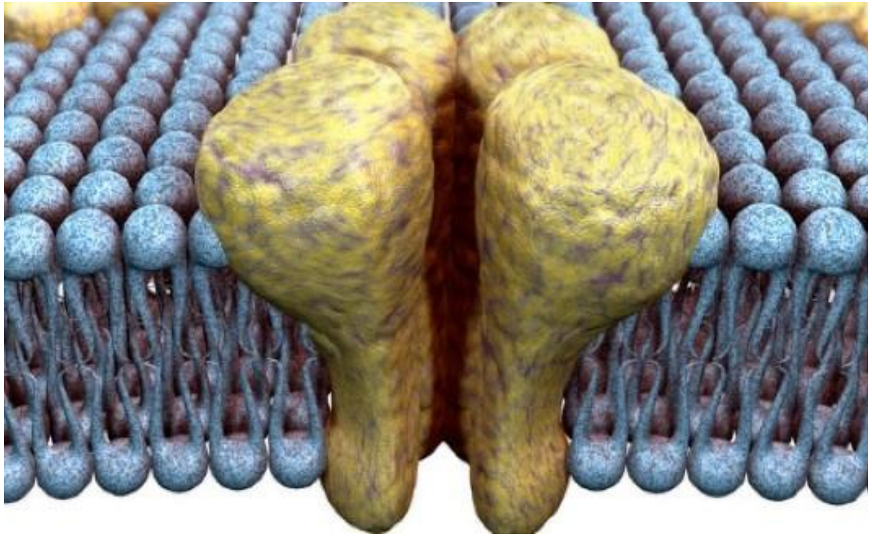
Up/down and left/right by the heart transcriptome

Dumitru Andrei Iacobas, PhD
PVAMU CCSB Personalized Genomics Laboratory
NELEN Rm.369, tel 936-261-9926, daiacobas@pvamu.edu

NATURE SCIENTIFIC REPORTS COLLECTION

Channelopathies: molecular and genetic mechanisms



www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

Transcriptomic uniqueness and commonality of the ion channels and transporters in the four heart chambers

Sanda Iacobas[1], Bogdan Amuzescu[2] & Dumitru A. Iacobas[3,4]

Myocardium transcriptomes of left and right atria and ventricles from four adult male C57Bl/6j mice were profiled with Agilent microarrays to identify the differences responsible for the distinct functional roles of the four heart chambers. Female mice were not investigated owing to their transcriptome

e estrous cycle phase. Out of the quantified

ight side exhibited differential expression

s were differently expressed between the

dy revealed also chamber differences in ge

hannels and transporters, and genes withi

rylation, glycolysis/gluconeogenesis, calci

e expression of *Ank2* oscillates in phase wi

ercentage of in-phase oscillating partners

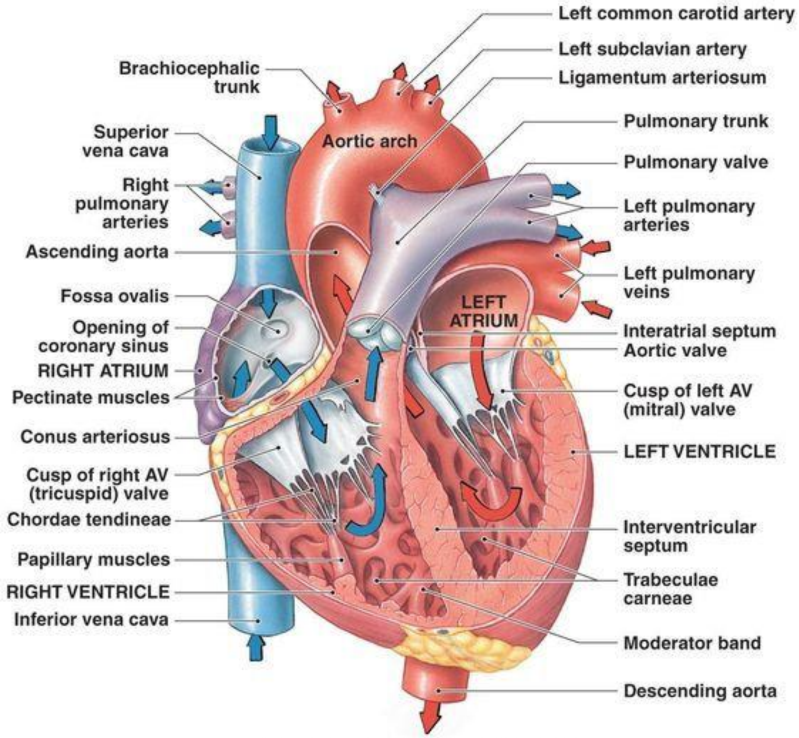
in the right ventricle. The analysis indicat

ssions and the substantially lower synchro

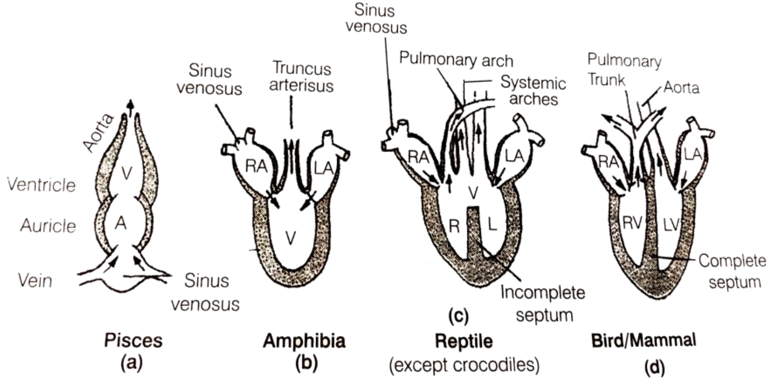
ventricle from the same side.

Chapter 1: Drug discovery, tools and theory

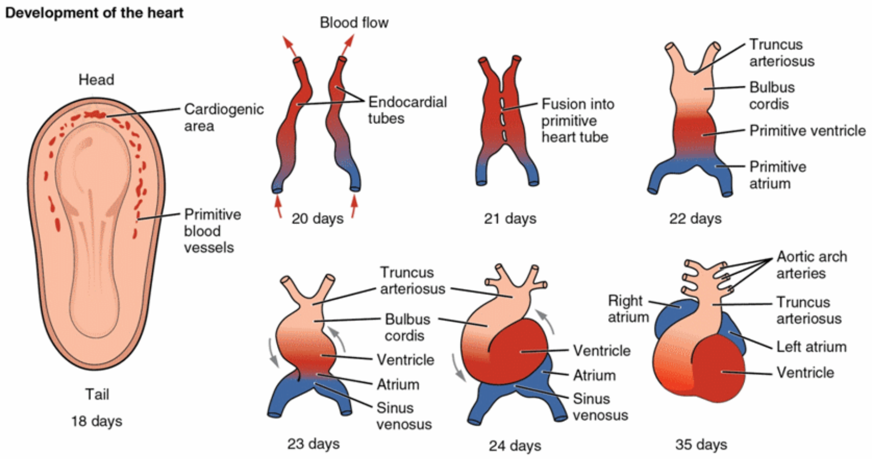
Heart



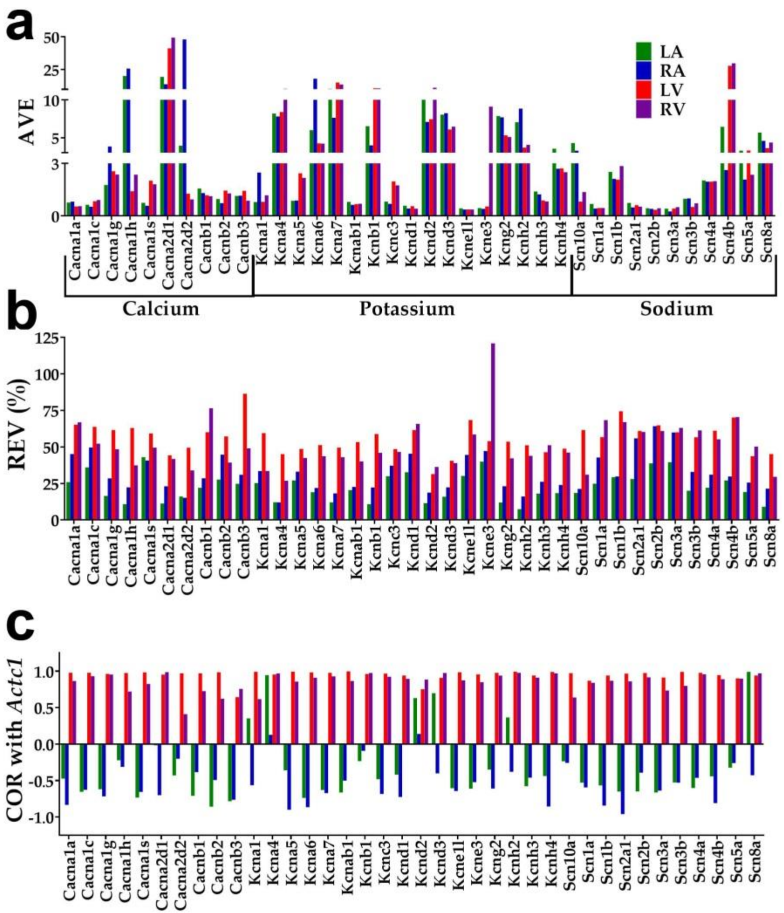
(a) Frontal section through the heart



Meckel-Serres Law "Ontogeny recapitulates philogeny



☆Cardiogenic area begins right in the middle of head pole



Three independent variables.
Actc1 = actin, alpha, cardiac muscle 1

Transcriptomic topology

Genomic fabric : F ≡ (Γ, Π, Ξ, Θ)
Γ = set of composing genes ({Γ} = number of genes),
Π = transcriptomic profile (set of the 95% confidence intervals of the composing genes expression levels)
Ξ = control of transcript abundance
Θ = topology (series of many-gene expression correlation functions)

$$AVE_i^{(chamber)} = \frac{1}{R_i}\sum_{k=1}^{R_i}\mu_{i,k}^{(chamber)} = \frac{1}{R_i}\sum_{k=1}^{R_i}\underbrace{\left(\frac{1}{4}\sum_{j=1}^{4}a_{i,k,j}^{(chamber)}\right)}_{\mu_i^{(chamber)}}$$

$$REV_i^{(chamber)} = \underbrace{\frac{1}{2}\left(\sqrt{\frac{r_i}{\chi^2(r_i;1-\alpha/2)}}+\sqrt{\frac{r_i}{\chi^2(r_i;\alpha/2)}}\right)}_{\text{redundancy correction coefficient}}\underbrace{\sqrt{\frac{1}{R_i}\sum_{k=1}^{R_i}\left(\frac{s_{ik}^{(chamber)}}{\mu_{ik}^{(chamber)}}\right)^2}}_{\text{pooled CV}_i^{(chamber)}}\times 100\%$$

$$\Theta\left(\overrightarrow{g_1},\overrightarrow{g_2},...,\overrightarrow{g_n}\right) = \bigcup_{k=1}^{n} A_k \boxed{F_k\left(\overrightarrow{g_{i1}},...,\overrightarrow{g_{ik}}\Big|_{1\le i1<...<ik\le n}\right)}$$

$$\boxed{F_2\left(\overrightarrow{g_{i1}},\overrightarrow{g_{i2}}\Big|_{1\le i1<i2\le n}\right)} = \left(\overline{g_{i1}}\,r\left(\overrightarrow{g_{i1}},\overrightarrow{g_{i2}}\right)\overline{g_{i2}} - \overline{g_{i1}}\,\overline{g_{i2}}\times\hat{1}\right)_{1\le i1<i2\le n} \quad \textit{pair-wise topology}$$

$r\left(\overrightarrow{g_{i1}},\overrightarrow{g_{i2}}\right)$ = *Pearson correlation coefficient between the sets of the expression levels of genes i1 and i2 within biological replicas*

recurrence relation: $\boxed{F_k\left(\overrightarrow{g_{i1}},...,\overrightarrow{g_{ik}}\Big|_{1\le i1<...<ik\le n}\right)} = \boxed{\overline{g_{ik}}\,r\left(\overrightarrow{g_{ik}},F_k\left(\overrightarrow{g_{i1}},...,\overrightarrow{g_{ik-1}}\Big|_{1\le i1<...<ik-1\le n}\right)\right)}$, *multi dimensional correlations*

$$A_1 \ge A_2 \ge \underbrace{A_3 \ge ... \ge A_n}_{neglect} \ge 0 \;\Rightarrow\; \Theta\left(\overrightarrow{g_1},\overrightarrow{g_2},...,\overrightarrow{g_n}\right) \simeq A_1\underbrace{\left(\widehat{\overline{g_{i1}}\times\hat{1}}\right)_{1\le i1\le n}}_{\text{single-gene topology}} + A_2\underbrace{\left(\overline{g_{i1}}\,r\left(\overrightarrow{g_{i1}},\overrightarrow{g_{i2}}\right)\overline{g_{i2}} - \overline{g_{i1}}\,\overline{g_{i2}}\times\hat{1}\right)_{1\le i1<i2\le n}}_{\text{pair-wise topology}}$$

Differential expression

$$\forall A, B = RA, LA, RV, LV \quad , \quad A \neq B$$

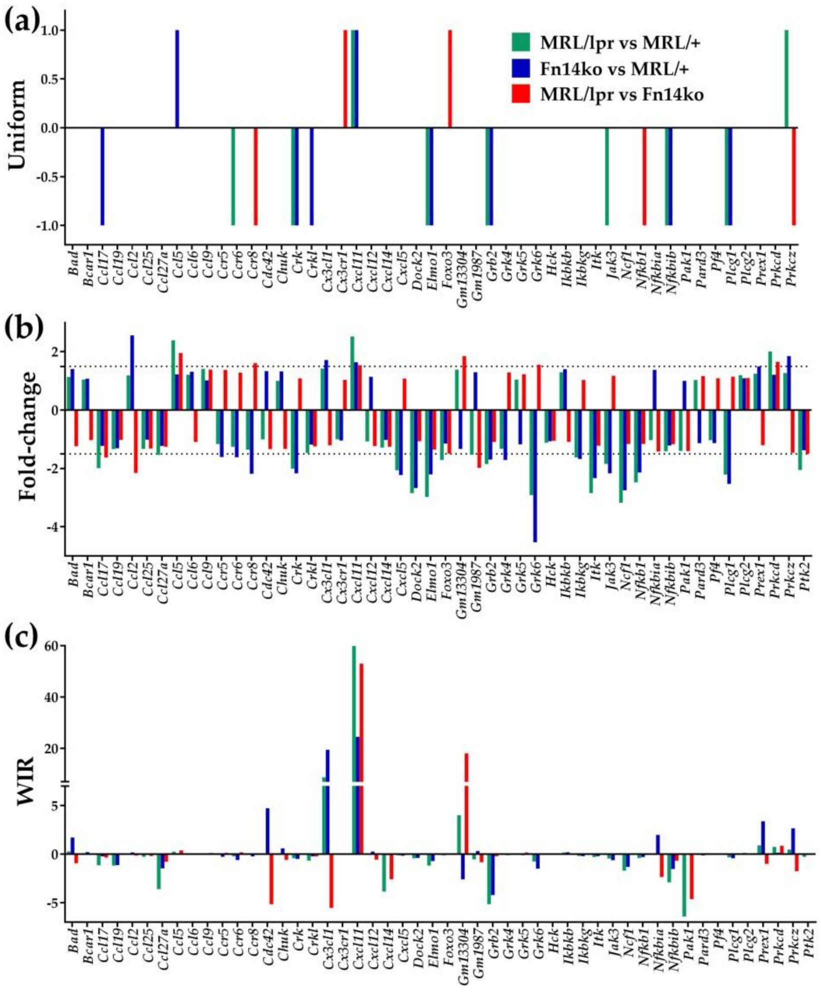
$$x_i^{(A \to B)} = \begin{cases} \sum_{k=1}^{R_i} \mu_{ik}^{(B)} / \sum_{k=1}^{R_i} \mu_{ik}^{(A)} & if \quad \sum_{k=1}^{R_i} \mu_{ik}^{(B)} \geq \sum_{k=1}^{R_i} \mu_{ik}^{(A)} \\ -\sum_{k=1}^{R_i} \mu_{ik}^{(A)} / \sum_{k=1}^{R_i} \mu_{ik}^{(B)} & if \quad \sum_{k=1}^{R_i} \mu_{ik}^{(B)} < \sum_{k=1}^{R_i} \mu_{ik}^{(A)} \end{cases} \quad , \quad \frac{1}{R_i} \sum_{k=1}^{R_i} \mu_{ik}^{(A)} = AVE_i^{(A)}$$

Statistically significant differential expression if:

$$\left| x_i^{(A \to B)} \right| > CUT_i^{(A \to B)} = 1 + \sqrt{2\left(\left(REV_i^{(A)} \right)^2 + \left(REV_i^{(B)} \right)^2 \right)} \quad \wedge \quad p_i^{(A \to B)} < 0.05$$

Weighted Iindividual gene Regulation (WIR):

$$WIR_i^{(A \to B)} \equiv AVE_i^{(A)} \underbrace{\frac{x_i^{(A \to B)}}{\left| x_i^{(A \to B)} \right|}}_{\text{regulation sign}} \underbrace{\left(\left| x_i^{(A \to B)} \right| - 1 \right)}_{\text{absolute net fold-change}} \underbrace{\left(1 - p_i^{(A \to B)} \right)}_{\text{confidence of the regulation}}$$



Transcriptomic chamber specificity

$$WPR_{\Gamma}^{(A\to B)} = \overline{\left(wpr_i^{(A\to B)}\right)_{i\in\Gamma}} \quad , \quad where:$$

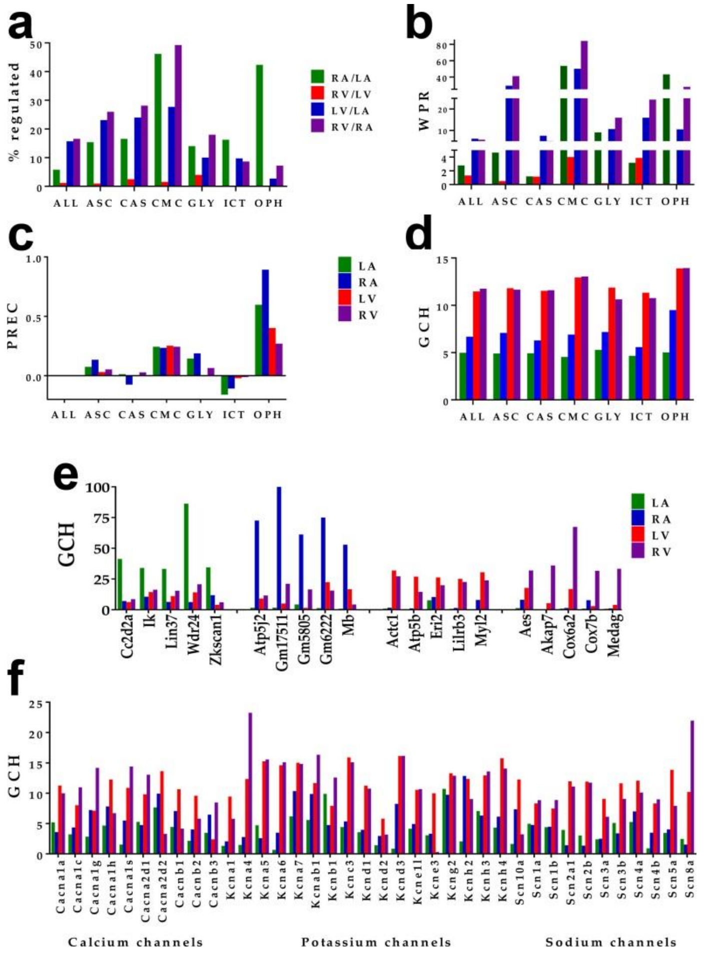
$$wpr_i^{(A\to B)} = \begin{cases} \mu_i^{(A)}\left(\left|x_i^{(A\to B)}\right| - CUT_i^{(A\to B)}\right)\left(1-p_i^{(A\to B)}\right) & if \quad \left|x_i^{(A\to B)}\right| > CUT_i^{(A\to B)} \\ 0 & if \quad \left|x_i^{(A\to B)}\right| \le CUT_i^{(A\to B)} \end{cases}$$

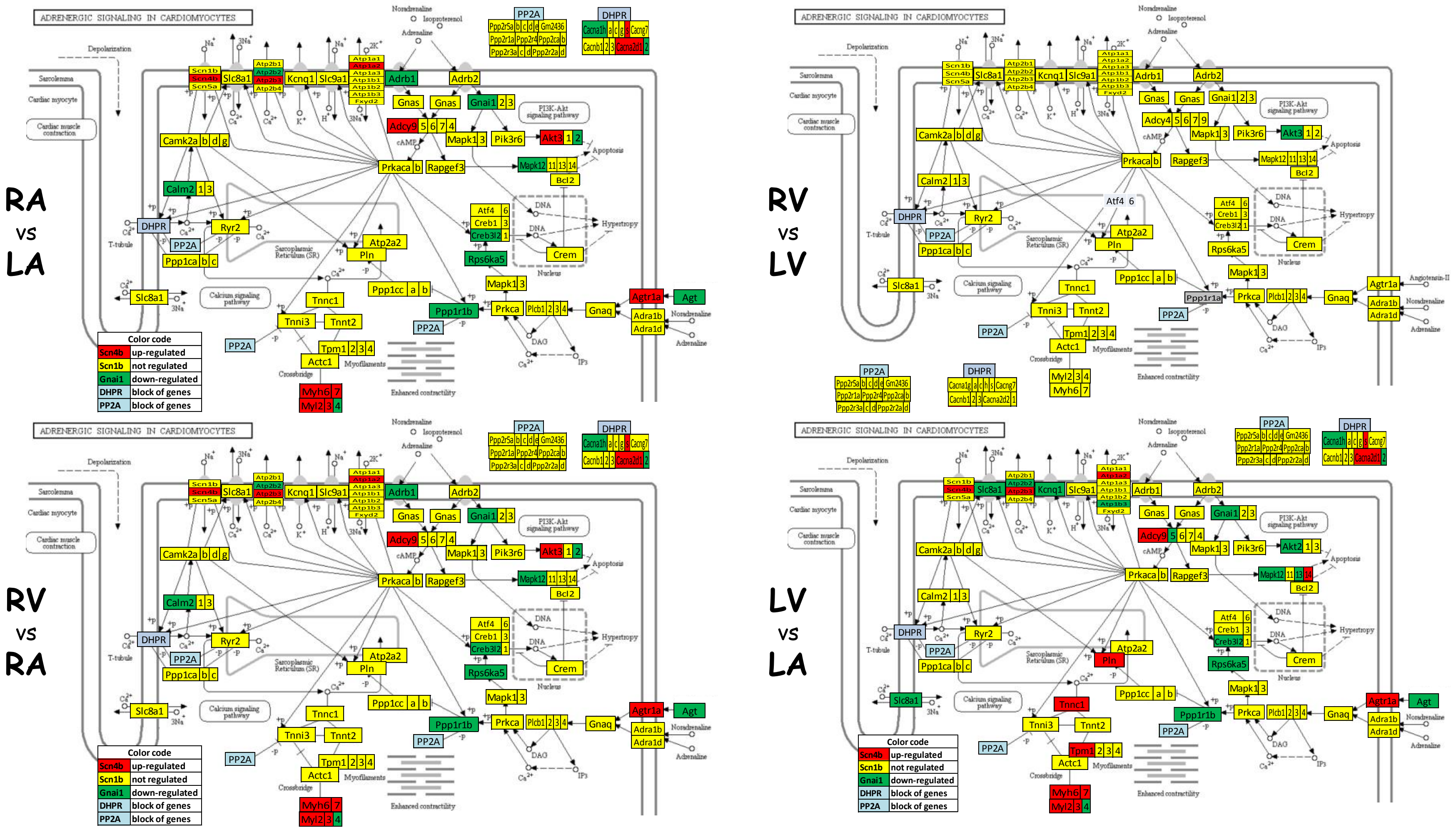
$p_i^{(A\to B)}$ = p-val of the heteroscedastic t-test of $\mu_i^{(B)} = \mu_i^{(A)}$

$$REC_i^{(chamber)} = \frac{\left\langle REV^{(chamber)}\right\rangle\Big|_{ALL}}{REV_i^{(chamber)}} - 1 \quad , \quad PREC_{\Gamma}^{(chamber)} = \frac{\left\langle REV^{(chamber)}\right\rangle\Big|_{ALL}}{\left\langle REV^{(chamber)}\right\rangle\Big|_{\Gamma}} - 1$$

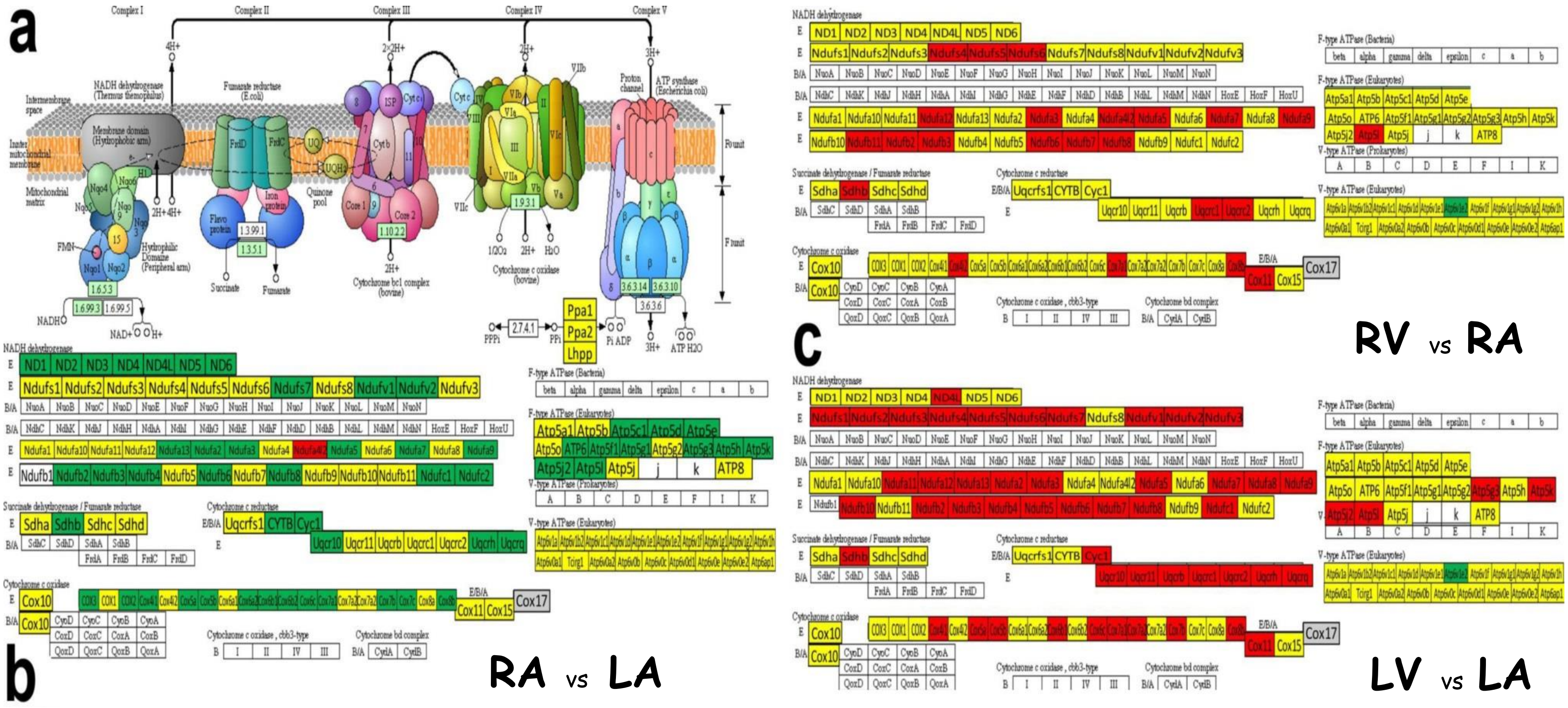
where: $\left\langle REV^{(chamber)}\right\rangle\Big|_{\Gamma/ALL}$ ≡ median of REV over pathway Γ / entire transcriptome

$$GCH_i^{(chamber)} = \left(REC_i^{(chamber)} + 1\right) \times \exp\left(4\overline{\rho_{ij}^2\Big|_{\forall j\ne i}^{(chamber)}}\right)$$

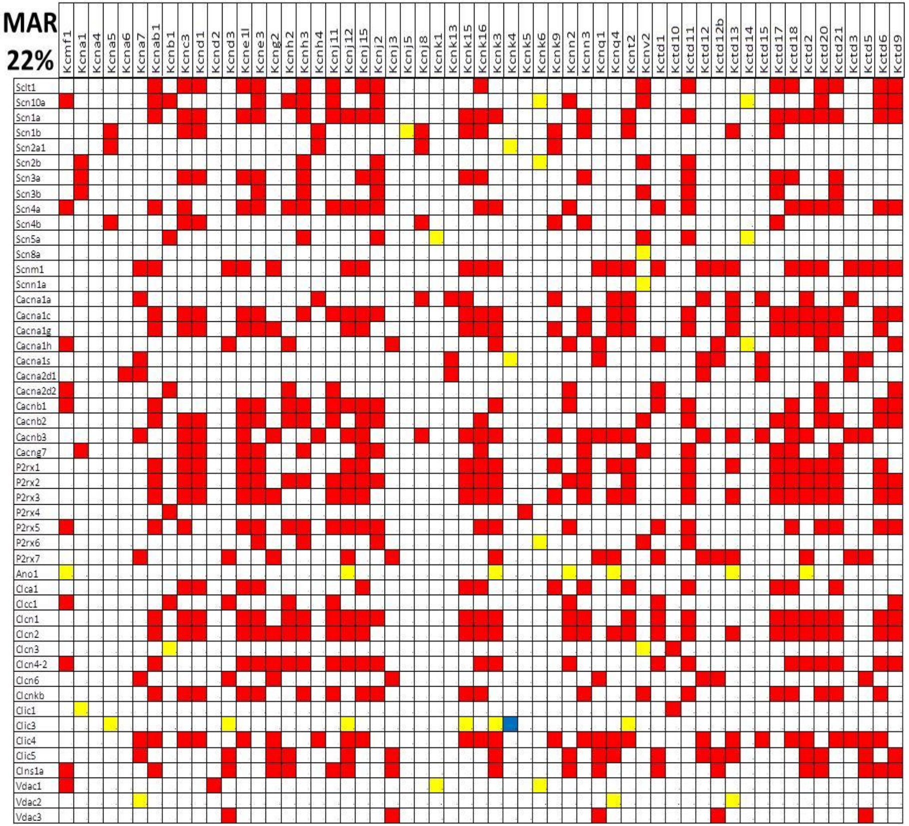


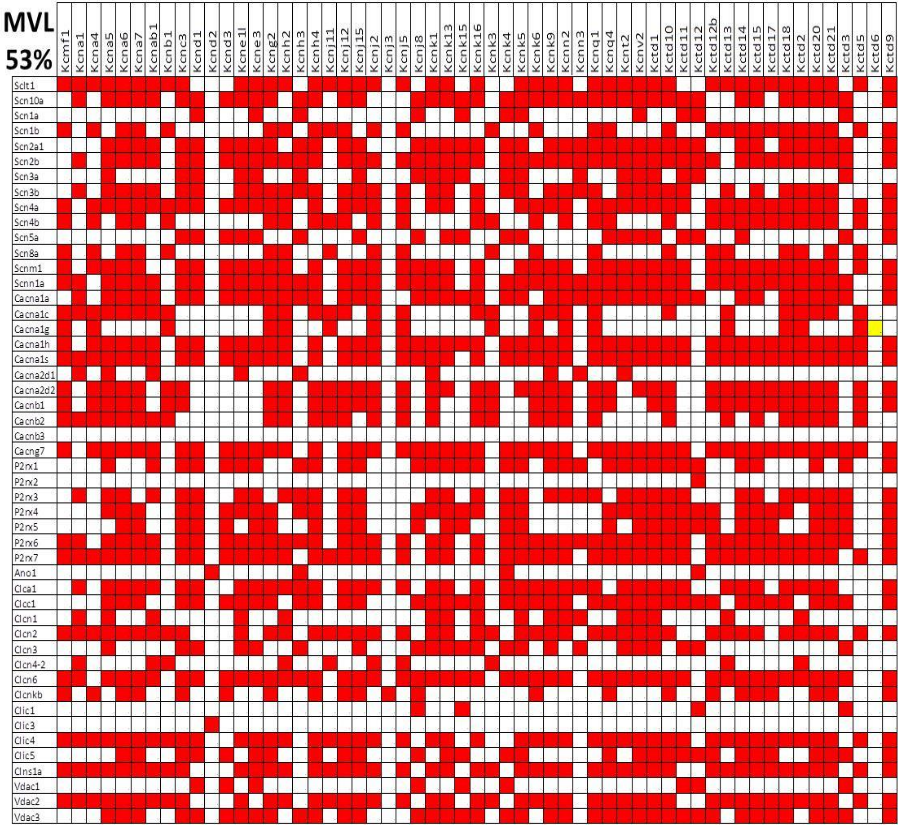

RA vs LA
RV vs LV
RV vs RA
LV vs LA
ADRENERGIC SIGNALING IN CARDIOMYOCYTES
PP2A
DHPR
Scn1b
Scn4b
Scn5a
Slc8a1
Kcnq1
Slc9a1
Adrb1
Adrb2
Gnas
Gnai1
Adcy9
Akt3
Pik3r6
Mapk1
Camk2a
Calm2
Prkaca
Rapgef3
Mapk12
Bcl2
Atf4
Creb1
Creb3l2
Rps6ka5
Crem
Ryr2
Atp2a2
Pln
Ppp1ca
Ppp1cc
Ppp1r1b
Prkca
Plcb1
Gnaq
Agtr1a
Agt
Adra1b
Adra1d
Tnnc1
Tnni3
Tnnt2
Tpm1
Actc1
Myh6
Myl2
Color code
Scn4b up-regulated
Scn1b not regulated
Gnai1 down-regulated
DHPR block of genes
PP2A block of genes

Differential oxidative phosphorylation

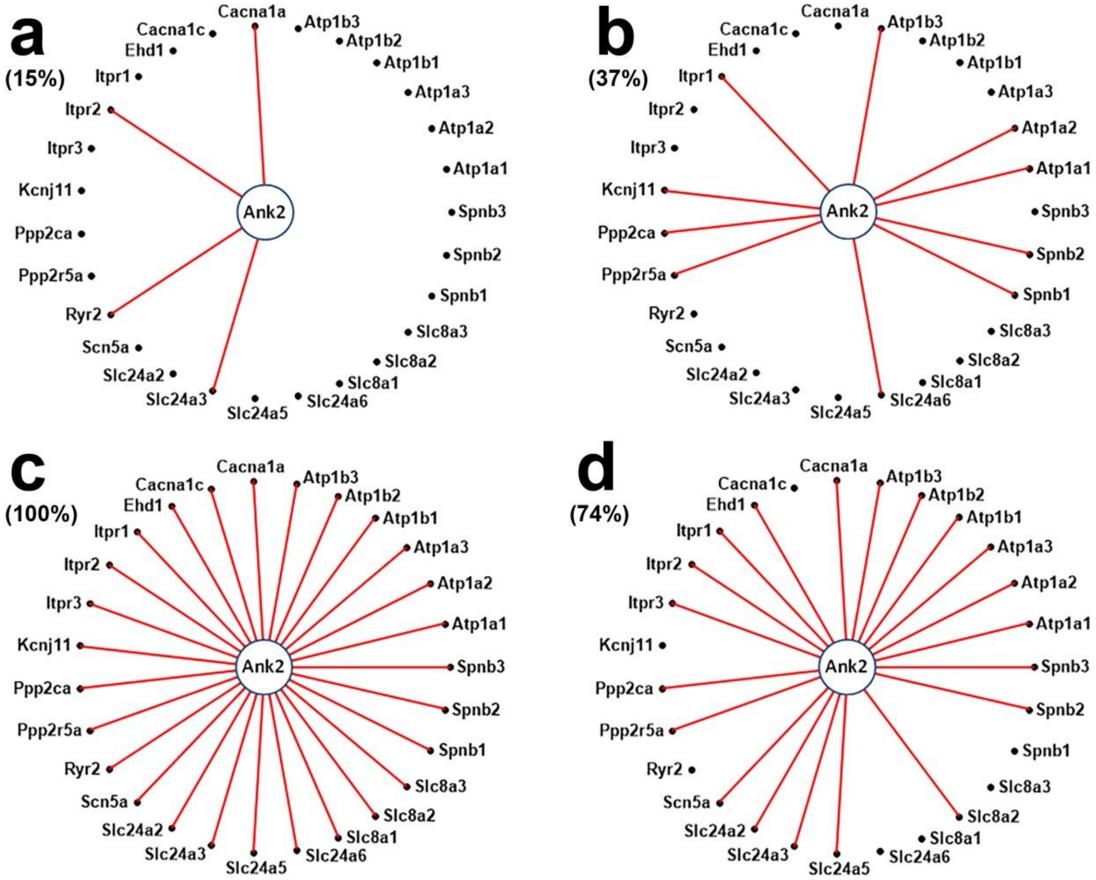


Differential gene networking



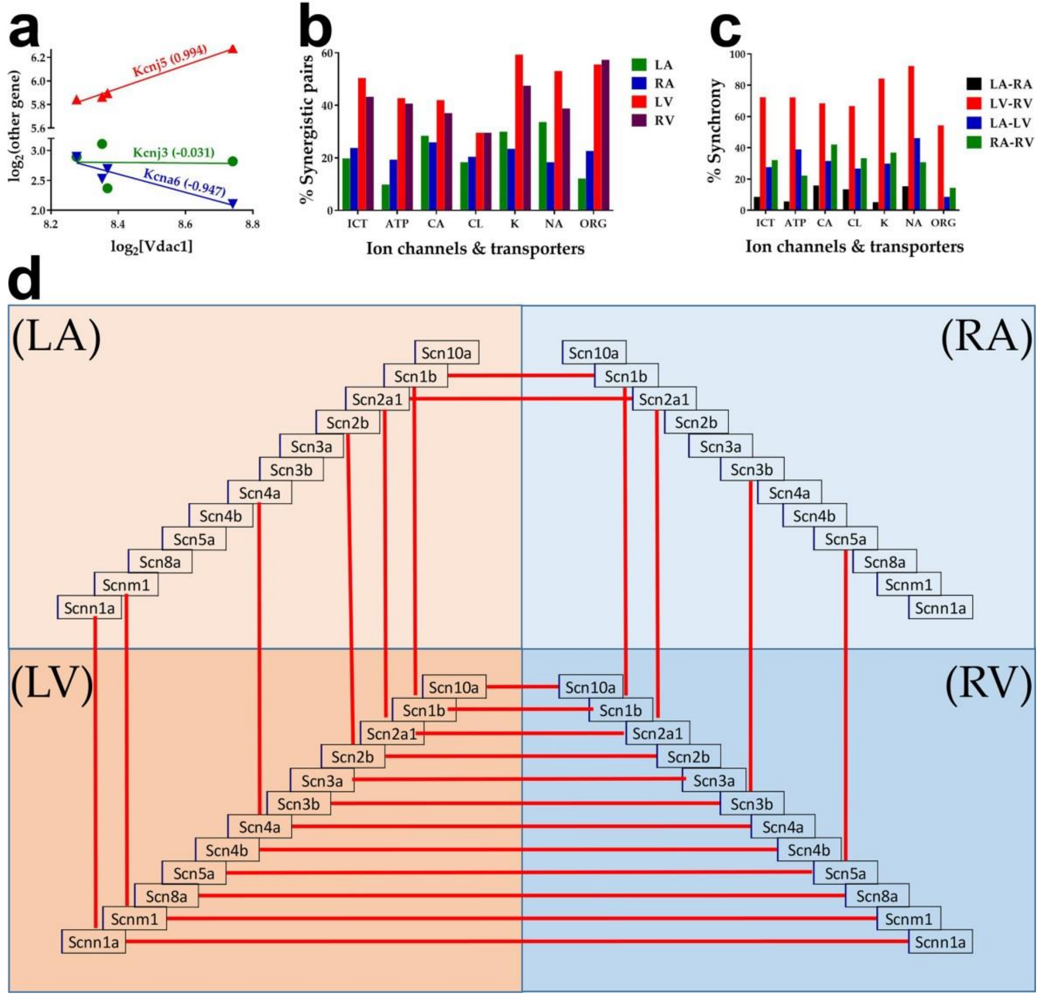


Differential gene networking



Expression coordination of *Ank2* (a major player in cardiac physiology and a hub-bottleneck gene in atrial fibrillation) with its known binding partners in: **a.** left atrium, **b.** right atrium, **c.** left ventricle, **d.** right ventricle.

Expression synchrony of ionic channels and transporters



Sexual dichotomy

Funct Integr Genomics (2010) 10:73–86
DOI 10.1007/s10142-009-0137-8

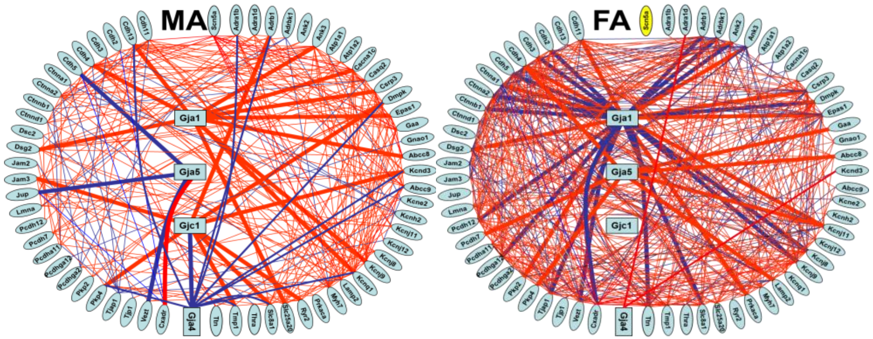
ORIGINAL PAPER

Sex-dependent gene regulatory networks of the heart rhythm

D. A. Iacobas · S. Iacobas · N. Thomas · I

Received: 30 April 2009 / Revised: 19 August 2009 ... hed online: 16 Sep

Abstract Expression level, control, and intercoordination of 66 selected heart rhythm determinant (HRD) genes were compared in atria and ventricles of four male and four female adult mice. We found that genes encoding various adrenergic receptors, ankyrins, ion channels and transporters, connexins, cadherins, plakophilins, and other components of the ... higher expression in atria than ventricles for males and higher expression in ventricles than atria for females. We have ranked the selected genes according to their prominence (new concept) within the HRD gene web defined as extent of expression coordination with the other web genes and stability of expression. Interestingly, the prominence ...



Biochemical and Biophysical Research Communications 406 (2011) 117–122

Contents lists available at ScienceDirect

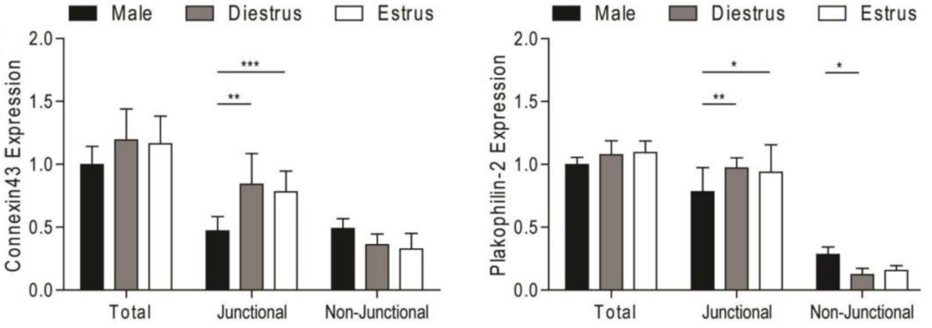
Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Sex differences in expression and subcellular localization of heart rhythm determinant proteins

N.M. Thomas [a,*], J.F. Jasmin [b], M.P. Lisanti [b], D.A. Iacobas [a]

[a] Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, 1300 Morris Park Ave., Kennedy Center, New York, NY 10461, USA
[b] Thomas Jefferson University, Department of Stem Cell Biology and Regenerative Medicine, Bluemle Building, 233 South 10th St., Philadelphia, PA 19107, USA



Gja1 (Cx43), Gja5 (Cx40), Gjc1 (Cx45)

Heart connexins

…able online at www.sciencedirect.com
ScienceDirect
…ophysics and Molecular Biology 94 (2007) 245–264
www.els…

Review

The role of connexins in controlling cell gr… and gene expression

Elissavet Kardami[a,*], Xitong Dang[a], Dumitru A. Iacobas[b], Barbara E. Nick… Madhumathy Jeyaraman[a], Wattamon Srisakuldee[a], Janna Makazan[a], Stephane Tanguy[a], David C. Spray[b]

[a]Institute of Cardiovascular Sciences, University of Manitoba and St. Boniface Research Centre, Winnipeg, Man., Canada
[b]Department of Neuroscience, Albert Einstein College of Medicine, NY 10461, USA

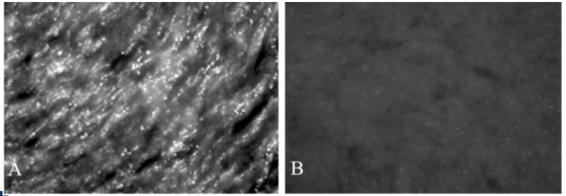
Available online 16 March…

Physiol Genomics 20: 211–223, 2005.
First published December 7, 2004; doi:10.1152/physiolgenomics.00229.2003.

Genes controlling multiple functional pathways are transcriptionally regulated in connexin43 null mouse heart

Dumitru A. Iacobas,[1] Sanda Iacobas,[1] W. E. I. Li,[1] Georg Zoidl,[3] Rolf Dermietzel,[3] an…
Departments of [1]Neuroscience and [2]Cardiology, Albert Einstein College of Medicine, Bronx, New Yo…
…anatomy and Molecular Brain Research, Ruhr-University, Bochum, Germa…

…accepted in final form 30 November 2004



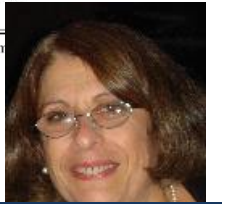
Gap Junctions and Chagas Disease

Daniel Adesse,[*,†] **Regina Coeli Goldenberg,** **Fabio S. Fortes,**[‡] **Jasmin,**[*,§] **Dumitru A. Iacobas,**[§] **Sanda Iacobas,**[§] **Antonio Carlos Campos de Carvalho,**[*,§] **Maria de Narareth Meirelles,**[†] **Huan Huang,**[¶] **Milena B. Soares,**[||] **Herbert B. Tanowitz,**[¶] **Luciana Ribeiro Garzoni,**[†] and **David C. Spray**[§]

ELSEVIER
Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neurochemistry International 45 (2004) 243–250
NEUROCHEMISTRY International
www.elsevier.com…

Gene expression alterations in connexin null mice extend beyond the gap junction

Dumitru A. Iacobas, Eliana Scemes, David C. Spray*

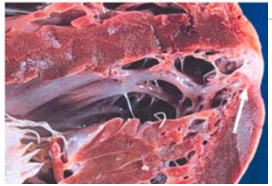


Chagas cardiomyopathy

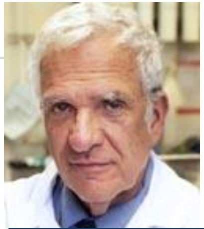
Parasitol Res (2003) 91: 187–196
DOI 10.1007/s00436-003-0937-z

ORIGINAL PAPER

Hipertrofia



Shankar Mukherjee · Thomas J
David C. Spray · Dumitru A. Ia
Richard N. Kitsis · Murray Wit
Philip E. Scherer · Aihao Ding ·



Bronx, NY

Microarray analysis of changes in gene expression model of chronic chagasic cardiomyopathy

Gene Expression Changes Associated with Myocarditis and Fibrosis in Hearts of Mice with Chronic Chagasic Cardiomyopathy

Milena Botelho Pereira Soares,[1,2] Ricardo Santana de Lima,[1] Leonardo Lima Rocha,[1] Juliana Fraga Vasc
Silvia Regina Rogatto,[3,4] Ricardo Ribeiro dos Santos,[1,2] Sanda Iacobas,[7] Regina Coeli Goldenberg,[5]
Dumitru Andrei Iacobas,[7] Herbert Bernard Tanowitz,[8,9] Antonio Carlos Campos de Carvalho,[5,6]
and David Conover Spray[7,8]

Chagas I, Brazil

Reversion of gene expression alterations in hearts of mice with chronic chagasic cardiomyopathy after transplantation of bone marrow cells

Milena B.P. Soares,[1,2,*] Ricardo S. Lima,[3] Bruno S.F. Souza,[1,2] Juliana F. Vasconcelos,[1,2] Leonardo L. Rocha,[1]
Ricardo Ribeiro dos Santos,[1,2] Sanda Iacobas,[4] Regina C. Goldenberg,[5] Michael P. Lisanti,[9] Dumitru A. Iacobas,[4]
Herbert B. Tanowitz,[6,7,*] David C. Spray[4,6] and Antonio C. Campos de Carvalho[4,5,8]

ELSEVIER

Institut Pasteur

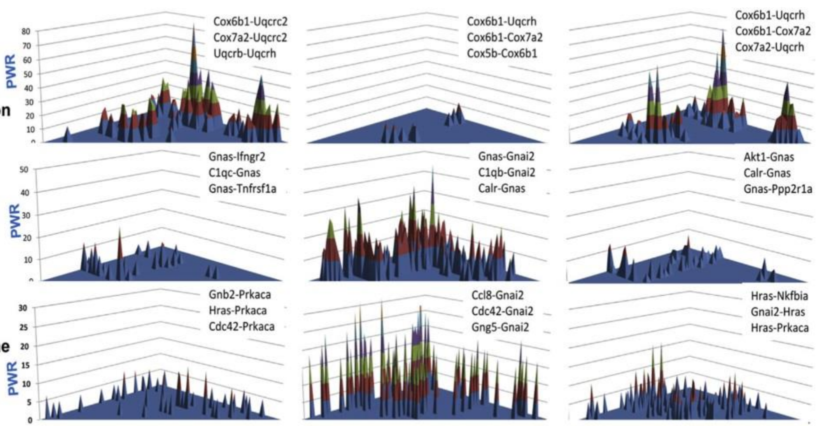
Microbes and Infection xx (2017) 1–11

Chagas I, Brazil

Original article

Functional genomic fabrics are remodeled in a mouse model of Chagasic cardiomyopathy and restored following cell therapy

Dumitru A. Iacobas [a,b,*], Sanda Iacobas [a], Herbert B. Tanowitz [c,d], Antonio Campos de Carvalho [b,e],
David C. Spray [b,c]



ELSEVIER

INSTITUT PASTEUR

Microbes and Infection 11 (2009) 1140–1149

www.elsevier.com/locate/micinf

Original article

Transcriptomic alterations in *Trypanosoma cruzi*-infected cardiac myocytes

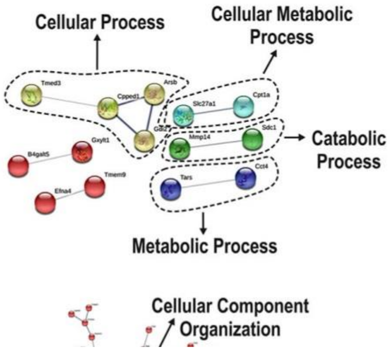
Regina Coeli dos Santos Goldenberg [a,b,c], Dumitru A. Iacobas [b], Sanda
Leonardo Lima Rocha [a,1], Fabio da Silva de Azevedo Fortes [a,b,c], Leandr
Fnu Nagajyothi [a], Antonio Carlos Campos de Carvalho [b,c], Herbert B. T
David C. Spray [b,*]

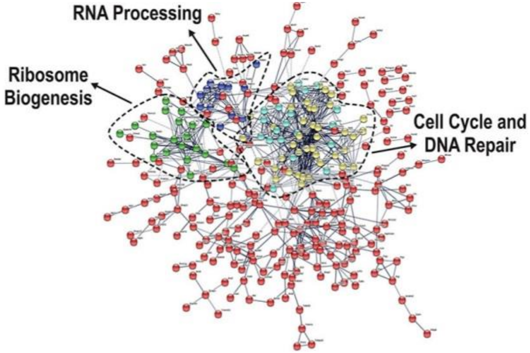
UFRJ, Brazil

Am. J. Trop. Med. Hyg., 82(5), 2010, pp. 846–854
doi:10.4269/ajtmh.2010.09-0399

Transcriptomic Signatures of Alterations in a Myoblast Cell Line Infected with Four Distinct Strains of *Trypanosoma cruzi*

Daniel Adesse,* Dumitru A. Iacobas, Sanda Iacobas, Luciana R. Garzoni, Maria de Nazareth Meirelles, Herbert B. Tanowitz, and David C. Spray



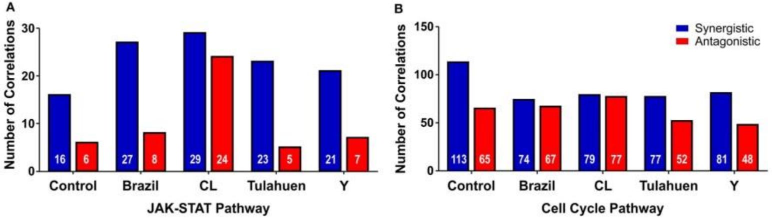


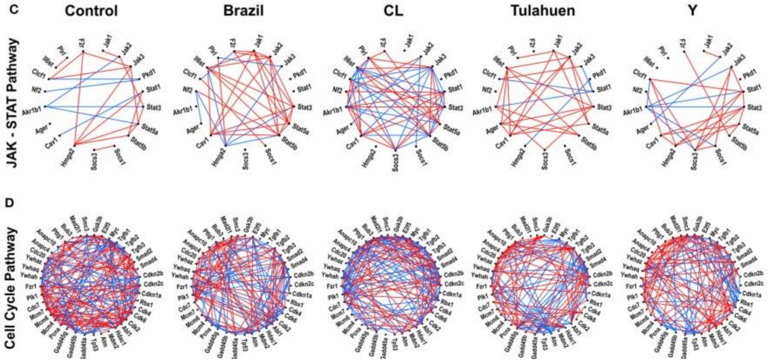
frontiers in Cellular and Infection Microbiology
ORIGINAL RESEARCH
published: 17 June 2020
doi: 10.3389/fcimb.2020.00255

Oswaldo Cruz, BRA

Trypanosoma cruzi Promotes Transcriptomic Remodeling of the JAK/STAT Signaling and Cell Cycle Pathways in Myoblasts

Lindice M. Nisimura [1], Laura L. Coelho [2], Tatiana G. de Melo [3], Paloma de Carvalho Vieira [4], Pedro H. Victorino [5], Luciana R. Garzoni [2], David C. Spray [6], Dumitru A. Iacobas [7], Sanda Iacobas [6], Herbert B. Tanowitz [6†] and Daniel Adesse [4*]





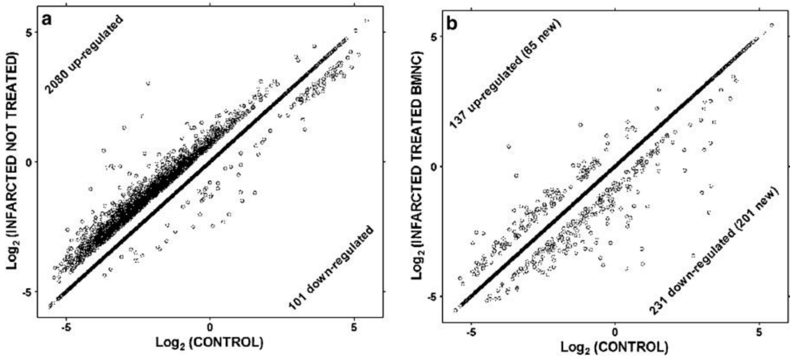
Cardiac ischemia

Stem Cell Rev and Rep (2012) 8:251–261
DOI 10.1007/s12015-011-9282-2

Functional and Transcriptomic Recovery of Infarcted Mouse Myocardium Treated with Bone Marrow Mononuclear Cells

Stephan Lachtermacher · Bruno L. B. Esporcatte · Fábio da Silva de Azevedo Fortes · Nazareth Novaes Rocha · Fabrício Montalvão · Patricia C. Costa · Luciano Belem · Arnaldo Rabischoffisky · Hugo C. C. Faria Neto · Rita Vasconcellos · Dumitru A. Iacobas · Sanda Iacobas · David C. Spray · Neil M. Thomas · Regina C. S. Goldenberg · Antonio C. Campos de Carvalho

Stem Cell Rev and Rep (2012) 8:251–261



Permanent myocardial infarcts produced by ligation of the descending branch of the left coronary artery
BMNC was directly injected using a 10 µl syringe into 3 different regions (30 µl total) at the borders of cardiac scar tissue 10 days after experimental infarction.

Braz J Med Biol Res, March 2010, Volume 43(4) 377-389

Cardiac gene expression and systemic cytokine profile are complementary in a murine model of post-ischemic heart failure

S. Lachtermacher, B.L.B. Esporcatte, F. Montalvão, P.C. Costa, D.C. Rodrigues, L. Belem, A. Rabischoffisky, H.C.C. Faria Neto, R. Vasconcellos, S. Iacobas, D.A. Iacobas, H.F.R. Dohmann, D.C. Spray, R.C.S. Goldenberg and A.C. Campos-de-Carvalho

Constant and Intermittent Hipoxia

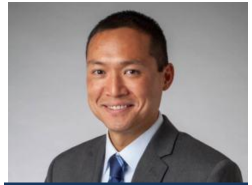
Physiol Genomics 22: 292–307, 2005.
First published May 31, 2005; 10.1152/physiolgenomics.00217.2004.

Gene expression and phenotypic characterization of mouse hear
after chronic constant or intermittent hypoxia

**Chenhao Fan,[1] Dumitru A. Iacobas,[2] Dan Zhou,[1] Qiaofang Chen,[1]
James K. Lai,[3] Orit Gavrialov,[1] and Gabriel G. Haddad[1,2]**

*Departments of [1]Pediatrics and [2]Neuroscience, Albert Einstein College of Medicine, Bronx, New Y
and [3]Department of Pharmaceutical Sciences, Idaho State University College of Pharmacy, Pocate*

mber 2004; accepted in final form 20 May 2005



Integrated transcriptomic response to cardiac chronic hypoxia: translation regulators and response to stress in cell survival

**Dumitru A. Iacobas · Chenhao Fan · Sanda Iacobas ·
Gabriel G. Haddad**

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

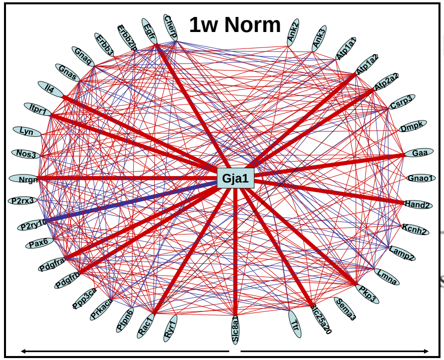
journal homepage: www.elsevier.com/locate/ybbrc

Heart rhythm genomic fabric in hypoxia

Dumitru A. Iacobas [a,*], Sanda Iacobas [a], Gabriel G. Haddad [b]

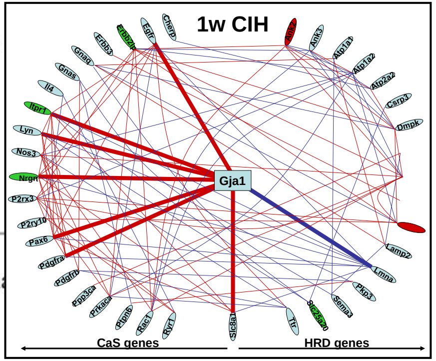
Effects of Chronic Intermittent Hypoxia on Cardiac Rhythm Transcriptomic Networks

2



Iacobas

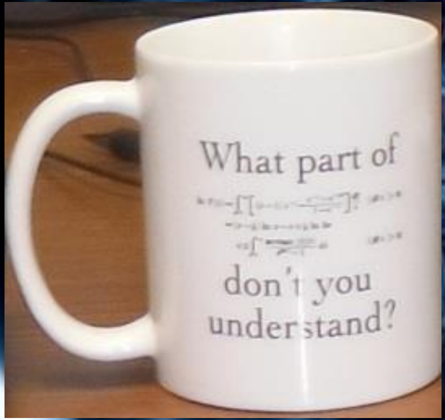
studies ana



Transcriptomic differences

- LA vs LV > RA vs RV > LA vs RA > LV vs RV in gene expression level, control and coordination
- Male vs female (changes during the estrogen cycle)
- Young vs adult
- Normoxic vs hypoxic (constant or intermittent) or ischemia
- Healthy vs Chagasic cardiomyopathy
- Wildtype vs connexin null/knockdown

Thank you!



Dumitru Andrei Iacobas, PhD
PVAMU CCSB Personalized Genomics Laboratory
NELEN Rm.369, tel 936-261-9926, daiacobas@pvamu.edu