Difusão do Conhecimento Através das Diferentes Áreas da Medicina 3

Lais Daiene Cosmoski
(Organizadora)

Atena Editora
Ano 2019

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Dados Internacionais de Catalogação na Publicação (CIP)
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D569 Difusão do conhecimento através das diferentes áreas da medicina 3 [recurso eletrônico] / Organizadora Lais Daiene Cosmoski. – Ponta Grossa, PR: Atena Editora, 2019. – (Difusão do conhecimento através das diferentes áreas da medicina; v. 3)

Formato: PDF
Requisitos de sistema: Adobe Acrobat Reader
Modo de acesso: World Wide Web
Inclui bibliografia
ISBN 978-85-7247-882-3
DOI 10.22533/at.ed.823192312

1. Medicina – Pesquisa – Brasil. 2. Saúde - Brasil. 3. Diagnóstico. I. Cosmoski, Lais Daiene. II. Série.
CDD 610.9

Elaborado por Maurício Amormino Júnior – CRB6/2422

Atena Editora
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APRESENTAÇÃO

Cada vez mais percebemos, que no mundo da ciência, principalmente da área da saúde, nenhuma profissão trabalha sozinha, é necessário que vários profissionais estão envolvidos e engajados em conjunto, prezando pela, prevenção, diagnóstico e tratamento de diversas patologias, visando sempre a qualidade de vida da população em geral.

A Coletânea Nacional “Difusão do Conhecimento Através das Diferentes Áreas da Medicina” é um *e-book* composto por 4 volumes artigos científicos, que abordam relatos de caso, avaliações e pesquisas sobre doenças já conhecidas da sociedade, trata ainda de casos conforme a região demográfica, onde os locais de realização dos estudos estão localizados em nosso país, trata também do desenvolvimento de novas tecnologias para prevenção, diagnóstico e tratamento de algumas patologias.

Abordamos também o lado pessoal e psicológico dos envolvidos nos cuidados dos indivíduos, mostrando que além dos acometidos pelas doenças, aqueles que os cuidam também merecem atenção.

Os artigos elencados neste *e-book* contribuirão para esclarecer que ambas as profissões desempenham papel fundamental e conjunto para manutenção da saúde da população e caminham em paralelo para que a para que a ciência continue evoluindo para estas áreas de conhecimento.

Desejo a todos uma excelente leitura!

Lais Daiene Cosmoski

SUMÁRIO

CAPÍTULO 3

CajaDB: A DATABASE OF COMMON MARMOSETS (*Callithrix jacchus)*

Data de aceite:19/11/2018

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ABSTRACT: Common marmoset (*Callithrix jacchus*), a small New World monkey, is a valuable model in different areas of investigation and recently it has been proposed for the study of neurological/neuropsychiatric diseases and cognition. One of the frontiers in neuroscience field requires handling omics large-scale data sets for connecting molecular pathways to nervous system behavior. Hence, to make the omics datasets for this species more accessible for the scientific community without a solid bioinformatics background, we have created CajaDB, a molecular database that provides a friendly interface for genomic, expression and alternative splicing data, including tools for biological analyses. Once lateralization is a crucial aspect of the functional brain architecture for cognitive abilities, we analyzed genes expressed in the marmosets' hemispheres to illustrate the use of CajaDB. We found 24 genes with left hemisphere bias and 25 genes with right hemisphere bias. CajaDB is available at cajadb.neuro.ufrn.br

KEYWORDS: Transcriptomics, molecular database, neuropsychiatric primate model, laterality, brain asymmetry

CajaDB: UMA PLATAFORMA PARA DADOS MOLECULARES DE SAGUI COMUM (*Callithrix jacchus*)

RESUMO: O sagui comum (*Callithrix jacchus*), um pequeno macaco do Novo Mundo, é um modelo valioso em diferentes áreas de investigação e recentemente foi proposto para o estudo de doenças neurológicas/neuropsiquiátricas e cognição. Uma das fronteiras no campo da neurociência requer o manuseio de conjuntos de dados em grande escala para conectar caminhos moleculares ao comportamento do sistema nervoso. Portanto, para tornar os dados das -ômicas desta espécie mais acessíveis à comunidade científica sem uma sólida formação em bioinformática, criamos o CajaDB, uma base de dados moleculares que fornece uma interface amigável para dados genômicos, de expressão e de *splicing* alternativo, incluindo ferramentas para análises biológicas. Uma vez que a lateralização hemisférica é um aspecto crucial da arquitetura funcional do cérebro para habilidades cognitivas, analisamos os genes expressos nos dois hemisférios de saguis para ilustrar do CajaDB. Foram encontrados 24 genes com viés no hemisfério esquerdo e 25 genes com viés no hemisfério direito. O CajaDB está disponível em cajadb.neuro.ufrn.br.

PALAVRAS-CHAVE: Transcriptômica, banco de dados moleculares, modelo de primata neuropsiquiátrico, lateralidade, assimetria cerebral

1 I INTRODUCTION

Animal models have been crucial in biomedical research once a large part of human experimentation is unfeasible or unethical. Common marmoset (*Callithrix jacchus*), a small New World primate, is widely used as a model in several areas of research. In the neuroscience field, it has progressively gained space for both cognitive studies and investigation of neuropsychiatric conditions such as Parkinson’s disease (PHILLIPS et al., 2017), Alzheimer’s disease (PHILIPPENS et al., 2017) and depression (Galvão-Coelho et al., 2008; 2017). Besides sharing some behavioral characteristics regarding their social organization with humans (MILLER et al., 2016), their use as a model holds advantages of easy handling in a lab setting and reproduction at a rate that makes genetically manipulated models of disorders feasible (KISHI et al., 2014).

Recently, large-scale technologies (the omics, e.g. genomics, transcriptomics, and proteomics) have revolutionized biological studies at a molecular level. The use of data generated by these technologies represents a great opportunity to molecular neuroscience research. One of the greater challenges in the omics is the organization of data to extract new scientific knowledge. Simple levels of data organization do not represent the inherent potential information, and it is noteworthy that integration of data across different observations is especially important in neurobiology (GESCHWIND; KONOPKA, 2009).

In this regard, we developed the CajaDB, an application for interactive visualization of omics data of common marmosets, including tools for biological analysis. The application was totally designed to facilitate its use by individuals without bioinformatics background. A database with interactive visualization of data from a neurobiological model will hopefully culminate in a greater prospect of new investigations for the alternative approaches for treatment of neurological diseases and in a deeper understanding of brain functioning.

The left and right cerebral hemispheres are functional and anatomical asymmetric, which is implicated in cognitive performance and behavior expression. This has been largely described in humans (HERVÉ et al., 2013); (POBRIC; LAMBON RALPH; ZAHN, 2016) and non-human primates (ATKINSON; ROGERS; CHEVERUD, 2016; CHANCE et al., 2013), including marmosets (GORDON; ROGERS, 2010, 2015); (HOOK-COSTIGAN; ROGERS, 1998); (HOOK; ROGERS, 2000); (PIDDINGTON; ROGERS, 2013). As hemispheric laterality is a conserved trait of the nervous system in vertebrates (OCKLENBURG; GÜNTÜRKÜN, 2012), genetics approaches on models can provide new insights on the complex polygenic neural pathways probable involved in handedness and language lateralization found in humans. Currently, there are no laterality studies of marmosets including a molecular contextualization reported in the literature. In this context, to illustrate the use of CajaDB, we studied genes differentially expressed in the left and right brain's hemispheres of common marmosets.

2 I METHODS

Tissue samples and data source

Common marmoset reference genome (MARMOSET GENOME SEQUENCING AND ANALYSIS CONSORTIUM, 2014) and transcriptome were downloaded from the UCSC genome browser. Public RNA sequencing (RNA-seq) reads showing high sequence coverage from three different projects were downloaded from the SRA/NCBI, as follows: 1) (CORTEZ et al., 2014) (frontal cortex, cerebellum, heart, kidney, liver – all from male and female. Ovary and testis); 2) (PENG et al., 2015) (bone marrow, brain left hemisphere, pituitary, brain right hemisphere, colon, heart, kidney, liver, lung, lymph node, skeletal muscle, spleen – all from female) and 3) (PIPES et al., 2013) (bladder, hippocampus, skeletal muscle - from male. Cerebral cortex and cerebellum from female). Those summarize expression data of 25 non-redundant common marmoset tissues, where male and female were treated separately.

Data processing

All RNA-seq reads were mapped using TopHat v2.1. 0 (Bowtie2 - 2.2.5, (LANGMEAD et al., 2009; TRAPNELL; PACHTER; SALZBERG, 2009) to the reference genome assembly. Cufflinks 2.2.1 (TRAPNELL et al., 2010) was used to calculate the expression in FPKM (fragments per kilobase of transcript per million mapped reads) values for all genes in the genome. To identify and visualize alternative splicing events (exon skipping, intron retention and alternative 5′ and 3′ splicing borders), Splicing Express (KROLL et al., 2015) was performed.

Classification of marmosets' genes with regards to transcriptional levels

For specificity classification of genes by tissues, a cutoff value of 0.5 FPKM was used. Each of the 16,206 genes were classified, described by (FAGERBERG et al., 2014), into one of eight categories based on the FPKM levels in 25 tissues: (1) Not detected - > 1 FPKM in all 25 tissues; (2) Tissue-specific - 50-fold higher FPKM level in one tissue compared with all other tissues; (3) Tissue enriched - fivefold higher FPKM level in one tissue compared with all other tissues; (4) Group enriched - fivefold higher average FPKM level in a group of 2–7 tissues compared with all other tissues; (5) Mixed low - detected in 1–24 tissues and at least one tissue < 10 FPKM; (6) Mixed high - detected in 1–24 tissues and all detected tissues > 10 FPKM; (7) Expressed in all low - detected in 25 tissues and at least one tissue < 10 FPKM; and (8) Expressed in all high - detected in 25 tissues and all tissues > 10 FPKM.

Marmoset genes associated with neuropsychiatric disorders

To list the common marmoset genes associated with neuropsychiatric disorders, comparative genomics analysis was applied focusing on the similarity between the annotation of human and marmoset genomes. The section "nervous system disease" in the catalog of published genome-wide association studies (GWAS, (WELTER et al., 2014)) has 756 candidate genes, which were used as the reference.

Application for interactive visualization of data

The CajaDB, available in cajadb.neuro.ufrn.br, has a modular architecture. Home module has information to guide in data exploration. Genome module has a genome visualization tool: interactive diagram with highlighted genes associated with neuropsychiatric disease. Expression module has an interactive heatmap (Clustergrammer from MaayanLab) with filtering, ordering and snapshot tools where is possible to estimate the ontology of a set genes through EnrichR tool (KULESHOV et al., 2016). Also in the expression module, there is a tool to visualize the protein-protein-network through STRING, an application with known and predicted protein-protein interactions (SZKLARCZYK et al., 2015). In the Splicing module, data of canonical and alternative isoforms combined to alternative splicing events are available for a specific gene, for all genes across all tissues.

EXAMPLE OF USE

Differential gene expression in laterality

Cuffdiff (TRAPNELL et al., 2012) was used to estimate the differential expression between brain left and right hemispheres data from Peng et al., 2014 at the transcript level. P-values were adjusted by false-discovery rate (FDR) (BENJAMINI; HOCHBERG, 1995).

Public gene expression data for several tissues was quantified to determine the normalized RNA abundance, calculated as FPKM-values. In these analyses, a cutoff of 0.5 FPKM was used. The number of detected genes ranged from 13.108 in the testis to 9.770 in skeletal muscle (Figure 1A). The transcriptome analysis of 25 samples allowed a classification of a set of 16,206 protein-coding genes regarding tissue-specific expression pattern (Figure 1B). This classification was divided into four major classes, afterward subdivided into subclasses according to the criteria determined by Fagerberg et al., (2014). The first class presents genes (approximately 35%) expressed ubiquitously in marmoset tissues, the “housekeeping genes”. The second class has genes expressed in only a subset (2–24) of tissues, but not identified as tissue-specific, which accounted for the largest part of marmoset genes (approximately 44%). This result diverges from the distribution of human transcriptome (Fagerberg et al., 2014), where the largest part of genes accounted for housekeeping genes. Elevated levels of expression in a particular tissue or a group of related tissues are placed in the third class accounting for approximately 14% of genes (categories Highly tissue enriched, Moderately tissue enriched and Group enriched). The fourth class was for non-detected genes (approximately 7%). These processed data can assist in the understanding of different tissue signatures and the associated biological functions, including sexual differences.

To make information of genes associated with neuropsychiatric disorders and tissue-specific RNA-seq data from common marmosets more accessible to the scientific community without a solid bioinformatics background, we created CajaDB (Figure 2), a web application available at cajadb.neuro.ufrn.br. This application provides a friendly interactive visualization tool for genomic, expression and alternative splicing data, including tools for enrichment analysis and PPI network. Users can navigate through the website by: (i) selecting genes of interest (either through imputed lists or pre-compiled lists containing neural/neuropsychiatric-associated genes); (ii) checking the expression of selected genes in a transcriptome visualization tool where it is possible to filter, reorganize, order the data and take high-quality snapshots to use in scientific publications; (iii) visualizing the selected genes in the protein-protein-network through STRING; and (iv) getting information about simple splicing alternative events (exon skipping, intron retention and alternative 5′ and 3′ splicing borders) by gene across tissues. It is also possible to retrieve all the data available in the CajaDB through a MySQL dump.

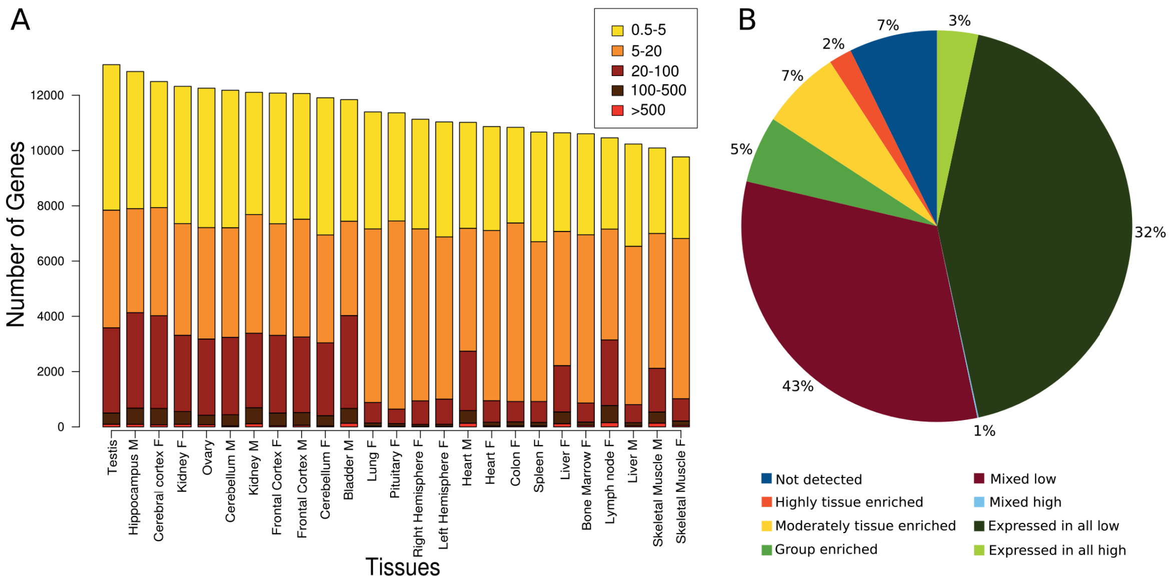
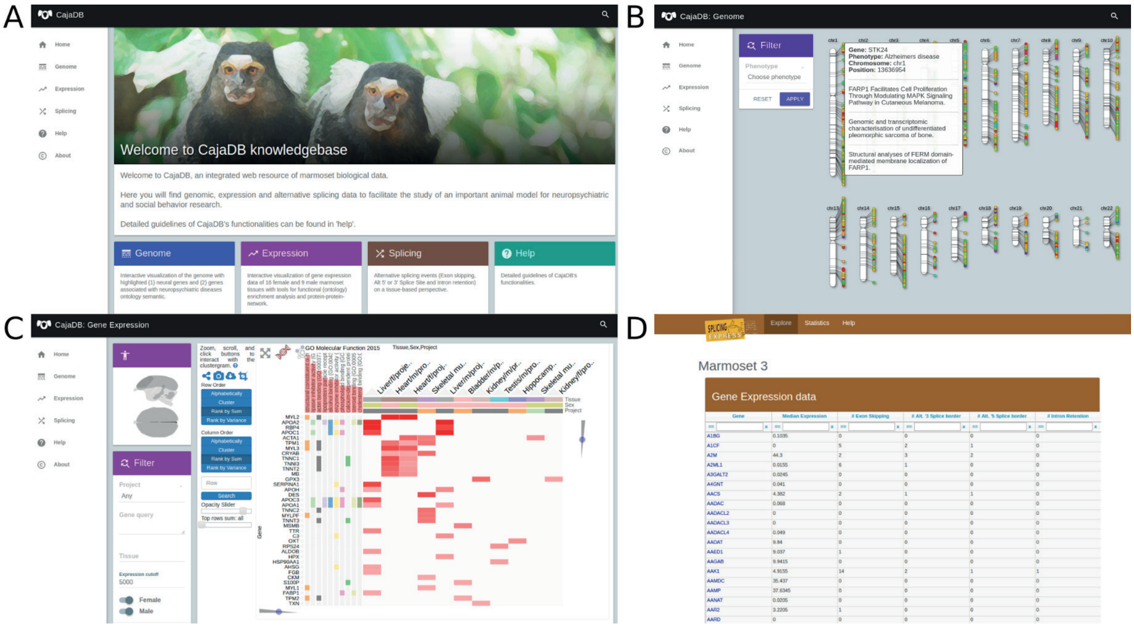


Figure 1 – Expression pattern of marmoset genes across tissues. A) Total number of genes with detected transcripts in each tissue using five different abundance levels for FPKM values: 0.5-5 FPKM (yellow), 5-20 FPKM (orange), 20-100 FPKM (light brown), 100-500 FPKM (dark brown), >500 FPKM (red). B) Distribution of 16,206 marmoset genes into eight different categories based on the number of detected tissues. Abbreviations: T – testis, Hi – hippocampus, Cc – Cerebral Cortex, K – Kidney, O – Ovary, Ce – Cerebellum, Fc – Frontal Cortex, Bl – Bladder, Lu – Lung, P – Pituitary gland, Rh – Brain Right Hemisphere, Lh – Brain Left Hemisphere, H – Heart, Cl – Colon, Sp – Spleen, Li – Liver, Bm – Bone Marrow, Ln – Lymph Node, Sk – Skeletal muscle and Go – Gonads.



Welcome to CajaDB, an integrated web resource of marmoset biological data.

Here you will find genomic, expression and alternative splicing data to facilitate the study of an important animal model for neuropsychiatric and social behavior research.

Detailed guidelines of CajaDB's functionalities can be found in 'help'.

Figure 2 - CajaDB: a platform for visualization of common marmosets' molecular data. A) Home module containing guidelines to easy-to-handle functionalities; B) Genome module with information of neural genes and genes associated with neuropsychiatric disorders; C) Expression module holding tissue-specific expression data with distinct samples quantification by sex, including tools for enrichment analysis and protein-protein-network visualization; D) Splicing module for alternative splicing data visualization, per gene, across all tissues.

Marmosets’ laterality

To illustrate the use of CajaDB, we studied marmosets’ RNA-seq of brain left and right hemispheres from Peng. et al., (2014). A total of 49 genes differentially expressed were found in the hemispheres. To understand the biological processes linked to these genes, we identified the enriched categories using the CajaDB tool for enrichment analysis. We also used the CajaDB to visualize gene expression in the hemispheres and to generate the Figure 3 (functionality of screenshot in the Expression module). The biological categories of innervation, synaptic transmission, and regulation of cGMP biosynthetic process were identified.

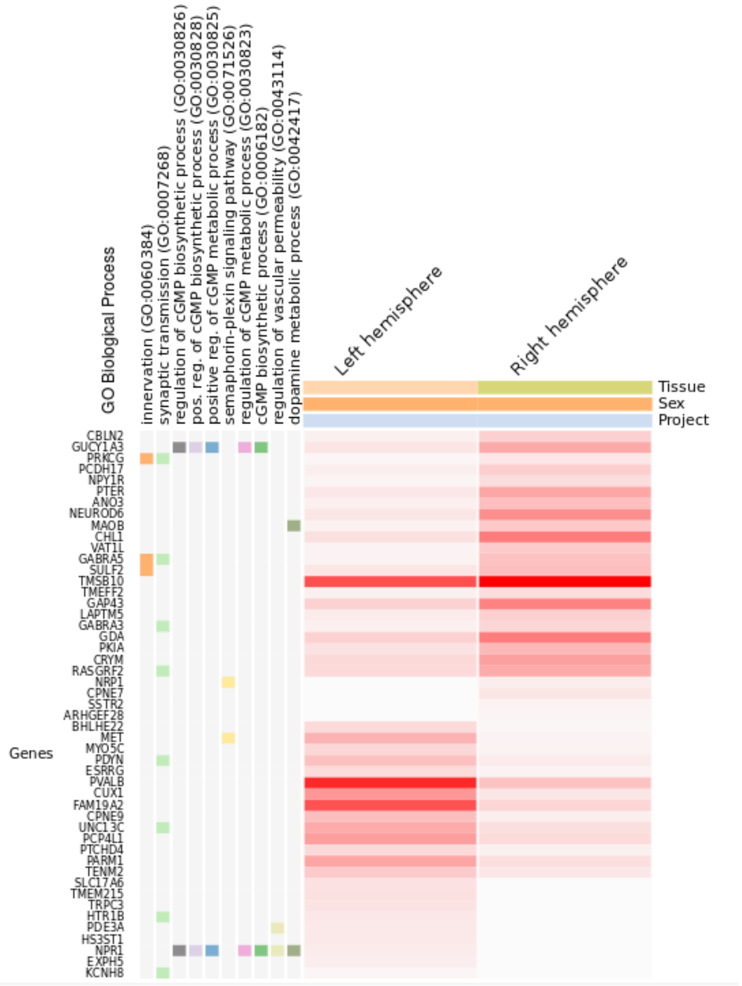


Figure 3 - Genes differentially expressed in the brain right and left hemispheres of common marmosets. Expression data of female marmoset from Peng et al. 2014 with differential expression elucidated by Cuffdiff. Categories of biological process from Gene Ontology is presented. Higher expression is represented by dark red. Lower expression is represented by light red.

Protein interactions mediate important biological processes. We generated the protein-protein interaction (PPI) network (data from StringDB, the tool is available at CajaDB) of genes with differential expression in the marmoset’s hemispheres.

Medium- and high-confidence interactions are shown in the Figure 4A and for this analysis, we excluded genes which have presented no protein connections.

Additionally, alternative splicing is one of the main biological mechanisms controlling the wide variability of mRNA and protein isoforms across tissues. In the CajaDB, it is possible to retrieve plots of alternative splicing events for all marmosets genes (generated through the Splicing Express). As an example, a specific alternative 3' splice site event in MET receptor, for brain left hemisphere, is shown in Figure 4B. MET gene is differentially expressed in the marmosets' hemispheres.

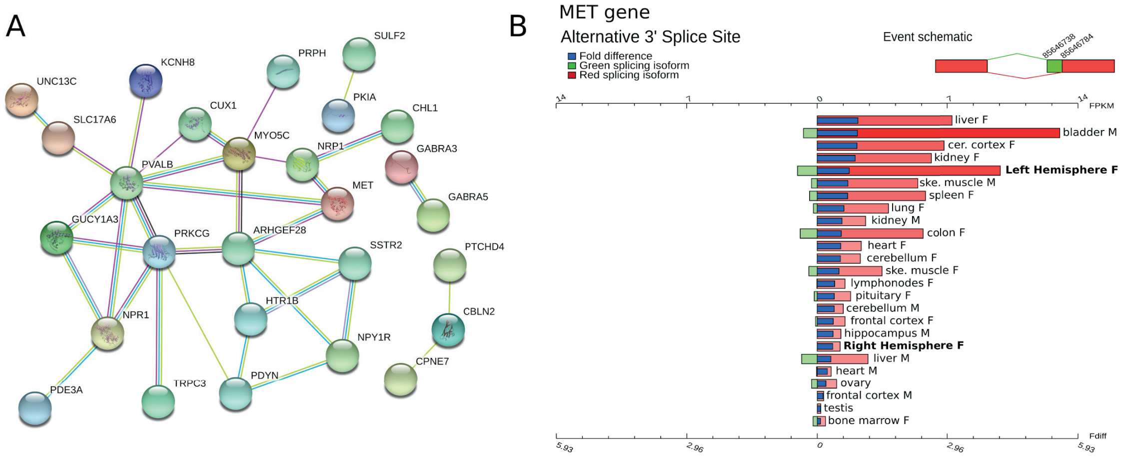


Figure 4 - Protein-protein network of genes differentially expressed in hemispheres of marmosets and alternative splicing of MET gene. A) Protein-protein-interaction network (STRING, visualized through CajaDB) of genes with differentially expressed in marmosets' brain right and left hemispheres. B) Alternative splicing across all tissues (alternative 3' splice site) of MET gene (also known as hepatocyte growth factor receptor, is a proto-oncogenic receptor tyrosine kinase), which has differential expression in the marmosets hemispheres.

In a human lateralization study with the focus on language, 75 genes were described as differentially expressed between the left and right hemispheres. These genes were related to the synaptic transmission, nervous system development and glutamate receptor activity categories. To provide the translational value of marmosets, we compared our set of genes with genes listed by them (KARLEBACH; FRANCKS, 2015). We found GABRA5, HTR1B, PDYN and PVALB genes present on both marmoset and human sets (Figure 5).

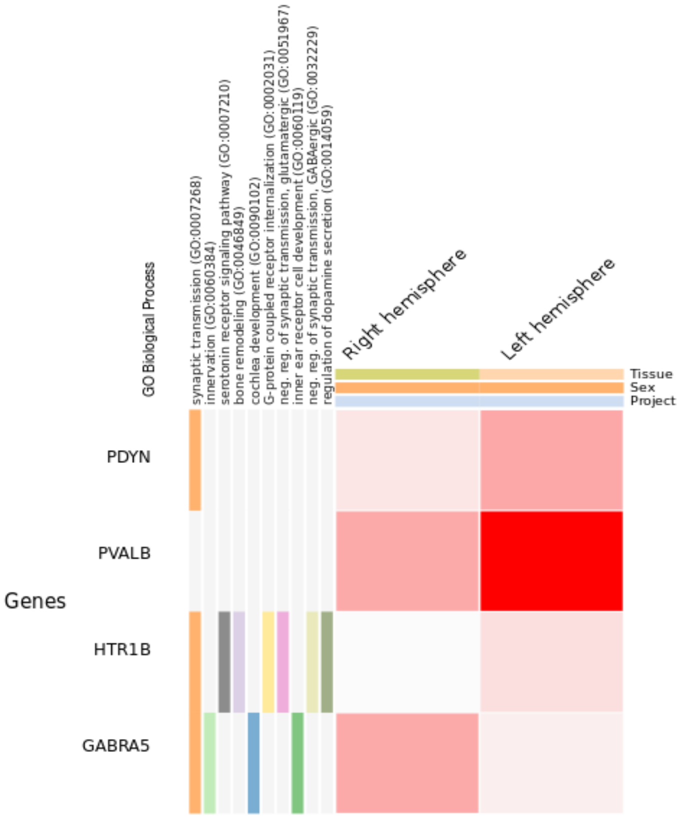


Figure 5 - Orthologs differentially expressed in the brain right and left hemispheres of marmosets and humans. The PDYN, PVALB, HTR1B and GABRA5 genes are a result of merging differentially expressed genes of brain right and left hemispheres in marmosets and genes differentially expressed in the same tissues in humans (by Karlebach and Francks 2015).

DISCUSSION

CajaDB, the most comprehensive molecular database in marmosets, provides an intuitive interface to visualize and explore genomic, transcriptomic and alternative splicing data. Our application not only allows the user to navigate the genomic data, but it is also possible to select human orthologs related to neuropsychiatric diseases, with information about the genes functions. CajaDB is a valuable resource for transcriptional studies once tissue-specific and sex-specific data are available and can guide research questions. A set of tools for biological analyses are supported such as enrichment analysis and protein-protein-network. Another important aspect of CajaDB is that the web design is suited for desktop and mobile devices. Researchers can explore data in genomic, expression, splicing alternative, functional (ontology) and protein-protein-network contexts. Hopefully, these centralized resources will provide numerous benefits to address and to respond to scientific questions.

Brain circuitry knowledge is limited, in part due to the technical limitations of measuring brain activity in humans. Animal models have been and will continue to be demanding to study many aspects of cerebral behavior. Evidence for hand preference associated with cognitive correlates was described in marmosets. Those with hand preference were able to perform simultaneously two tasks (foraging and predator detection) better than those without hand preference (PIDDINGTON; ROGERS, 2013). In the laterality context, we found hemisphere-biased expression in 49 genes, where 24 were biased for left hemisphere and 25 were biased for right hemisphere. (HOOK-COSTIGAN; ROGERS, 1998) showed that marmosets present laterality for (1) negative emotions expressions and vocalizations and (2) communication in social contact, in right and left hemispheres, respectively. This pattern is also found for speech and emotional control expressions in humans (GRUBER; GRANDJEAN, 2017).

Indeed, humans and marmosets share features of cognition (MILLER et al., 2016). Our findings show GABRA5, HTR1B, PDYN and PVALB differentially expressed in both humans and marmosets. PDYN is a precursor of some molecules, including the dynorphin which modulates responses to several psychoactive substances. The dynorphin/kappa opioid receptor system has been the target of research for neuropsychiatric disorders and normal brain functioning (SHIPPENBERG, 2009). Lateralization in the mechanism mediating the response of dynorphin A was observed in a traumatic brain injury (HUSSAIN et al., 2012). We envision that studying cerebral asymmetry comparing gene expression patterns would be a good strategy to investigate laterality of cognition in marmosets.

ACKNOWLEDGEMENTS

This research was supported by Amazonas State Research Support Foundation (FAPEAM), Federal University of Rio Grande do Norte (UFRN), Brain Institute, Bioinformatics Multidisciplinary Environment (BioME), NPAD/UFRN and Brazilian Council for Research and Technological Development (CNPq Proc. No. 30.6018/2013-6). We would like to give special thanks to the BioME core, for their endless patience during this work.

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