largely the result of unique combinations of expressed gene products, and its precise regulation is what keeps to a large cerebral homeostasis degree. This approach is useful for understanding the functional circuitry of the nervous system, and thus generates new knowledge about the relationship between genes, brain and behavior [3-5]. Therefore, the analysis of gene expression profiles provides huge information about brain connectivity and its relationship with the higher cognitive functions. As an example there is the influence of genetic factors in understanding the normal brain development and mental disorders [5-8]. Consequently, the cellular diversity of the brain requires a focus on understanding the functional genomics of the nervous system, leading to the incorporation of all these modalities in an overall analysis having the potential to improve the discovery and highlighting its importance in comparison with methods that analyse each mode separately. Data associations between these three approaches are relevant in the study of diseases, since gene expression in the brain plays a key role in the flow of information between brain networks and performing cognitive tasks [3,5].

For that reason, the inherent importance of brain homeostasis and the complexity involved in the development and maintenance of the nervous system can result in a series of neuropathology that lead to changes in brain structure such as decreasing different types of motricity, cognitive impairment, among others [6]. Down Syndrome (DS), which is caused by the total or partial presence of three copies of chromosome 21, is becoming the most frequent aneuploidy leading to vary degrees of cognitive impairment [9-11]. On the other hand, studies of segmental trisomies have allowed to characterize an area within the chromosome called "Critical Region of the Down Syndrome" (DSCR), which is located at the distal end of the long arm of chromosome 21 (21q22.1-22.3), and which

contains possible candidate genes whose imbalance of dose could induce marked cognitive deficit, like the other pathologies and traits associated [12-17].

However, the involvement of the DSCR as the sole cause of the symptoms of DS is still a matter of debate. Several studies suggest that this region plays a major role in the genetic interactions that would be related to the pathogenesis of DS [18-20]. In spite of this, the expression of the genes which are found within this region is not fully known in the brain. Therefore, their study in normal human brains could provide a better understanding of their participation in the regulation of all processes that must be performed for proper operation. Additionally, a comprehensive approach would make significant correlations between gene expression and regulation, the function of the nervous system and the resulting phenotype. This would be too informative for neurogenetic and study of brain diseases, especially in the neurological disorders associated with the DS.

Actually, few studies focus on the functional analysis correlation of gene expression in the brain. Moreover, the techniques that have been used, usually cover large regions of the brain creating a difficulty in interpreting data in the substructures, or generally made by a gene at a time, leaving patterns of expression of many genes uncharacterized. As a result, Atlas Allen Human Brain Project has adopted a global approach for understanding the structural and genetic architecture of the brain by generating gene expression profiles obtained from DNA microarrays from post-mortem human brains. In this context, it is possible to extract complete and detailed information on those levels of transcription in different brain structures that can be found in the database of free access of the Allen Brain Atlas [21]. This database contains anatomical and genomic information from human brains, which is supplemented with extra information and set of visualization tools and data mining. Microarray experiments include data of more than 62,000 probes, covering 93% of the 21,245 genes consigned, from which it is possible to obtain information on thousands transcriptional gene referenced with Entrez gene codes.

This study was designed to construct an in silico model of the expression profiles of 38 genes located in the critical region of DS. Data were based to correlate them with the functionality of a healthy human brain of a 55 y old male donor, besides, a network of expression and interaction of these genes with others that expression was built. The results allowed us to approach to a systemic model of expression that can be modified bioinformatically to extrapolate it to what happens in other diseases of the brain, providing a powerful tool for its understanding.

Materials and Methods

Data collection

The gene expression levels were calculated from the z-score values of 38 genes DSCR (Annex 1) in different substructures of the basal ganglia and the limbic lobe. These were obtained from the graphical display of the database of the human brain the Allen Institute for Brain Sciences. All procedures used for collecting data are reported extensively in the technical report "Allen Institute for Brain Sciences" [23].

In all cases, the data of each gene of available experiments using different probes was obtained. Standard values (z score) of the expression levels through 24 substructures of the brain nuclei and 18 from the Limbic Lobe (Annex 2) were recorded. These values were recorded in electronic sheets in Excel format for further analysis. Three values were taken at three different points of each substructure and the average z score was regarded as final data.

Protein interaction network and cluster analysis

A network of interaction of proteins encoded by 36 of the DSCR genes with other human proteins in different databases was built through a Cytoscape program version 3.1.1 [24]. Besides, a hierarchical clustering was performed based on the z score of these 36 genes in each cerebral substructure. The test conditions used were the plugin clusterMaker Algorithm maximum link by pairs and metric distance metric Pearson correlation.

Statistical analysis

For ranking each expression of genes in different brain substructures, a Principal Component Analysis (PCA) for both the limbic lobe and the brain nuclei was performed by reducing the R space of 38 collinear variables to 6 main components (R38>R6) in each area. This analysis was performed using IBM SPSS 20.0.0 program [25].

Results

DSCR overall transcription of genes in the brain

A differential expression of 38 genes DSCR along different brain substructures, specific and dependent on the associated substructure brain, was determined. In turn it was confirmed the existence of regulation of gene expression dependent on the physiology of each brain area (Figure 1). From the brain areas studied, the caudate nucleus, putamen and globus pallidus are substructures that had a higher level of expression by the majority of genes in the basal nuclei (Figure 1A). The most expressed areas in the limbic lobe were the central and the parahippocampal gyrus (Figure 1B).

The PCA allowed reducing to six components the 38 genes *DSCR* in each structure. In brain, nuclei represented 79.89% of the variance while the limbic lobe 76.03%. It was observed that the distribution of the 38 *DSCR* genes was differential in the two brain structures (Figure 2). In brain nuclei component 1 was the most complex, which includes 19 genes, in contrast to the limbic lobe where 19 of the 38 genes *DSCR* distributed between components 1 and 2 (Table 1).

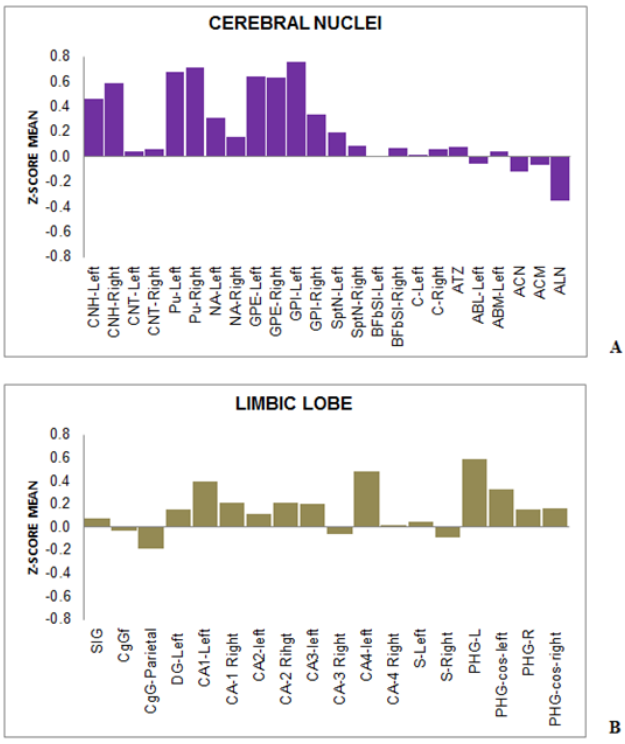

Figure 1. *Comparison of the total average level of expression of all genes from in each brain substructure. A. Brain nuclei. B. Limbic lobe. The structures most expressed in the basal nuclei were caudate nucleus, putamen and globus pallidus, and for the limbic lobe were the central areas and the parahippocampal gyrus.*

In addition, comparative analysis of graphics Biplot establishes two groups of genes having a statistically significant correlation for each structure. At Limbic lobe, the first association is composed by the *IGSF5, C21orf88, TRAPPC10, TTC3, B3GALT5, DSCR3, KCNJ15* and *C21orf24*; and the second by the *DSCR1, SIM2, RUNX1, ERG, DSCAM* and *DSCR4* (Figure 2A) genes. While in brain nuclei, the stronger association included the *BACE2, SIM2, ERG, CSTB, PTTG1IP, TMEM50B, TRAPPC10* genes (Figure 2B).

The PCA analysis showed that gene co-expression varies depending on the brain area. Both in brain nuclei and the limbic lobe, two groups presented where the genes that compose them are highly correlated, but all the associations that occur differ in both structures. Similarly, the cluster analysis showed the same pattern of co-expression (Figure 3), leaving also areas of high and low expression mentioned before, and the existence of an opposite expression of certain genes in these two areas.

Protein interaction network

The interaction network showed a master node that stands out within seven DSCR proteins interacting within them and with a variable number of others human proteins. The network showed that in the primary node *DYRK1A* gene product is found (Figure 4). It had one of the highest values of interactions within the network (Figure 5), and interacts directly with another six proteins DSCR: HMGN1, BRWD1, TTC3, RCAN1, ARE and DCSR3.

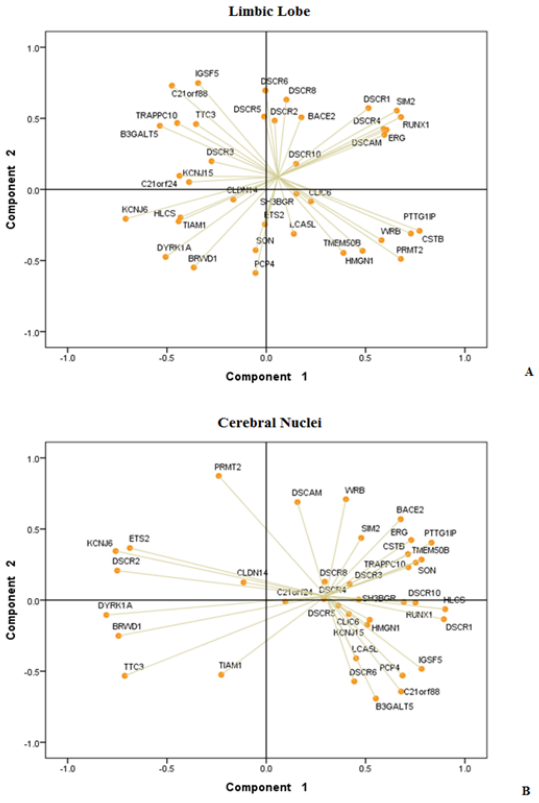

Figure 2. *Biplot representation of the Cartesian plane that shows the distribution of genomic variables grouped because of the corresponding principal component analysis. A. Brain nuclei. B. Limbic lobe.*

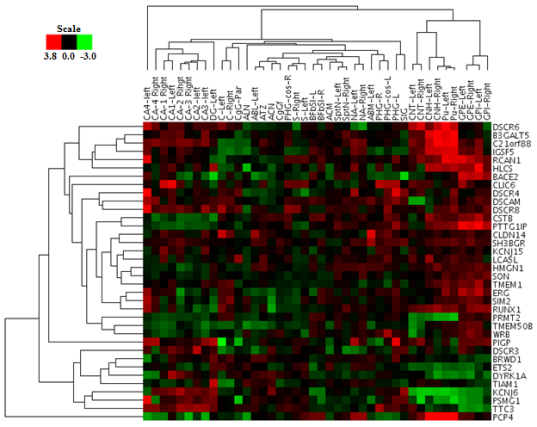

Figure 3. *Cluster analysis of the expression of 38 genes located in the critical region SD along the various substructures of the limbic lobe and the brain nuclei. The structures with highest expression are represents in red, whilst the structures with less expression are represents in green.*

In the same way, the top ten GO categories with highest statistical significance in terms of biological process were analysed. As shown in Table 2, most of the proteins studied in the interaction network regulate positively and/or negatively

various biological and metabolic processes, mechanisms of apoptosis, modification of macromolecules, among others.

Table 1. Discrimination on the weight of each of the variables within six components.

Brain structure	Component						
	1		2	3	4	5	6
Cerebral nuclei	*KCNJ15*	*DSCR1*	*DSCAM*	*DSCR4*	*DSCR2*	*CLIC6*	*DSCR3*
	LCA5L	*DSCR5*	*ETS2*	*DSCR6*	*BRWD1*	*DYRK1A*	*TIAM1*
	C21orf88	*DSCR10*	*WRB*	*DSCR8*	*C21orf24*		
	B3GALT5	*BACE2*	*PRMT2*	*SIM2*	*HMGN1*		
	TRAPPC10	*ERG*		*CLDN14*	*KCNJ6*		
	IGF5	*RUNX1*		*TTC3*			
	PCP4	*SH3BGR*					
	CSTB	*SON*					
	TMEM50B	*HLCS*					
	PTTG1IP						
Limbic lobe	*DSCAM*		*DSCR1*	*DSCR10*	*BRWD1*	*KCNJ6*	*DSCR3*
	DSCR4		*DSCR2*	*CLDN14*	*ETS2*	*SH3BGR*	*CLIC6*
	RUNX1		*DSCR6*	*KCNJ15*	*SON*		*DYRK1A*
	ERG		*DSCR8*	*C21orf24*	*HLCS*		*PCP4*
	WRB		*DSCR5*	*LCA5L*	*HMGN1*		
	SIM2		*BACE2*	*B3GALT5*	*TRAPPC10*		
	CSTB		*TTC3*		*TIAM1*		
	TMEM50B		*C21orf88*				
	PTTG1IP		*IGSF5*				
	PRMT2						

Table 2. Main GO categories of biological process established in the interaction network.

GO-ID	Description	P-value	Cluster frequency	Total frequency
48523	Negative regulation of cellular process	5.35E-17	179/702 (25.4%)	1840/14274 (12.8%)
48519	Negative regulation of biological process	1.32E-15	186/702 (26.4%)	2016/14274 (14.1%)
6464	Protein modification process	1.49E-13	148/702 (21.0%)	1527/14274 (10.6%)
43412	Macromolecule modification	3.63E-13	152/702 (21.6%)	1608/14274 (11.2%)
10941	Regulation of cell death	1.13E-12	99/702 (14.1%)	868/14274 (6.0%)
43067	Regulation of programmed cell death	1.46E-12	98/702 (13.9%)	861/14274 (6.0%)
9987	Cellular process	1.46E-12	553/702 78.7%	9353/14274 (65.5%)
42981	Regulation of apoptosis	1.73E-12	97/702 (13.8%)	853/14274 (5.9%)
48518	Positive regulation of biological process	3.67E-12	186/702 26.4%	2207/14274 (15.4%)
9893	Positive regulation of metabolic process	4.28E-12	108/702 15.3%	1020/14274 (7.1%)

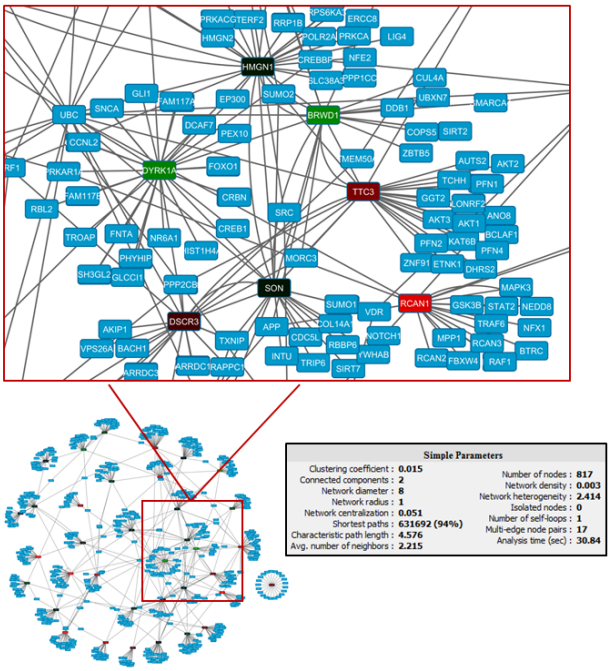

Figure 4. *Network interaction of 36 proteins with other DSCR proteins contained in different databases.*

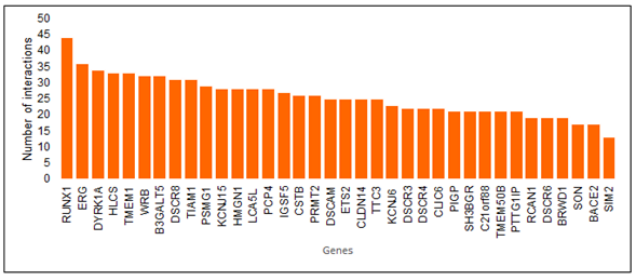

Figure 5. *Number of interactions established by each of the 36 DSCR proteins within the network.*

Annex 1. *Names and symbols of different substructures in limbic lobe and cerebral nuclei. The names were extracted from the Allen Institute for Brain Sciences.*

Structure name	**Symbol**
Brain nuclei	
Caudate nuclei head-left	CNH-Left
Caudate nuclei head-right	CNH-Right
Caudate nuclei tail-left	CNT-Left
Caudate nuclei tail-right	CNT-Right
Putamen left	Pu-Left
Putamen right	Pu-Right
Nucleus accumulus left	NA-Left
Nucleus accumulus right	NA-Right
Globus pallidum external left	GPE-Left
Globus pallidum external right	GPE-Right
Globus pallidum internal left	GPI-Left
Globus pallidum internal right	GPI-Right
Septal nuclei left	SptN-Left
Septal nuclei right	SptN-Right
Basal forebrain substantia innominata left	BFbSI-Left
Basal forebrain substantia innominata right	BFbSI-Right
Claustrum left	C-Left
Claustrum right	C-Right
Amigdala transition zone	ATZ
Amigdala basolateral left	ABL-Left
Amigdala basomedia right	ABM-Right
Central amigdala nucleus	ACN
Corto medial amigdala	ACM
Left nucleus amigdala	ALN
Limbic lobe	
Short insular gyrus	SIG
Cyngulate girus, frontal part	CgGf
Cyngulate girus, parietal part	CgG-Parietal
Dental gyrus left	DG-Left
Central area 1 left	CA1-Left
Central area 1 right	CA-1 Right
Central area 2 left	CA2-Left
Central area 2 right	CA-2 Right
Central area 3 left	CA3-Left
Central area 3 right	CA-3 Right
Central area 4 left	CA-4-Left
Central area 4 right	CA-4 Right
Subiculum left	S-Left
Subiculum right	S-Right
Parahipocampus gyrus left	PHG-Left
Parahipocampus gyrus -cos-left	PHG-cos-Left
Parahipocampus gyrus right	PHG-Right
Parahipocampus gyrus -cos-right	PHG-cos-Right

Annex 2. *Standard values (z score) of the expression levels through 24 substructures of the brain nuclei and 18 from the limbic lobe.*

Gene	Common	Entrez ID	SIG	CgGf	CgG-Par	DG-Left	CA1-Left	CA-1-Right	CA2-left	CA-2 Right
RCAN1	NM_004414.5	1827	0.139	-0.3595	-0.228	-1.03	0.149	0.491	0.213	0.703
PSMG1	NM_203433.1	8624	1.131	0.2285	-2.309	1.292	0.513	0.478	0.692	0.96
DSCR3	NM_006052.1	10311	1.018	-0.2485	-0.233	0.711	1.29	0.705	2.176	0.883
DSCR4	NM_005867.2	10281	1.436	-0.2535	1.096	-0.25	0.892	0.411	0.557	-0.383
DSCR6	NM_018962.1	53820	0.572	-0.249	0.43	0.764	0.993	0.174	0.781	0.928
DSCR8	NR_026838.1	84677	0.387	-0.291	1.114	0.844	1.037	1.204	0.371	1.292
PIGP	NM_153681.1	51227	0.373	-0.149	-2.107	2.122	0.217	0.122	0.662	0.467
CLIC6	NM_053277.1	54102	0.09	-0.316	0.563	-1.035	2.807	2.411	0.433	0.891
BACE2	NM_012105.3	25825	-2.501	0.0305	-0.676	-2.431	0.359	0.614	-0.189	-1.031
BRWD1	NM_018963.3	54014	0.08	0.0605	0.095	1.178	0.719	-0.654	-0.007	0.307
DSCAM	NM_001389.3	1826	0.836	0.011	0.189	0.79	0.913	-0.216	0.427	0.023
DYRK1A	NM_130438.1	1859	-0.101	0.5235	0.503	0.663	1.946	0.385	0.32	1.257
ERG	NM_001136154.1	2078	-0.204	-0.341	0.072	-0.643	0.56	0.485	-0.772	-1.711
ETS2	NM_005239.4	2114	-0.427	-0.501	0.145	0.889	0.381	-0.193	-0.168	-0.625
KCNJ6	NM_002240.2	3763	1.76	0.257	0.086	1.574	1.393	1.096	1.257	1.932
RUNX1	NM_001122607.1	861	0.387	-0.571	-0.101	-1.355	0.679	-0.473	-1.171	-0.701
SH3BGR	NM_001001713.1	6450	1.151	0.7375	-0.112	0.185	0.747	0.367	0.48	1.069
SIM2	NM_005069.2	6493	0.306	-0.365	-0.105	-1.081	0.279	-0.674	-0.37	-1.133
CLDN14	NM_012130.2	23562	-0.012	0.107	-0.283	0.126	0.486	0.911	-0.223	0.458
TTC3	NM_001001894.1	7267	0.437	0.551	0.465	1.175	0.930	0.751	1.810	1.811
SON	NM_138927.1	6651	0.162	-0.184	-0.023	0.489	0.020	0.072	-0.182	-0.535
HLCS	NM_000411.4	3141	0.179	-0.257	0.300	1.808	1.033	0.599	0.771	0.186
KCNJ15	NM_002243.3	3772	-0.668	0.453	-0.081	0.010	0.487	1.387	-0.419	0.777
HMGN1	NM_004965.6	3150	-0.345	-0.094	-0.328	0.530	-0.139	-0.494	-0.276	-1.138
WRB	NM_004627.4	7485	0.401	0.699	-0.782	-0.269	-0.814	-1.034	-0.582	-0.443
LCA5L	NM_152505.2	150082	0.224	0.088	1.671	-0.057	-0.512	1.029	-0.221	0.520
C21orf88	NR_026542.1	114041	-0.480	-0.039	-0.959	0.507	1.034	1.153	0.938	1.449
B3GALT5	NM_033173.1	10317	-0.776	0.138	-0.924	0.257	0.900	0.980	-0.099	1.172
TMEM1	NM_003274.3	7109	-0.627	-0.313	-0.645	0.433	0.681	0.001	-0.051	-0.205
IGSF5	NM_001080444.1	150084	-0.828	0.078	-1.009	-0.323	-0.010	0.871	0.202	0.930
PCP4	NM_006198.2	5121	-0.237	-0.532	-0.822	-0.042	0.263	-1.461	-0.538	-1.004
CSTB	NM_000100.2	1476	0.202	0.618	-0.271	-1.553	-0.379	-0.754	-1.051	-1.122
TMEM50B	NM_006134.4	757	-0.144	-0.230	-0.464	-0.858	-0.984	-1.133	-0.718	-0.107
PTTG1IP	NM_004339.2	754	0.741	0.070	-0.814	-0.563	-0.999	-1.028	-0.975	-1.228
TIAM1	NM_003253.1	7074	-0.849	-0.899	-0.171	2.290	-0.643	-0.706	0.566	-0.099
PRMT2	NM_206962.1	3275	-0.013	-0.110	-0.430	-0.171	-0.751	-0.905	-0.544	-0.639

Gene	Common	Entrez ID	CA3-left	CA-3 Right	CA4-left	CA-4 Right	S-Left	S-Right	PHG-L	PHG-cos-L
RCAN1	NM_004414.5	1827	0.056	0.106	2.641	-0.137	0.993	0.888	1.169	0.129
PSMG1	NM_203433.1	8624	1.166	1.28	2.823	-1.401	0.636	0.083	1.117	0.361
DSCR3	NM_006052.1	10311	0.204	0.484	0.808	-0.976	0.001	0.561	0.909	-0.65
DSCR4	NM_005867.2	10281	0.373	-0.008	2.99	-0.104	-1.547	-0.703	2.645	1.119
DSCR6	NM_018962.1	53820	0.788	0.151	2.237	1.182	0.363	-1.39	0.537	0.037
DSCR8	NR_026838.1	84677	1.743	0.886	2.721	0.713	0.323	1.434	0.281	1.503
PIGP	NM_153681.1	51227	1.587	0.349	1.877	2.006	0.483	0.479	2.774	0.311
CLIC6	NM_053277.1	54102	-0.285	-0.627	0.37	-0.175	1.233	1.134	1.951	1.908
BACE2	NM_012105.3	25825	-1.167	-1.363	0.975	-0.495	-0.757	-0.471	-0.823	-0.755
BRWD1	NM_018963.3	54014	0.357	0.213	-1.598	-0.154	0.048	-0.003	1.129	-0.24
DSCAM	NM_001389.3	1826	0.494	-0.249	1.917	1.463	0.421	0.486	1.517	1.064
DYRK1A	NM_130438.1	1859	-0.093	0.687	-1.506	-1.329	0.504	0.053	-0.078	0.348
ERG	NM_001136154.1	2078	0.197	-0.49	1.694	0.293	0.027	-0.761	0.983	0.493
ETS2	NM_005239.4	2114	-0.689	-0.923	-0.125	0.247	0.754	0.531	-0.075	-0.078
KCNJ6	NM_002240.2	3763	1.05	1.2	-1.101	1.01	0.159	0.398	0.377	0.3
RUNX1	NM_001122607.1	861	-0.713	-0.173	1.753	0.657	-0.173	-0.57	0.705	-0.035
SH3BGR	NM_001001713.1	6450	0.35	0.561	0.273	0.44	0.144	-0.024	0.954	0.926
SIM2	NM_005069.2	6493	-0.09	0.011	1.959	0.76	0.565	-0.792	0.715	0.193
CLDN14	NM_012130.2	23562	0.983	-0.230	-0.532	0.265	0.403	-0.355	0.470	1.218
TTC3	NM_001001894.1	7267	1.744	1.642	1.470	1.470	0.336	0.494	0.924	0.849
SON	NM_138927.1	6651	-0.581	-0.381	-0.230	-0.475	-0.258	-0.183	-0.138	-0.564
HLCS	NM_000411.4	3141	-0.086	-0.457	-0.123	-0.451	0.138	-0.505	0.297	-0.774
KCNJ15	NM_002243.3	3772	1.133	-0.131	-0.558	0.282	0.304	-0.489	0.182	0.735
HMGN1	NM_004965.6	3150	-0.556	-0.821	-0.288	-0.455	-0.303	-0.400	0.266	0.471
WRB	NM_004627.4	7485	-1.105	0.111	-0.242	-0.748	-1.128	-0.129	0.578	1.933
LCA5L	NM_152505.2	150082	0.270	-0.424	-0.362	-0.354	-0.480	-0.504	0.265	1.114
C21orf88	NR_026542.1	114041	1.453	1.421	1.167	1.509	-0.278	-0.323	-0.132	0.387
B3GALT5	NM_033173.1	10317	1.402	0.127	0.081	0.265	0.181	-0.354	0.271	0.147
TMEM1	NM_003274.3	7109	0.709	-0.091	0.030	0.258	-0.243	-0.436	0.456	-0.972
IGSF5	NM_001080444.1	150084	0.089	0.623	1.201	-0.136	-0.484	-0.805	-0.884	-0.324
PCP4	NM_006198.2	5121	-2.043	-2.133	-1.909	-1.466	0.928	0.411	-1.056	-1.272
CSTB	NM_000100.2	1476	-0.686	-1.037	-0.192	-1.277	-0.084	-0.146	0.895	1.200
TMEM50B	NM_006134.4	757	-1.411	-0.288	-0.602	-0.898	-0.415	-0.669	-0.295	-0.223
PTTG1IP	NM_004339.2	754	-0.924	-0.868	-0.354	-0.701	-0.977	-0.747	1.681	0.642
TIAM1	NM_003253.1	7074	-0.279	-0.631	-0.479	-0.096	0.020	-0.422	-0.525	-0.215
PRMT2	NM_206962.1	3275	-0.825	-0.706	-0.407	-0.743	-0.364	-0.496	0.439	0.351

Gene	Common	Entrez ID	PHG-R	PHG-cos-R	CNH-Left	CNH-Right	CNT-Left	CNT-Right	Pu-Left	Pu-Right
RCAN1	NM_004414.5	1827	0.261	0.931	1.112	1.433	0.699	1.525	2.827	2.66
PSMG1	NM_203433.1	8624	-0.305	0.457	-0.589	-1.794	-0.8	-2.495	-1.758	-2.499
DSCR3	NM_006052.1	10311	-0.363	-0.393	0.707	-0.423	-0.716	-0.079	-0.19	-0.601
DSCR4	NM_005867.2	10281	-0.354	-0.031	-0.433	0.216	0.322	0.886	-0.271	1.416
DSCR6	NM_018962.1	53820	-0.238	-0.233	1.281	2.312	2.049	2.619	3	2.3
DSCR8	NR_026838.1	84677	0.095	1.576	-0.749	0.793	0.268	0.522	0.874	1.463
PIGP	NM_153681.1	51227	-1.419	0.108	0.306	-0.548	0.821	1.478	0.632	-1.044
CLIC6	NM_053277.1	54102	2.147	1.22	0.849	-0.397	1.12	0.861	0.382	0.375
BACE2	NM_012105.3	25825	-1	-0.327	0.169	-0.164	-0.604	-0.524	0.077	0.436
BRWD1	NM_018963.3	54014	0.244	0.179	-0.403	-0.196	0.259	0.013	-0.132	-0.059
DSCAM	NM_001389.3	1826	0.475	0.693	-0.643	-0.1475	-1.899	-1.938	0.48	1.086
DYRK1A	NM_130438.1	1859	0.304	0.268	-0.94	-1.861	0.056	0.018	-1.485	-1.604
ERG	NM_001136154.1	2078	0.594	-0.424	-0.025	0.317	-0.183	0.088	1.575	0.86
ETS2	NM_005239.4	2114	-0.417	-0.085	-0.952	-1.439	-1.118	-0.995	-1.09	-0.997
KCNJ6	NM_002240.2	3763	0.489	0.165	-2.365	-2.283	-1.931	-2.37	-2.403	-2.162
RUNX1	NM_001122607.1	861	-0.179	-0.555	1.408	1.79	0.886	1.165	1.257	1.402
SH3BGR	NM_001001713.1	6450	0.59	0.364	0.75	0.965	-0.142	0.26	1.005	1.154
SIM2	NM_005069.2	6493	-0.164	-0.608	0.02	0.645	0.055	-0.27	0.736	0.678
CLDN14	NM_012130.2	23562	0.797	0.035	0.285	0.633	0.595	0.236	0.196	0.637
TTC3	NM_001001894.1	7267	1.949	0.823	-0.938	-0.508	0.973	-0.061	-0.265	-0.403
SON	NM_138927.1	6651	0.339	-0.493	0.478	0.242	0.011	0.041	0.932	0.608
HLCS	NM_000411.4	3141	0.793	-0.003	2.027	2.049	0.505	-0.759	1.854	2.089
KCNJ15	NM_002243.3	3772	0.849	-0.073	0.268	0.553	0.631	-0.143	0.099	0.442
HMGN1	NM_004965.6	3150	0.781	-0.015	0.664	1.308	0.438	0.336	0.605	0.804
WRB	NM_004627.4	7485	0.776	-0.265	-0.032	-0.433	-1.818	-0.729	0.424	0.563
LCA5L	NM_152505.2	150082	0.473	0.518	1.770	0.294	1.005	0.164	0.579	1.030
C21orf88	NR_026542.1	114041	0.040	0.782	2.238	3.418	1.441	0.966	2.863	2.942
B3GALT5	NM_033173.1	10317	0.180	0.505	2.611	3.416	0.951	0.983	2.646	3.120
TMEM1	NM_003274.3	7109	-0.206	-0.284	0.654	0.979	0.090	-0.121	1.299	0.887
IGSF5	NM_001080444.1	150084	-1.103	-0.869	2.376	2.394	0.897	1.149	2.617	2.648
PCP4	NM_006198.2	5121	-1.141	-0.147	3.066	3.867	0.677	1.410	3.414	3.575
CSTB	NM_000100.2	1476	-0.054	0.944	1.688	1.104	-0.759	0.179	0.859	0.858
TMEM50B	NM_006134.4	757	-0.192	-0.570	0.167	0.230	-1.636	-1.064	0.570	0.496
PTTG1IP	NM_004339.2	754	0.617	0.684	1.041	1.404	-0.454	-0.357	1.411	1.608
TIAM1	NM_003253.1	7074	-0.251	-0.431	0.295	0.396	0.076	0.556	-0.180	-0.009
PRMT2	NM_206962.1	3275	0.030	0.157	-1.436	-1.944	-1.538	-1.240	-1.926	-2.274

Gene	Common	Entrez ID	NA-Left	NA-Right	GPE-Left	GPE-Right	GPI-Left	GPI-Right	SptN-Left	SptN-Right
RCAN1	NM_004414.5	1827	0.518	0.353	2.669	2.12	1.656	1.154	0.158	0.062
PSMG1	NM_203433.1	8624	-0.198	-0.237	-1.912	-1.563	-1.507	-0.453	-0.304	-0.553
DSCR3	NM_006052.1	10311	-1.337	-0.935	1.089	0.614	-0.215	0.1	-0.095	-1.509
DSCR4	NM_005867.2	10281	1.824	0.04	-0.064	-0.09	0.656	0.66	0.29	0.061
DSCR6	NM_018962.1	53820	-1.268	-1.834	0.102	0.174	0.467	-1.081	-0.134	-0.063
DSCR8	NR_026838.1	84677	0.724	-0.348	0.543	0.748	0.524	1.272	0.507	0.519
PIGP	NM_153681.1	51227	1.971	0.633	1.055	1.131	1.101	1.357	0.029	-0.255
CLIC6	NM_053277.1	54102	-0.692	0.335	1.797	0.752	0.166	0.208	-0.66	-0.354
BACE2	NM_012105.3	25825	-0.457	0.258	2.444	2.176	2.367	1.661	0.669	0.796
BRWD1	NM_018963.3	54014	0.282	0.369	-0.644	-0.429	-0.887	-0.938	0.285	0.187
DSCAM	NM_001389.3	1826	0.493	0.662	0.107	0.637	1.049	0.804	0.25	0.731
DYRK1A	NM_130438.1	1859	-0.328	-0.616	-1.358	-1.694	-0.495	-1.305	-0.309	-0.754
ERG	NM_001136154.1	2078	-0.372	0.465	2.089	1.617	2.218	1.03	-0.352	0.375
ETS2	NM_005239.4	2114	0.665	0.517	-1.152	-1.27	-0.705	-0.126	-0.38	-0.544
KCNJ6	NM_002240.2	3763	-0.618	-0.177	-1.778	-1.569	-1.531	-0.836	0.196	-0.095
RUNX1	NM_001122607.1	861	0.286	0.49	0.687	1.482	1.719	1.638	0.257	1.002
SH3BGR	NM_001001713.1	6450	0.833	0.688	0.77	1.241	0.718	0.631	-0.445	0.195
SIM2	NM_005069.2	6493	0.285	-0.461	0.983	1.313	1.155	0.416	0.352	-0.166
CLDN14	NM_012130.2	23562	0.019	-0.507	0.663	0.971	0.406	0.582	0.294	-0.088
TTC3	NM_001001894.1	7267	0.028	-0.539	-1.828	-1.589	-1.753	-1.217	-0.580	-0.336
SON	NM_138927.1	6651	0.119	0.864	0.879	1.192	0.904	1.349	0.687	0.047
HLCS	NM_000411.4	3141	1.349	0.169	1.705	1.717	2.981	1.134	0.286	-0.004
KCNJ15	NM_002243.3	3772	0.119	0.118	0.683	0.197	0.630	-0.047	-0.126	0.794
HMGN1	NM_004965.6	3150	0.849	0.944	0.793	0.885	1.170	0.843	0.766	0.765
WRB	NM_004627.4	7485	0.297	0.532	0.955	1.493	1.088	0.486	0.224	-0.309
LCA5L	NM_152505.2	150082	0.359	0.152	0.673	0.551	0.767	-0.553	0.565	0.346
C21orf88	NR_026542.1	114041	1.415	1.150	0.893	0.536	1.441	-0.358	0.029	0.674
B3GALT5	NM_033173.1	10317	0.574	0.258	-0.012	-0.198	0.446	-0.474	0.333	1.056
TMEM1	NM_003274.3	7109	-0.146	-0.854	1.312	1.226	1.922	0.611	0.184	0.190
IGSF5	NM_001080444.1	150084	1.273	0.944	1.142	1.000	1.552	-0.189	0.814	-0.224
PCP4	NM_006198.2	5121	1.689	1.727	0.917	0.822	0.121	0.419	0.268	0.509
CSTB	NM_000100.2	1476	0.445	0.752	1.407	1.522	2.112	1.083	0.509	-0.118
TMEM50B	NM_006134.4	757	0.235	0.661	0.932	1.167	1.186	-0.244	0.595	-0.293
PTTG1IP	NM_004339.2	754	0.547	0.144	2.952	2.643	3.572	2.054	1.049	0.600
TIAM1	NM_003253.1	7074	0.576	0.324	0.104	-0.381	-0.655	-0.637	-0.011	0.154
PRMT2	NM_206962.1	3275	-0.156	0.382	0.693	0.768	0.438	0.725	0.510	0.228

Gene	Common	Entrez ID	BFbSI-L	BFbSI-R	C-Left	C-Right	ATZ	ABL-Left	ABM-Left	ACN	ACM	ALN
RCAN1	NM_004414.5	1827	0.339	0.888	-1.268	-0.295	-0.696	-0.202	0.105	-0.432	0.163	-0.031
PSMG1	NM_203433.1	8624	-0.357	-1.262	-0.008	-0.075	0.427	0.715	-1.349	0.082	-0.4	-0.157
DSCR3	NM_006052.1	10311	0.069	0.247	-1.554	-0.976	-0.597	-1.358	0.187	0.901	-1.281	-0.398
DSCR4	NM_005867.2	10281	-0.48	-0.274	0.785	0.542	-0.79	-0.704	0.126	-0.453	0.198	-1.022
DSCR6	NM_018962.1	53820	0.318	-0.471	1.397	0.668	-0.565	-0.538	-0.18	-0.429	0.508	-0.987
DSCR8	NR_026838.1	84677	-0.366	-0.358	1.896	0.677	0.413	0.528	0.434	-0.211	0.662	-1.128
PIGP	NM_153681.1	51227	-0.397	-0.122	-3	-0.34	0.497	-0.453	-0.921	-0.084	-0.936	-0.343
CLIC6	NM_053277.1	54102	0.001	-0.472	0.549	-0.4	0.787	-0.402	-0.015	-0.721	-0.124	0.032
BACE2	NM_012105.3	25825	0.962	-0.024	-0.803	0.42	-1.092	-1.61	-0.81	-0.688	-0.957	0.158
BRWD1	NM_018963.3	54014	-0.492	-0.269	0.381	0.861	0.858	0.918	0.678	0.343	0.288	0.117
DSCAM	NM_001389.3	1826	0.908	0.67	1.005	0.999	-0.687	-0.165	1.202	-0.438	0.201	-0.029
DYRK1A	NM_130438.1	1859	-0.648	-0.661	-0.782	0.348	0.788	0.578	-0.481	0.939	-0.231	-0.02
ERG	NM_001136154.1	2078	-1.04	0.744	0.812	0.873	-0.759	-0.969	0.073	-1.195	0.461	-0.659
ETS2	NM_005239.4	2114	-1.182	-0.191	0.859	0.392	-0.01	0.082	0.462	-0.672	0.901	0.623
KCNJ6	NM_002240.2	3763	-1.357	-1.297	-0.526	-0.427	0.089	0.387	-0.279	1.319	-0.097	-0.565
RUNX1	NM_001122607.1	861	-0.387	-0.245	1.299	0.532	0.389	-0.623	0.126	-1.933	-0.105	0.384
SH3BGR	NM_001001713.1	6450	0.014	0.715	0.224	0.013	0.739	0.855	1.876	-0.094	-0.38	0.065
SIM2	NM_005069.2	6493	-0.112	0.797	0.863	1.395	-0.327	-0.424	0.278	-1.618	0.449	0.704
CLDN14	NM_012130.2	23562	-0.457	-0.435	2.331	1.152	0.665	1.782	2.665	0.421	0.119	-0.366
TTC3	NM_001001894.1	7267	-0.387	-0.479	0.033	-0.076	-0.102	0.633	0.038	-0.419	-0.341	0.501
SON	NM_138927.1	6651	-0.131	-0.471	-0.180	-0.024	0.161	-0.226	-0.038	-0.060	-0.424	-0.455
HLCS	NM_000411.4	3141	-0.659	0.685	-1.000	-0.859	-0.164	-0.043	-0.942	-1.009	-1.019	-2.202
KCNJ15	NM_002243.3	3772	-0.831	0.222	-0.155	0.149	0.270	-0.152	-0.569	0.159	-0.059	-0.527
HMGN1	NM_004965.6	3150	0.619	-0.296	0.035	-0.482	0.977	0.726	0.811	0.398	0.414	-0.573
WRB	NM_004627.4	7485	0.621	0.362	0.020	0.004	-0.295	-0.540	0.290	0.392	-0.072	0.567
LCA5L	NM_152505.2	150082	0.434	-0.533	-0.320	0.330	0.976	0.024	0.603	-0.066	-0.091	-0.542
C21orf88	NR_026542.1	114041	0.387	0.172	-1.228	-1.098	0.923	0.131	-0.037	0.337	0.223	-1.015
B3GALT5	NM_033173.1	10317	0.024	0.313	-0.031	0.068	-0.174	0.288	-0.085	0.217	0.030	-0.492
TMEM1	NM_003274.3	7109	-0.372	-0.344	0.889	1.019	0.262	-0.133	-0.219	-0.180	-0.322	0.048
IGSF5	NM_001080444.1	150084	0.942	0.528	-1.210	-1.394	0.285	-0.509	-0.629	0.125	0.199	-1.339
PCP4	NM_006198.2	5121	1.241	1.255	-0.416	-0.324	0.104	-0.071	-0.639	0.253	-0.788	-1.824
CSTB	NM_000100.2	1476	0.953	1.087	0.600	0.044	0.630	0.286	0.127	0.816	0.131	-0.481
TMEM50B	NM_006134.4	757	0.547	0.274	-1.117	-1.051	-1.241	-1.184	-1.103	-0.844	-0.976	-1.617
PTTG1IP	NM_004339.2	754	0.253	0.097	0.048	-0.169	0.390	0.109	0.425	0.094	0.172	-0.106
TIAM1	NM_003253.1	7074	0.158	-0.206	-1.369	-1.539	0.399	0.493	0.514	0.731	0.421	0.878
PRMT2	NM_206962.1	3275	0.785	0.718	0.715	0.827	0.029	-0.754	-0.242	-0.307	-0.063	-0.570

Discussion

Until now, many studies have reported in DS mouse models a generalized overexpression of triplicate genes [26,27]. Thus, other researches on human trisomic tissues showed that only a subset of genes of chromosome 21 are over-expressed related to euploid controls, and the set of genes vary between cell types [28,29], indicating that the presence of three copies of a gene does not necessarily result in a global overexpression.

The expression pattern of a gene provides indirect information about its importance at a functional level, but it also provides information about the area in which it is expressed, correlating the importance of the functional role of this structure for the maintenance of homeostasis and efficiency of brain functioning. Thus, our results provided strong evidence that these areas have a marked gene activity, leading to think that they are sites of vital importance in various biological processes.

The caudate nucleus, putamen and globus pallidus are substructures that had a higher level of expression by the majority of genes in the basal nuclei. The caudate nucleus, takes part in the modulation of motion, just as it has been involved in learning and memory. On the other hand, putamen appears to play an important role in operant conditioning learning through reinforcement. Finally, the globus pallidus receives information from the caudate nucleus and the putamen and sends information to the substantia nigra [30,31]. Its function is to relate maintenance of a basal muscle tone for voluntary movements, carrying out precise activities with hands and feet as well as to keep the body in a specific position [32,33]. Moreover, the most expressed areas in the limbic lobe were the central ones and the parahippocampal gyrus, which are closely related substructures in maintaining memory and possible learning centers [34,35]. Studies based on connectivity changes in the brains of patients with DS have shown significant changes in the above-mentioned areas, demonstrating that those are relevant to the emotional and learning processes. Therefore, alterations in the dose of any of these genes in these critical areas would fit with poor cognitive performance of patients with DS [36].

On the other hand, PCP4 also known as protein 4 Purkinje cells, had the highest level of over expression in brain nuclei and the lower sub-expression in the limbic lobe on all genes analysed. The PCP4 (PEP-19) belongs to a family of proteins involved in a signal transduction of calcium modulating through this interaction calmodulin activity. Erhardt et al. suggested that PCP4 protects cells from induced apoptosis, but their exact functions remain unknown yet [12,37]. It is known to be involved in brain development, being present in almost all regions and most abundant in the cerebellum way; besides that it has a very specific expression pattern in adult neurons [12,38]. A previous study revealed a high expression of this gene in various brain structures between which the putamen and basal forebrain is included [39], being consistent with the results obtained in this study.

The transgenic mouse models with DS have shown that over-expression of the gene induces PCP4 early neuronal differentiation, in which the additional copy of it, produces a stronger and broader expression in neurons compared with disomic controls. Thus, the highest protein levels have direct consequences in the early stages of differentiation of neurons [12,40]. It is important for proper brain function. We can conclude from our results that a large expression related to learning, memory and motor control structures are crucial for both normal adult brain and it becomes a starting point for linking malfunction or overdose of this gene with possible implications for neurological damage in DS or other neuropathology brains.

The *KCNJ6* (*GIRK2*) gene showed great expression in different limbic lobe substructures related to cognitive processes. It is shown as a mediator of different motor functions, playing a key role in learning and memory [41]. DS studies in mice have shown a high over expression in the frontal cortex and hippocampus, and it has been linked in neurogenesis processes and synapses of the latter, suggesting that cognitive disorders, memory and motors in these mice could be related to over expression or malfunction of this gene [42-44].

Additionally, the increased expression of *KCNJ6* has been associated with the deterioration in GABAergic function, which appears to contribute to the mechanisms responsible for the cognitive impairments in DS and mice models. This has led to postulate it as a key gene both, in the contribution cognitive deficits and dysfunction of fine motor skills in DS, and possible investigations of gene therapy [41,44,45].

RCAN1 and *DSCR2* genes, showed a remarkable expression in many of the studied substructures allowing postulate that these genes are important for the proper functioning of those regions. *RCAN1* (*DSCR1*) presented a remarkable expression in the central areas, the putamen and globus pallidus. Studies have shown that chronic expression of this gene has been associated with several pathologies among which include Alzheimer's disease, cardiac hypertrophy and conditions related to learning and memory in DS associating this with the deficit occurred in the late phase of long-term potentiation [46]. Similarly, the *DSCR2* gene showed an opposite expression between brain nuclei and the limbic lobe, with high activity in the latter. It is known that this gene is an important factor associated with DS, expressing in different tissues and fulfilling various functions that are key in regulating the functioning of chromosome 21 [47].

In addition, DYRK1A showed a lot of interactions within the protein network. DYRK1A, is a serine/threonine kinase of dual activity which phosphorylates exogenous substrates on serine/threonine residues, but it has to autophosphorylate on tyrosine residues [15,48,49]. Because of their participation in various structural and functional aspects of the central nervous system, it has been proposed that it could play an important role in the pathogenesis of DS during pregnancy and adult life. These assertions are based on the discovery of a highly characteristic pattern of expression in both fetal and adult tissues [50-52] further that this gene is over expressed in the brains with DS

and in Ts65Dn mice [50]. Similarly, other experimental data have suggested that this is a sensitive dose gene, for example the variation in gene copies is accompanied by a corresponding variation. It is important to highlight that seven DSCR proteins composing this master node are widely expressed in the brain; they also have in common to be very important for neurogenesis processes. Therefore, it has been observed that the gene *RCAN1* interacts with calcineurin A and inhibits signaling pathways dependent on calcineurin, affecting maybe the central nervous system development. Moreover, it has been found that is over expressed in the brain of fetuses with DS and is involved in the development of Alzheimer's disease in these patients. On the other hand, *BRWD1*, *TTC3* and *DSCR3* genes are related to processes of neuronal differentiation, signal transduction and are critical candidates to explain the pathogenesis of DS. Moreover, the *HMGN1*, *BRWD1* and *SON* genes expressed in brain and interacted with the *DYRK1A* gene showing a strong correlation between them (group that remains in the heatmap for *HMGN1* and *SON* genes). It has been observed that these three genes are key for the regulation of cell cycle and apoptotic processes, besides being involved in the assembly of components involved in transcriptional activation [18,53,54].

Based on these results and in addition to the great anatomical correlation with the differential expression of genes DSCR, it is possible to state that the deficit in the dosage of any of these genes in the substructures of the brain nuclei and the limbic lobe (especially in regions with higher expression) can be an extremely important fact in the regulation of their associated functions. This lead to dysfunction of learning, memory and motor skills, which are characteristic, observed in varying degrees in the symptoms of DS [55]. Although it is worth noting that the results obtained come from databases, giving a bioinformatics approach which may propose models of the effect of altering gene dosage [56].

However, the mechanisms involved in the pathogenesis of DS, are still not fully understood, indicating that more studies to elucidate more about the complex biological processes associated with this disorder are needed. Consequently, exploration in databases related to brain gene expression, are a great help to clarify the picture at a genomic and proteomic level, both in normal brain and with DS or other neuropathology.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets supporting the conclusions of this article are available in the Human brain atlas repository, (http://human.brain-map.org/), and its additional file (Dataset).

Disclosure statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

We declared that the Universidad del Valle and the Universidad Autonoma de Occidente financed the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

DF participated in the acquisition of data, analysis and interpretation of data, and was involved in drafting the manuscript. JRO, FGV and AS participated in the design of the study and performed the statistical analysis. KV, JCM and JMS were involved in drafting the manuscript and its critical review. All authors read and approved the final manuscript.

Acknowledgment

The current work was financially support by a scientific internal call of the Vice-rectory of Investigations of the Universidad del Valle and the Universidad Autonoma de Occidente, Cali-Colombia.

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