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Chapter 3

Functional Neurogenomics: A New Approach to Study Cognitive Disability in Down Syndrome Brain

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Abstract

Functional neurogenomics is the interface between neurosciences knowledge and Omics sciences data. It characterizes, identifies, and analyzes expression of genes involved in the function of several structures of brain and cognition. Its major goal is to understand the main pathways of brain function, plasticity, and the etiopathogenesis of brain diseases. We have done an integrate analysis of global brain gene expression linked to cognitive disability in Down syndrome. It is a new approach to better understand the control of complex brain networks of gene expression involved in this syndrome. The objective of the chapter is to present computationally simulate data of global expression of 108 genes associated with cognitive disability and neuroplasticity from DNA microarray experiments of postmortem brain from normal controls and patients with Down syndrome. Some genes that were studied are involved in metabolic process and also promote hippocampal plasticity; interventions reawaken the neural plasticity may permit improved cognition. One of the striking findings was that some of the causes of dysregulation appear to result in the brain being trapped in an immature state of synaptic development. Understanding the functional neurogenomics of Down syndrome brain, emerge a new scenario to partially overcome cognitive disability through new prospective genomic therapies.

Keywords: brain, functional neurogenomics, omics sciences, Down syndrome, neuroplasticity, cognitive disability, data mining, DNA microarrays, computational biology

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1. Introduction

Never before in brain research, the development of modern brain imaging technologies and the application of new brain analyses by using the Omics sciences, have provided new knowledge to explore not only the biological essence of human intelligence as well as the relationship between brain function and cognition. As results of such studies, actually we have an unprecedented state to understand the relationship between brain and intelligence [1]. Brain function and its dysfunction throughout life are determined by the interaction of genetic factors with internal and external environmental events, signals, and stimuli [2]. Most of this process occur early in life and exert many effects that persist throughout adulthood. In this scenario, the hippocampus is one of the targets that plays a crucial role in learning, memory storage and retrieval, and in general cognitive function; the study and management of hippocampal neuronal networks, open the real possibility to induce adaption by increasing its function, as a base for a real hippocampal rehabilitation combined therapies [3–5].

This chapter presents the main results of our investigations in the Down syndrome global gene expression from an integrative approach of functional neurogenomics (FN) as the interface of neurosciences and omics sciences (OS). NF emerges as an integrative research approach which applies several methods of computational sciences and OS strategies, to get understanding of how their gene-product interacts in complex networks and regulates the brain homeostasis. The information derived from the functional neurogenomics approach, could serve in the future, to develop new promising therapeutic protocols and genome editing strategies for trustworthy cognitive rehabilitation based on the hippocampal neuroplasticity [6–9].

2. Generalities of Down syndrome

Down syndrome (DS) is the most common aneuploidy in children caused by an extra 21 chromosome, affecting worldwide 1 in 600 live births and 1 in 150 conceptions [10]; however, remarkable differences are registered among countries that depend on sociocultural variables [11]. The triplication of genes on HSA21 causes a wide spectrum of neurological phenotypes in DS, including intellectual and cognitive disabilities. Patients with DS display not only delayed linguistic skills and a variable degrees of cognitive and intellectual disabilities, but also behavioral issues such as attention-deficit disorder (ADD, sometimes with hyperactivity) and autism spectrum disorder (ASD) [12–16]. The cognitive impairments extend further after development, as individuals with DS are more prone to develop Alzheimer's type dementia [17]. In addition, patients with DS are susceptible to epilepsy in the form of infantile spasms and tonic-clonic seizures with myoclonus at early ages [16].

It was reported that brain of Down syndrome has a reduction of size and diminishing number of neuron density. Part of the cognitive dysfunction in DS, lies not only in the progressive neuronal degeneration/cell death and impaired neurogenesis seen in this developmental and degenerative disorder, but also in the reduction in dendrite formation and spine density, which result in a disruption of synaptic function. These pathological abnormalities in humans are, in part, replicated in DS animal models which show defects in learning, social interactions, memory, and seizures [18–22].

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3. Functional neurogenomics: the systemic integration of brain global gene expression

The spectacular advances in OS, had led to obtain comprehensive global information regarding the transcriptome of some neurological diseases [23]. In this regard, the use of DNA microarrays to study global transcription is widely spread. This methodology has allowed performing comprehensive analysis of changes in transcriptional expression of many genes associated with the pathophysiology of DS [24]. In addition, previous studies have shown the importance of using postmortem brain tissue to analyze the transcriptome of different conditions and different regions of the human brain including those individuals with DS [25]. The gene expression profile of the central nervous system (CNS) is unique. At least 30–50% of approximately 22,000 known protein-coding genes are expressed across all structures of the human brain [26]. Moreover, the human brain has the highest level of gene expression compared with other mammal species [27]. Neurogenomics research applies genomic strategies to identify and analyze genes that are involved in the function of nervous system. One of the main goals is to build a really systemic approach that contributes to explain the brain development, function, plasticity, and associated diseases [6, 7, 28, 29].

As shown in **Figure 1**, the major goal in functional neurogenomics is to analyze the global gene expression among different structures of the brain in order to identify the normal regulation of transcription and characterize genes associated with several neurological pathologies with cognitive and intellectual disabilities phenotypes [28–31].

The functional neurogenomic analysis starts with planning of global gene expression in brain. In this sense, DNA microarray experiments are a powerful experimental tool to study the transcriptome profile of brain which varies within specific regions and changes with age and with internal and external environmental conditions [32, 33].

DNA microarray experiments generate large amounts of data; for example, in a gene expression microarray study, 22,000 genes x 100 samples will generate 2.2 million data points. This terabyte amount data of information is necessary to be analyzed by computational simulation procedures that use bioinformatics analysis tools to get information about the spatial and temporal gene expression. Moreover, the bioinformatics analysis permits to extract information about genes which are expressed in normal and pathological samples of postmortem brains [34, 35].

In addition, genomic experiments are often noisy and are not normally distributed, and usually contain missing values in the expression matrix. To overcome such problem and to obtain biological relevant interpretations of the genome expression data, robust biostatistical analyses are required [36, 37]. In general, statistical analyses of genomic data can be divided into two major categories: supervised and unsupervised methods [36]. Supervised analysis is used to identify genes that are differentially expressed between groups of samples, as well as to find genes that can be used to accurately predict the characteristics of groups. The unsupervised approaches characterize genomic data without prior input or knowledge of predetermined pattern. Unsupervised analysis is used to identify internal structure in the genomic data set. The most commonly used unsupervised analysis tool is Hierarchical clustering and Principal Components Analysis (PCA) [37].

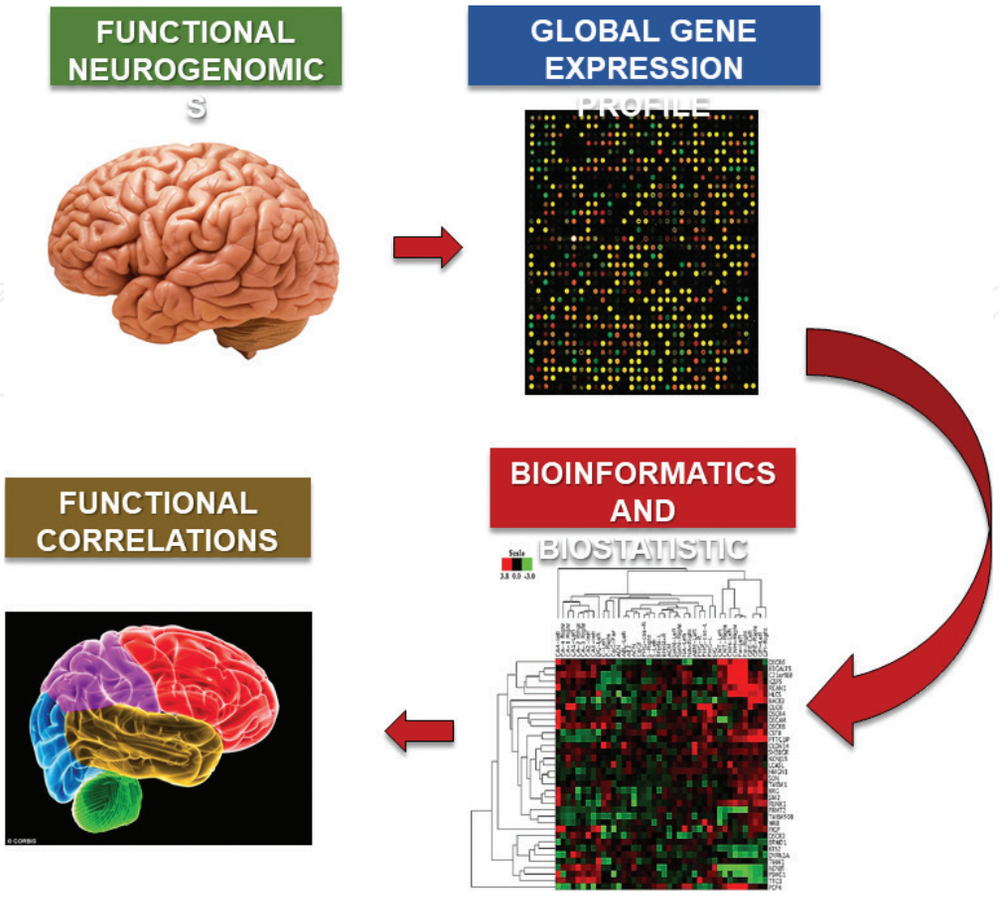


Figure 1. The experimental and analytical procedures applies in functional neurogenomics. The flow of procedures starts with the analysis of global gene expression profiles, using the technology of DNA microarray, which is followed by a trend of bioinformatics and statistical analysis of the results of the big data generated by DNA microarray experiments. As a result of the integrative analysis, the functional correlation between global gene expression and several interaction processes are obtained.

The final result of the flow of analytical process previously described, is to correlate the gene expression profiles variation within specific regions of the brain to obtain a better knowledge about the functional correlations. In this sense, DNA microarray experiments showed that the transcriptome profile of the CNS is specific of brain structure and also the signals that modulate it [38, 39].

4. Cognitive disability and neuroplasticity: our main approach

Cognition refers to the mental processes that are involved in acquiring knowledge and comprehension. These processes include thinking, knowing, remembering, judging, and problem solving. All of them are higher level functions of the brain and encompass language, imagination, perception, and planning [40]. Neuroplasticity is the ability of the nervous system to adapt to different environmental conditions and stimuli; it requires a well-conserved and flexible repertoire of molecular mechanisms [41]. Neural plasticity, allows neurons to regenerate

both anatomically as well as functionally, in a process call neurogenesis; also to form new synaptic connections—synaptogenesis, and in some cases of new dendrites generation—dendritogenesis [42, 43]. Because neuroplasticity is based on the ability of brain to recover and restructure itself, it allows us to consider that its adaptive potential to recover after disorders or injuries, would be a point of departure for developing therapeutic strategies toward reducing the effects of altered structures due to cognitive associated pathologies including DS among others [44].

The point of departure of our studies lies in the fact that a failure in the crosstalk between cognitive process and neuroplasticity would be a major effector for cognitive disability (CD) in DS brain [45–48]. Some genetic mechanisms or even alteration of brain development homeostasis has important neurodevelopmental consequences produced by CD [49].

4.1. Our methodological approach

In order to test our proposal, the initial approach started with a bibliographic search of full papers in PubMed of publications reported neuroplasticity and CD in Down syndrome. We used the following crossed descriptors to perform that search: DS, neuroplasticity and cognition and cognitive disability, and genes associated. We filtered six full papers describing genes that involved in cognition and neuroplasticity in DS. Information consigned in this article led us to pick up 106 genes involved in neuroplasticity and cognitive process such as memory and learning. Those genes were the initial background to perform our computational simulations and identify their functional roles in several structures of brain cortex. Moreover from gender and age gene expression values, we obtain data about their temporal and spatial regulations. The list and main characteristics of selected genes are consigned in Supplementary **Table 1**.

As a source to calculate the values of expression for selected gene, this initial bibliographic search was crossed with DNA microarray experiments consigned in the database of GEO DataSet of NCBI (https://www.ncbi.nlm.nih.gov/gds/). Combining the descriptors: Down syndrome and global transcription and neuroplasticity and cognition and brain, we found nine DNA microarray experiments. However, only one of them fitted the statistical significance sample size to obtain trustable information about the functional neurogenomics in DS.

We used the log10 transformed expression values of a DNA microarray experiment whose registration code and free access in the GEO database was GSE59630 (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE59630), previously deposited by Olmos et al. [50]. The microarray experiment selected included gene expression data of 47,000 probes from 58 DS patients (25 females and 33 males) and 58 healthy controls (25 females and 33 males) of postmortem brain samples classified by gender and age, and in 11 structures of cerebral cortex.

4.2. Functional analysis

Free use Cytoscape 3.2 open software platform was used for visualizing and analyzing the genetic interaction networks among the selected human genes associated with cognition and neuroplasticity processes. Biological Networks Gene Ontology v2.6 plugin (BiNGO

ID	Gen symbol	Name	Locus	Function—gene ontology (GO)
90	ACVR1	Activin A receptor type 1	2q24.1	ATP binding
9509	ADAMTS2	ADAM metallopeptidase with thrombospondin type 1 motif 2	5q35.3	Metalloendopeptidase activity, metallopeptidase activity
9370	ADIPOQ	Adiponectin	3q27.3	Cytokine activity, hormone activity
152	ADRA2C	Adrenoceptor alpha 2C	4p16.3	Alpha-2A adrenergic receptor binding, epinephrine binding
8906	AP1G2	Adaptor related protein complex 1 gamma 2 subunit	14q11.2	Protein transporter activity
361	AQP4	Aquaporin 4	18q11.2	Protein binding
10317	B3GALT5	Beta-1,3-galactosyltransferase 5	21q22.2	Protein glycosylation
25825	BACE2	Beta-site APP-cleaving enzyme 2	21q22.2–q22.3	Amyloid-beta metabolic process
627	BDNF	Brain-derived neurotrophic factor	11p14.1	Neurotrophin TRKB receptor binding
666	BOK	BCL2 family apoptosis regulator	2q37.3	BH domain binding
54014	BRWD1	Bromodomain and WD repeat domain containing 1	21q22.2	Cytoskeleton organization
55969	C20orf24	Chromosome 20 open reading frame 24	20q11.23	Olfactory receptor activity
114041	B3GALT5-AS1	B3GALT5 antisense RNA 1	21q22.2	Putative uncharacterized
721	C4B	Complement C4B	6p21.33	Carbohydrate binding, endopeptidase inhibitor activity
23562	CLDN14	Claudin 14	21q22.13	Protein complex assembly
54102	CLIC6	Chloride intracellular channel 6	21q22.12	NOT glutathione metabolic process
1277	COL1A1	Collagen type I alpha 1 chain	17q21.33	Protease binding, extracellular matrix structural constituent, protein binding
1278	COL1A2	Collagen type I alpha 2 chain	7q21.3	SMAD binding, identical protein binding
1476	CSTB	Cystatin B	21q22.3	Adult locomotory behavior
7852	CXCR4	C-X-C motif chemokine receptor 4	2q22.1	C-C chemokine binding
51523	CXXC5	CXXC finger protein 5	5q31.2	Sequence-specific DNA binding, signal transducer activity, transcription factor binding
147991	DPY19L3	DPY-19-like 3	19q13.11	Mannosyltransferase activity, transferase activity
1812	DRD1	Dopamine receptor D1	5q35.2	Dopamine binding

ID	Gen symbol	Name	Locus	Function—gene ontology (GO)
3920	DSCAM	DS cell adhesion molecule	21q22.2	Nervous system development, Locomotory behavior, dendrite morphogenesis
10311	DSCR3	DSCR3 arrestin fold containing	21q22.13	Intracellular protein transport
53820	DSCR6	Ripply transcriptional repressor 3	21q22.13	Negative regulation of cell proliferation
84677	DSCR8	Down syndrome critical region 8 (non-protein coding)	21q22.13	Biological_process
1846	DUSP4	Dual specificity phosphatase 4	8p12	MAP kinase serine/threonine phosphatase activity
1859	DYRK1A	Dual specificity tyrosine phosphorylation regulated kinase 1A	21q22.13	Circadian rhythm
1958	EGR1	Early growth response 1	5q31.2	RNA polymerase II regulatory region sequence-specific DNA binding
2078	ERG	ERG, ETS transcription factor	21q22.2	Cell proliferation
2114	ETS2	ETS proto-oncogene 2, transcription factor	21q22.2	Skeletal system development
2199	FBLN2	Fibulin 2	3p25.1	Extracellular matrix binding, calcium ion binding
252995	FNDC5	Fibronectin type III domain containing 5	1p35.1	Hormone activity, molecular_function
2487	FRZB	Frizzled-related protein	2q32.1	Wnt-activated receptor activity, G protein-coupled receptor activity
2670	GFAP	Glial fibrillary acidic protein	17q21.31	Structural constituent of cytoskeleton, protein binding
2719	GPC3	Glypican 3	Xq26.2	Heparan sulfate proteoglycan binding, peptidyl-dipeptidase inhibitor activity
10457	GPNMB	Glycoprotein nmb	7p15.3	Integrin binding, heparin binding, chemoattractant activity
3141	HLCS	Holocarboxylase synthetase	21q22.13	Enzyme binding
3150	HMGN1	High mobility group nucleosomal binding domain 1	21q22.2	Transcription-coupled nucleotide-excision repair
9456	HOMER1	Homer scaffolding protein 1	5q14.1	G protein-coupled glutamate receptor binding
9454	HOMER3	Homer scaffolding protein 3	19p13.11	G protein-coupled glutamate receptor binding
3479	IGF1	Insulin-like growth factor 1	12q23.2	Growth factor activity, hormone activity, insulin-like growth factor receptor binding, insulin-like growth factor receptor binding

ID	Gen symbol	Name	Locus	Function—gene ontology (GO)
3488	IGFBP5	Insulin-like growth factor binding protein 5	2q35	Fibronectin binding, protein binding
3489	IGFBP6	Insulin-like growth factor binding protein 6	12q13.13	Growth factor binding, receptor binding
3600	IL15	Interleukin 15	4q31.21	Cytokine activity, cytokine receptor binding
3623	INHA	Inhibin alpha subunit	2q35	Cytokine activity, growth factor activity
3708	ITPR1	Inositol 1,4,5-trisphosphate receptor 1	3p26.1	Calcium channel inhibitor activity
170850	KCNG3	Potassium voltage-gated channel modifier subfamily G member 3	2p21	Delayed rectifier potassium channel activity
3772	KCNJ15	Potassium voltage-gated channel subfamily J member 15	21q22.13-q22.2	Potassium ion import
3775	KCNK1	Potassium two pore domain channel subfamily K member 1	1q42.2	Inward rectifier potassium channel activity
57576	KIF17	Kinesin family member 17	1p36.12	Microtubule motor activity, ATP binding, microtubule binding,
7071	KLF10	Kruppel-like factor 10	8q22.3	RNA polymerase II core promoter proximal region sequence-specific DNA binding
11202	KLK8	Kallikrein related-peptidase 8	19q13.41	Serine-type endopeptidase activity
150082	LCA5L	LCA5L, lebercilin like	21q22.2	Protein binding
9663	LPIN2	Lipin 2	18p11.31	Phosphatidate phosphatase activity
4058	LTK	Leukocyte receptor tyrosine kinase	15q15.1	ATP binding, protein binding
4147	MATN2	Matrilin 2	8q22.1-q22.2	Calcium ion binding
4239	MFAP4	Microfibril associated protein 4	17p11.2	Protein binding
283078	MKX	Mohawk homeobox	10p12.1	Sequence-specific DNA binding
25902	MTHFD1L	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1 like	6q25.1	Formate-tetrahydrofolate ligase activity, methylenetetrahydrofolate dehydrogenase (NADP+) activity
1463	NCAN	Neurocan	19p13.11	Calcium ion binding
4885	NPTX2	Neuronal pentraxin 2	7q22.1	Carbohydrate binding
51299	NRN1	Neuritin 1	6p25.1	C-terminal protein lipidation
51559	NT5DC3	5′-Nucleotidase domain containing 3	12q23.3	Metal ion binding
4908	NTF3	Neurotrophin 3	12p13.31	Chemoattractant activity, neurotrophin p75 receptor binding

ID	Gen symbol	Name	Locus	Function—gene ontology (GO)
64881	PCDH20	Protocadherin 20	13q21.2	RNA binding, calcium ion binding
5121	PCP4	Purkinje cell protein 4	21q22.2	Positive regulation of neuron differentiation
5179	PENK	Proenkephalin	8q12.1	Neuropeptide hormone activity
51227	PIGP	Phosphatidylinositol glycan anchor biosynthesis class P	21q22.13	Preassembly of GPI anchor in ER membrane
130271	PLEKHH2	Pleckstrin homology, MyTH4 and FERM domain containing H2	2p21	Actin binding, identical protein binding
57460	PPM1H	Protein phosphatase, Mg2+/Mn2+ dependent 1H	12q14.1-q14.2	Phosphoprotein phosphatase activity, protein serine/threonine phosphatase activity
3275	PRMT2	Protein arginine methyltransferase 2	21q22.3	Developmental cell growth
8624	PSMG1	Proteasome assembly chaperone 1	21q22.2	Proteasome assembly
754	PTTG1IP	PTTG1 interacting protein	21q22.3	Protein import into nucleus
51655	RASD1	RAS related dexamethasone induced 1	17p11.2	GTPase activity, GTP binding
10633	RASL10A	RAS like family 10 member A	22q12.2	Signal transduction, small GTPase mediated signal transduction
1827	RCAN1	Regulator of calcineurin 1	21q22.12	Central nervous system development
5997	RGS2	Regulator of G protein signaling 2	1q31.2	G-protein alpha-subunit binding
85397	RGS8	Regulator of G protein signaling 8	1q25.3	GTPase activator activity
56475	RPRM	Reprimo, TP53 dependent G2 arrest mediator homolog	2q23.3	Protein binding
861	RUNX1	Runt related transcription factor 1	21q22.12	Peripheral nervous system neuron development
347735	SERINC2	Serine incorporator 2	1p35.2	L-serine transmembrane transporter activity
5271	SERPINB8	Serpin family B member 8	18q22.1	Serine-type endopeptidase inhibitor activity
6450	SH3BGR	SH3 domain binding glutamate rich protein	21q22.2	Positive regulation of signal transduction
6470	SHMT1	Serine hydroxymethyltransferase 1	17p11.2	L-allo-threonine aldolase activity, glycine hydroxymethyltransferase activity
6493	SIM2	Single-minded family bHLH transcription factor 2	21q22.13	Embryonic pattern specification
6574	SLC20A1	Solute carrier family 20 member 1	2q14.1	High-affinity inorganic phosphate:sodium symporter activity
65012	SLC26A10	Solute carrier family 26 member 10	12q13.3	Anion:anion antiporter activity

ID	Gen symbol	Name	Locus	Function—gene ontology (GO)
57709	SLC7A14	Solute carrier family 7 member 14	3q26.2	Amino acid transmembrane transporter activity
114826	SMYD4	SET and MYND domain containing 4	17p13.3	Metal ion binding, methyltransferase activity
6651	SON	SON DNA binding protein	21q22.11	Negative regulation of apoptotic process
6664	SOX11	SRY-box 11	2p25.2	RNA polymerase II core promoter sequence-specific DNA binding
8869	ST3GAL5	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	2p11.2	Beta-galactoside (CMP) alpha-2,3-sialyltransferase activity
27090	ST6GALNAC4	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	9q34.11	Alpha-N-acetylgalactosaminide alpha-2,6-sialyltransferase activity
7058	THBS2	Thrombospondin 2	6q27	Heparin binding, protein binding
7059	THBS3	Thrombospondin 3	1q22	Heparin binding, calcium ion binding
7074	TIAM1	T-cell lymphoma invasion and metastasis 1	21q22.11	Neuron projection extension
757	TMEM50B	Transmembrane protein 50B	21q22.11	Biological_process
7109	TRAPPC10	Trafficking protein particle complex 10	21q22.3	Early endosome to Golgi transport
10098	TSPAN5	Tetraspanin 5	4q23	Enzyme binding
7267	TTC3	Tetratricopeptide repeat domain 3	21q22.13	Protein K48-linked ubiquitination
84959	UBASH3B	Ubiquitin associated and SH3 domain containing B	11q24.1	Identical protein binding, phosphoprotein binding
221044	UCMA	Upper zone of growth plate and cartilage matrix associated	10p13	Negative regulation of osteoblast differentiation
7422	VEGFA	Vascular endothelial growth factor A	6p21.1	Chemoattractant activity, cytokine activity
7485	WRB	Tryptophan rich basic protein	21q22.2	Tail-anchored membrane protein insertion into ER membrane

Table 1. Description of genes associated with neuroplasticity and cognition. Information taken from the NCBI—Genbank platform (Supplementary table).

tool) was used to search which gene ontology (GO) categories are significantly overrepresented in a set of genes. A hypergeometric test was applied to determine which categories were significantly represented (P-value < 0.05); significant values were adjusted for multiple hypotheses testing using the Bonferroni family wise error rate correction [51]. From network analyzer plugin of the Max Planck Institute Informatik, network topology parameters were calculated.

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4.3. Z-score transformation

The raw intensity data for each gene in the DNA microarray experiment was log10 transformed and then used for the calculation of Z score [52]. Z scores were calculated by subtracting the mean log gene intensities (within a single experiment) from the log intensity data for each gene, and dividing that result by the SD of all measured log intensities, according to the Z-score transformation (1):

$$Z - score = \frac{(Log\ intensity\ of\ G - mean\ log\ intensity\ G \ldots Gn)}{Standard\ deviation\ log\ G \ldots Gn} \quad (1)$$

All Z-score values were normalized on a linear scale −3.0 < 0 > +3.0. In this, the corresponding gene is overexpressed if the value of Z-score is greater than zero; on the contrary, it is underexpressed, if its value is negative.

4.4. Multivariate statistical analysis

Nonparametric analyses for comparing median values of Z-score were performed among gender and age variables between DS patients and healthy control. Wilcoxon signed-rank test was used to calculate differences between medians of two samples.

Data of Z-score values of samples from DS and controls were compared to establish significant difference in gender in DS and controls and by age ranks since 16 weeks of gestation to 6 months; since 7 months up to 1 year; 2–3 years; 10–19 years; and 22 years and older groups. Moreover, Z-scores for the genes included in the study, were compared between DS and control samples in 11 structures of brain cortex including: dorsolateral prefrontal cortex (DFC), visual cortex (V1C), cerebellar cortex (CBC), orbitofrontal cortex (OFC), ventral frontal cortex (VFC), inferior temporal cortex (ITC), hippocampus (HIP), medial frontal cortex (MFC), somatosensory cortex (S1C), inferior parietal cortex (IPC), and superior temporal cortex (STC). To perform the HCA, Euclidean distance was used as a measure of distance between DS and control samples of Z-score values in several structures of brain cortex; $p < 0.05$ was defined as a threshold [53].

5. Our results

5.1. Protein network and gene interactions

A total of 3135 protein interactions among genes associated with cognition and neuroplasticity process expressed in brains of DS subjects were recorded (**Figure 2A** and **B**). The central proteins of the main node of the network corresponded to RUNX1 (runt related transcription factor 1) at 21q22.12; SON (SON DNA binding protein) at 21q22.11; RGS2 (regulator of G protein signaling 2) at 1q31.2; UBASH3B (ubiquitin associated and SH3 domain containing B) at 11q24.1; DYRK1A (dual specificity tyrosine phosphorylation regulated kinase 1A) at 21q22.13; GFAP (glial fibrillary acidic protein) at 17q21.31; TIAM1 (T-cell lymphoma

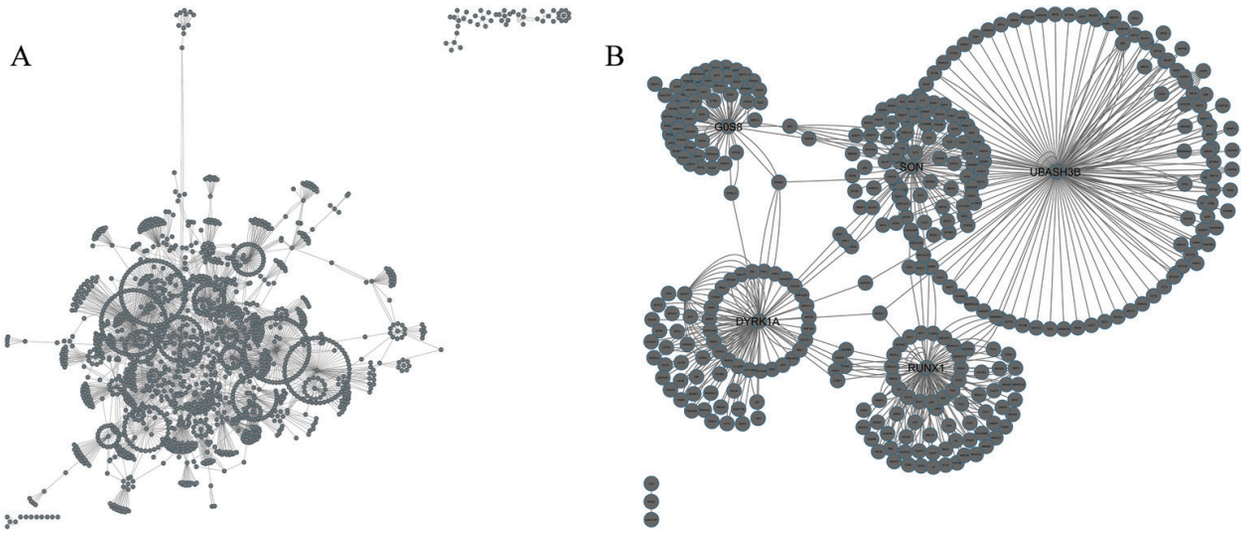


Figure 2. Protein-protein interaction (PPI) networks of genes associated with cognition and neuroplasticity constructed from data experiments of DNA microarray of genes expressed in Down syndrome postmortem brain samples. Data of log2 intensity values were obtained from DNA microarray experiment by Olmos-Serrano et al. [50], (GEO Dataset accession GSE59630). (A) Full network of 108 genes associated with cognition and neuroplasticity; (B) sub-network showing five of the major nodes found in the original network; Cytoscape 3.2 program was used to generate the graphical representation of built networks; UBASH3B, ubiquitin associated and SH3 domain containing B; SON, SON DNA binding protein; G0S8 (RGS2), regulator of G protein signaling 2; DYRK1A, dual specificity tyrosine phosphorylation regulated kinase 1A; RUNX1, runt-related transcription factor 1.

invasion and metastasis 1) at 21q22.11; and THBS3 (thrombospondin-3) at 1q22. The most important topological parameters of the network were: clustering coefficient with a value of 0.33; average number of neighbors 2367; network density 0.001 and 12 connected components (**Table 2**).

From GeneMANIA Cytoscape plugin, we identified the top five functions of that genes. They corresponded to regulation of behavior, behavior, muscle cell migration, hormone activity, and G coupled glutamate receptor.

5.2. Differential gene expression in post-mortem brains of DS patients

Overall no statistical differences between the median values in Z-score of the 108 gene in controls and DS patients were recorded (Controls 0.2869 vs. DS 0.3318; Wilcoxon rank test $p > 0.05$). However, significant differences in the medians of Z-score in some genes were determined. Thus, in the DS brains, the overexpression levels corresponded to genes CXXC5 (Controls −1.2376 vs. DS 0.7492), EGR1 (controls −1.2266 vs. DS 0.5442), and NCAN (controls −1.2901 vs. DS 0.5440).

The main GO categories of brains processes associated with DS involved in its etiopathogenesis included: respiratory electron transport chain (3.31E − 41), positive regulation of cell death (1.17E − 39), positive regulation of release of cytochrome c from mitochondria (9.19E − 37), negative regulation of cell motility involved in cerebral cortex radial glia guided migration

Topological parameter	Value
Clustering coefficient	0.33
Connected components	12
Network diameter	12
Network radius	1
Network centralization	0.056
Shortest paths	3.454.424 (93%)
Characteristics path length	5.340
Avg. number of neighbors	2.367
Number of nodes	1919
Network density	0.001
Network heterogeneity	3.105
Isolated nodes	0
Number of self-loops	25
Multi-edge node pairs	595

Table 2. Values of the main topological parameters of the protein interaction network including 106 genes associated with cognitive and neuroplasticity process in brain of DS patients.

(5.20E − 35), telomere maintenance (1.16E − 34), negative regulation of angiogenesis (4.11E − 32), and axonogenesis (1.40E − 31) (**Table 3**). Moreover, focal adhesion (P-value 7.69E − 23) and neurotrophin signaling pathway (P-value 3.62E − 19) were also important pathways associated with cognitive and neuroplasticity process in brains of DS individuals.

5.3. Evaluation of gene expression by sex and age variables

We observed differential brain expression in 72 genes associated with CD among women and men. Medians of brain gene expression in men patients with DS were higher than in DS women ($p < 0.005$ Kruskal-Wallis test) (**Figure 4A**). Such difference were statically significant for the expression of DMXL2 (Z-score of men 1.33 vs. −1.75 in women); CAMTA1 (Z-score of men 1.16 vs. −1.73 in women); HCN1 (Z-score of 1.05 vs. −1.73 in women); and ATL1 (Z-score of men 0.85 vs. −1.73 in women). On the contrary, we recorded non-significant differences by gender in medians values of genes associated with neuroplasticity in brains of DS.

Global gene expression among the different ranks of age in DS brains was variable and dependent of the type of gene. However, slight differences of expression in brain genes associated with neuroplasticity process of Down syndrome and its age dependency were recorded in samples of DS brains in comparison with that of normal controls in age ranks since 16 weeks of gestation to more than 22 years old. It is noteworthy that DYRK1A, NCAM AND TSPN5 genes were under-expressed in prenatal brains (**Figure 3A–G**).

GO_ID	Process	P-value*
9987	Respiratory electron transport chain	3.31E – 41
48522	Positive regulation of cell death	1.17E – 39
48518	Positive regulation of release of cytochrome c from mitochondria	9.19E – 37
48523	Negative regulation of cell motility involved in cerebral cortex radial glia guided migration	5.20E – 35
44260	Telomere maintenance	1.16E – 34
48519	Negative regulation of angiogénesis	4.11E – 32
16043	Axonogenesis	1.40E – 31
43170	Glycoprotein biosynthetic process	3.33E – 30
10604	Positive regulation of telomerase activity	1.82E – 29
9893	Positive regulation of protein processing in phagocytic vesicle	5.01E – 28

*P-values were calculated using the correction of Bonferroni.
Ontology v2.6 plugin (BiNGO tool) was used to search gene ontology (GO) categories.

Table 3. The top 10 GO categories of brains processes associated with DS involved in its etiopathogenesis.

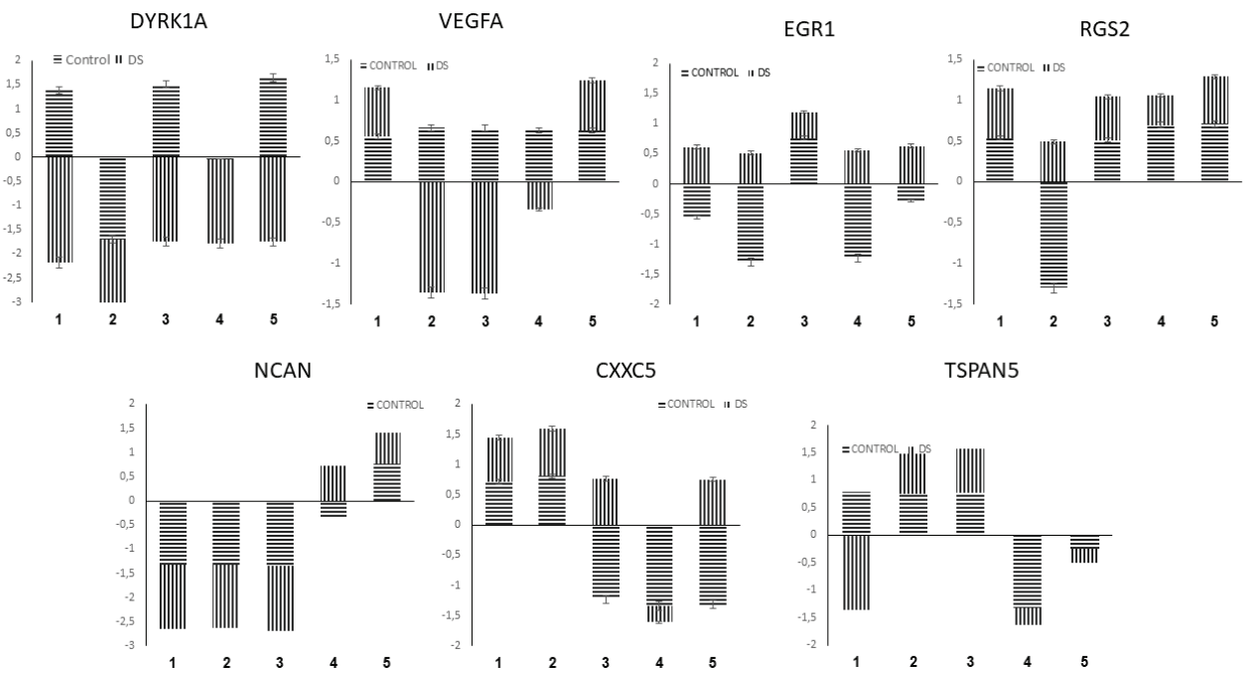


Figure 3. Differential values of median Z-score by age rank for six principal genes associated with cognitive disability and neuroplasticity expressed in brain samples of Down syndrome. (1) 16 Weeks of gestation to 6 months; (2) 7 months to 1 year; (3) 2–3 years; (4) 8–18 years; and (5) over 22 years of age. Y-axis values are the median of Z-score.

5.4. Gene expression in cerebral cortex

Some of the most differentially expressed genes across the cerebral cortex are shown in **Figure 4A–H**. In particular, expression in S1C showed significant differences for SERPIB8 (Control 0.2288 vs. DS −2.0288), SHMT1 (control 0.1542 vs. DS −2.1269) and THBSH3 (control

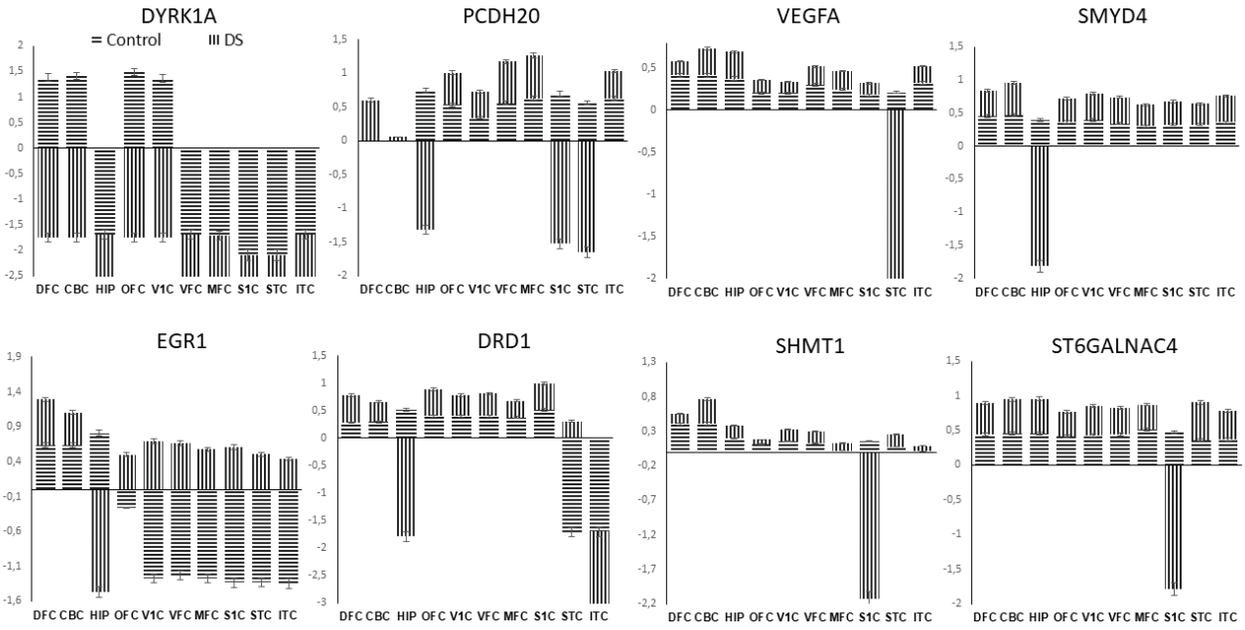


Figure 4. Differential gene expression in different structures of brain cortex of genes associated with cognitive disability and neuroplasticity in DS samples of brain. DFC, dorso lateral prefrontal cortex; V1C, visual cortex; CBC, cerebellar cortex; OFC, orbito frontal cortex; VFC, ventral frontal cortex; ITC, inferior temporal cortex; HIP, hippocampus; MFC, medial frontal; S1C, cortex somatosensory cortex; IPC, inferior parietal cortex and STC, superior temporal cortex. Y-axis values are the median of Z-score.

0.1542 vs. −2.0709) genes. In hippocampus, we recorded differential expression for EGR1 (control 0.8084 vs. DS −1.4648), SMYD4 (control 0.3946 vs. −1.8171), PCDH20 (control 0.7462 vs. DS −1.3194), DYRK1A (control 1.4284 vs. DS −1.7390), and VEGFA (control 0.6648 vs. DS −1.3280). In S1C, the most under expressed genes in Down syndrome were MFAP4 (control 0.1711 vs. DS −2.1461), BDNF (control 0.2136 vs. DS −2.1039), RGS8 (control 0.4013 vs. DS −1.9024), and SERINC2 (control 0.2584 vs. DS −1.8843). Finally in V1C, ADIPOQ (control −0.0035 vs. DS −2.1880), and TSPAN5 (control 0.7392 vs. DS −1.3315) were the most under-expressed genes in DS samples.

6. Discussion

In general, our results provided strong evidence to propose that in brains of DS, a fail in the cross talk of global expression between genes associated with cognition and neuroplasticity process (most of them located out of chromosome 21), is complex and is associated not only with pathological profiles but with gender, age, and is also dependent of the brain cortex structures. However, according with the functional roles, differential expression of particular groups of genes would cause a considerable impact on the metabolic pathways, in which they participate and are directly or indirectly involved in the regulation of molecular events associated with cognition and neuroplasticity in brain of patients with DS.

Overall, this study also support the hypothesis of a systemic imbalance of brain protein homeostasis, or proteostasis network as an important effect of trisomy not only in loci of

chromosome 21 but also in genes located in other chromosomes [54]. Together our results and others collectively suggest that disturbance in the proteostasis network of cognitive and neuroplasticity process, could contribute to the accumulation of protein aggregates, such as amyloid deposits and NFTs, which occur very early in DS. It is likely that a sub-optimal functioning of degradative systems occur in DS neurons, which in turn provide the basis for further accumulation of toxic protein aggregates which have an indirect impact on the neuroplastic process in several structures of brain cortex [55, 56].

According to our results and with the information reviewed in literature, V-CAM1, SPTAN1, DYNC1H1, PAFAH1B1, H3F3A, ACVR1, THBS3, and TSPAN5 were the proteins with the highest number of protein interactions. All of them directly or even indirectly regulate several brain processes associated with cognition and neuroplasticity [57, 58]. In this sense, it is relevant to get more knowledge about the implication in those neurophysiological processes whose function is altered by either overexpression or by disruption in the network functional interaction architecture in DS brains.

For the first time, we obtain strong evidence that brain of male DS had, in general, a higher gene expression of cognitive and neuroplasticity process in comparison with that of females. The outstanding differences were specifically for DMXL2 (RKPM = 8.02 ± 1.61), CAMTA1 (RKPM = 4977 ± 1.246), HCN1 (RKPM = 4.88 ± 2.29), and ATL1 (RKPM = 34.764 ± 11.66) genes, all of them highly expressed in human brain. Previous evidence indicates that male-biased genes are highly enriched for genes involved in neurological and psychiatric disorders such as schizophrenia, bipolar disorder, Alzheimer's disease, and autism, while no such pattern was seen for the female-biased genes, suggesting that the differences in brain disorder susceptibility between males and females are likely rooted from the sex-biased gene expression regulation during brain development [59]. Moreover, it was previously reported that the excess of male cases with Down syndrome is not restricted to free trisomy 21 alone, but appears in translocation cases [60] and with the life expectancy found in males with DS, which is significantly greater in females [61]. Collectively, our and others analyses reveal the important role of sex-biased genes in brain development and neurodevelopmental disorders including the effects in cognitive disability in DS.

DYRK1A, BDNF, PENK, and DRD1 genes are strongly under-expressed in dorsolateral prefrontal cortex, hippocampus, orbitofrontal cortex, and ventral frontal cortex in subjects with DS in contrast with non-trisomic. Prefrontal cortex is implicated in planning complex cognitive behavior, personality expression, decision-making, and moderating social behavior [62], and also plays key roles in cell proliferation and survival, neuronal differentiation, synaptic plasticity, and neurodegeneration (for review, see [63, 64]). Supporting our proposal, it has been reported that DYRK1A/RCAN1 and NFAT lead to neurodevelopmental alterations that might have an impact not only in the brain size and neuronal density, but also in the altered common features found in patients with DS [65]. Additionally, a reduction of vesicular GABA transporter punctate specifically on parvalbumin-positive interneurons was identified [66, 67]. Overall, our results and others suggest that dysfunction of cortical fast-spiking interneurons might be central to the pathophysiology of DS.

The under-expression of key genes for brain function correlates with previous reports that showed that DS brains are smaller than normal brains and they exhibit neuronal deficits in

several regions, including the cerebral cortex structures [68]. Moreover, infants with DS also present hypocellularity in this brain structure [69, 70], indicating that defects in prenatal development are a major determinant of the deficit in adults. Indeed, fewer cells and disorganized laminas are evident in the cerebral cortex of DS fetuses from as early as the second trimester of gestation [71, 72]. Altogether, the different lines of evidence support the hypothesis that DS brain is severely affected by the disturbance of proteostatic network, which is major responsible for the cerebral phenotype of DS.

Differential gene expression in hippocampus visual cortex, and somatosensory cortex of DYRK1A (dual specificity tyrosine-phosphorylation-regulated kinase 1A), TSPAN5 (tetraspanin 5), DRD1 (dopamine receptor D1), EGR1 (early growth response 1), GFAP (glial fibrillary acidic protein), and PENK (proenkephalin), which encode proteins that play important roles in several brain processes of cognition, learning and the maintenance of homeostasis, lead us to proposed them as functional potential predictors to follow up the homeostatic imbalance in DS brain.

Finally, this study showed that the integration of knowledge and use of cross talk between neurotranscriptomics and bioinformatics is a powerful work to develop transdisciplinary and systems biology studies to deal with many insight still remains to be solve in Down syndrome. We recommend continuing to study much deeper the complexity of interaction networks in the DS etiopathogenesis and brain homeostasis. On the other hand, our approach could serve as a starting point for the implementation of strategies to the management of cognitive and mental disabilities based on functional neurogenomics and the hippocampal neuroplasticity.

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