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Data Article

Dataset for clinical parameters and disease transcriptome networks associated with exposure to citalopram in zebrafish (*Danio rerio*) larvae

Kira J. Kazi[a], Cole D. English[a], Emma Ivantsova[a], Christopher L. Souders II[a], Christopher J. Martyniuk[a,b,*]

[a] *Center for Environmental and Human Toxicology, Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32611, USA*
[b] *UF Genetics Institute, Interdisciplinary Program in Biomedical Sciences Neuroscience, USA*

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ABSTRACT

Citalopram, a selective serotonin reuptake inhibitor (SSRI), is often detected in aquatic ecosystems. In this investigation, developing zebrafish were continuously exposed to one nominal concentration of either 0, 10, or 1000 µg/L citalopram for 7 days. Ribonucleic acids were then extracted from zebrafish for RNA-sequencing using the NovoSeq 6000 (Illumina). Clean reads were obtained following the removal of both the adapter and poly-N sequences. Alignment and differential gene expression analysis was conducted using programs HISAT2 and StringTie assembler. Data were converted to FPKM to quantify differentially expressed transcripts. Significant clinical subnetworks enriched following citalopram exposure included sympathetic nerve activity, blood pressure, vascular tone, and arterial pressure. Regulated transcripts were related to diseases such as mechanical hyperalgesia, pain, inflammatory pain, obstructive hypertrophic cardiomyopathy, fatigue, Diamond-Blackfan anemia, and hypertrophic cardiomyopathy. Following exposure to 10 µg/L citalopram, several transcripts were linked to brain dysfunction like prostaglandin-endoperoxide synthase 2, microtubule associated protein tau, cathepsin B, and dystrophin. Genes

* Corresponding author.
E-mail address: cmartyn@ufl.edu (C.J. Martyniuk).

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related to cardiac dysfunction were altered in zebrafish following exposure to 1000 µg/L citalopram. Using literature and databases that describe gene interactions, molecular networks (clinical and disease networks) were constructed to understand effects of citalopram.

Specifications Table

Subject	Biological Sciences.
Specific subject area	SSRI, aquatic toxicology, animal and human disease
Type of data	Table, Figure, Supplemental File. Raw, Analyzed, and Filtered.
Data collection	Approximately 15-20 zebrafish embryos were placed into 10 mL volume of embryo rearing media (ERM). Zebrafish eggs were exposed at 6 hours post-fertilization to one concentration of citalopram. Exposure groups included ERM, 10 µg/L, and 1000 µg/L citalopram (n=4 beakers/treatment). Water with the chemical was changed every day. On day 7 post fertilization, fish were euthanized and aliquots snap-frozen in liquid nitrogen prior to RNA-sequencing.
Data source location	Institution: University of Florida Aquatic Toxicology Laboratory City/Town/Region: Gainesville, Florida Country: USA
Data accessibility	In repository Repository name: NCBI Gene Expression Omnibus Data identification number: GSE217875 Direct URL to data: https://www.ncbi.nlm.nih.gov/geo/download/?acc=GSE217875
Related research article	Kira J. Kazi, Cole D. English, Emma Ivantsova, Christopher L. Souders II, Christopher J. Martyniuk. Transcriptome networks and physiology related to cardiac function and motor activity are perturbed in larval zebrafish (*Danio rerio*) following exposure to the antidepressant citalopram. In review.

1. Value of the Data

- Data can be applied as clinical and disease biomarkers of SSRI exposure in aquatic species.
- Data can be used to better understand the link between animal/human disease and chemical exposures.
- Society benefits as limits for safe drinking water can be determined using toxicity data.
- Data can be used to inform researchers on how transcriptional networks are regulated in zebrafish.

2. Background

Environmental pollutants can perturb molecular signaling cascades in aquatic species, leading to adverse outcomes and altered phenotypes. It is important to understand how chemicals regulate the transcriptome to better understand the potential impact of exposures on organismal health. These early molecular changes can be used to predict downstream consequences. This motivated us to determine the molecular alterations in fish following exposure to the antidepressant citalopram. This research article adds value to the original dataset by presenting additional gene networks perturbed by citalopram in larval zebrafish that are related to clinical parameters and diseases. Such data compliments the dataset in the original manuscript, which presents gene sets and subnetworks related to biological processes and metabolic pathways. Together, the datasets provide an overarching view of citalopram-mediated effects in zebrafish.

3. Data Description

Citalopram, a selective serotonin reuptake inhibitor (SSRI), is used to treat depression. The rising prevalence of depression in the past decade has increased the number of people being treated with antidepressants, including SSRIs [3]. Consequently, pharmaceutical contaminants from treatment facilities can enter various water sources and impact the health of aquatic organisms. In this study, we treated larval zebrafish (AB x Tu strain) to either 0, 10, or 1000 µg/L citalopram for 7 days. Transcriptomics analysis was conducted in whole zebrafish larvae using an RNA-seq approach. Expression data was further explored using Pathway Studio (v12) (Elsevier) to uncover clinical and disease-associated networks to better quantify the effects of citalopram in non-target species following exposure to the drug. Additional morphometric and physiological data that accompany this Data in Brief article are presented in Kazi et al. (under review).

For the sequencing, 12 libraires underwent processing for Illumina NovoSeq 6000 following methods presented in [1,2,4]. The "Name + Alias" feature in Pathway Studio (v12) was used to map genes to human homologs. SNEA was performed in the program to identify clinical and disease biomarkers associated with citalopram exposure. The p-value for the enrichment of molecular pathways was set at $p < 0.05$.

Table 1 shows the top clinical parameter networks in zebrafish treated with citalopram (10 or 1000 µg/L) ($P < 0.001$). In the table, the pathway or gene set seed, total number of neighbours or genes predicted to be in the network, number of neighbours or genes measured in the network, the median fold change, and the p-value are presented. Table 1 shows the most significant clinical subnetworks enriched following citalopram exposure to one of two concentrations. In the 10 µg/L exposure group, subnetworks included sympathetic nerve activity and firing rate (downregulated), while gene networks associated with blood pressure, vascular tone, and arterial pressure were upregulated. In the 1000 µg/L treatment, subnetworks of vascular resistance, risk of mortality, pulse rate, and villus height were up regulated in larval fish treated with the highest concentration of citalopram (Supplemental Data).

Table 2 lists the top networks of disease in zebrafish treated with either the low (10 µg/L) or high (1000 µg/L) citalopram dose ($P < 0.001$). In the table, the pathway or gene set seed, total number of neighbours or genes predicted to be in the network, number of neighbours or genes measured in the network, the median fold change, the p-value, and the activation score

Table 1
Top 10 subnetworks for clinical parameters enriched following citalopram exposure to one of two concentrations.

Treatment	Gene Set Seed	Total # of Neighbors	# of Measured Neighbors	Median change	p-value
10 µg/L	sympathetic nerve activity	362	266	-1.01674629	1.58395E-10
	arterial pressure	366	250	1.004735554	5.58999E-10
	pain threshold	252	182	1.02033486	1.05818E-08
	therapeutic efficacy	1236	881	1.02783519	1.18217E-08
	vascular resistance	221	157	1.009710712	2.28009E-08
	cardiac output	256	178	-1.033356806	2.53984E-08
	firing rate	423	329	-1.041211966	2.84662E-08
	blood pressure	1267	860	1.014632171	2.94639E-08
	evoked potential	261	198	1.009710712	3.73448E-08
	vascular tone	466	365	1.027480333	4.7151E-08
1000 µg/L	vascular resistance	221	156	1.022015227	6.6878E-08
	risk of mortality	250	167	1.070997857	3.61808E-06
	pulse rate	70	50	1.204788126	5.72733E-06
	villus height	63	44	1.186869487	7.3238E-06
	sleep efficiency	24	19	-1.195902517	1.07673E-05
	arterial pressure	370	253	1.014720427	1.27123E-05
	lymphocyte response	169	97	1.099218553	1.52336E-05
	long-term graft survival	58	36	1.102501723	1.77535E-05
	body weight changes	168	122	1.025096625	2.03042E-05
	lean body mass	116	88	1.111071221	2.14483E-05

Table 2
Top disease networks in larval fish treated with citalopram (10 or 1000 µg/L) ($P < 0.001$). The table presents the gene set seed, total number of neighbors in the network, number of measured neighbors, median fold change, p-value, and activation score. Transcriptome data are in NCBI GEO Accession (GSE217875).

Dose	Gene Set Seed	Total # of Neighbors	# of Measured Neighbors	Median change	p-value	Activation Score
10 µg/L	mechanical hyperalgesia	325	236	1.014337	1.28E-12	0.92582
	pain	1182	827	1.007003	1.34E-12	0.436436
	dextran sodium sulfate-induced colitis	749	510	1.065025	2.41E-11	1.60591
	skin disease	490	310	1.078366	3.54E-11	2.309401
	psoriasis	828	500	1.066476	4.76E-11	2.213594
	inflammatory pain	441	317	1.0217	5.8E-11	-0.64889
	dermatitis	700	426	1.078894	7.25E-11	0.884652
	respiratory hypersensitivity	646	420	1.065609	1.84E-10	1.637846
	atopic dermatitis	430	245	1.082087	3.32E-10	2.523573
	neuropathic pain	989	664	1.028579	1.23E-09	1.016001
1000 µg/L	obstructive hypertrophic cardiomyopathy	71	61	-1.07107	7.39E-07	0.377964
	allergic asthma	404	251	1.123921	1.04E-06	-1.37199
	fatigue	252	183	-1.04969	1.45E-06	-0.87039
	Diamond-Blackfan anemia	37	30	1.282103	1.88E-06	-0.44721
	atopic dermatitis	430	245	1.078101	1.94E-06	3.544745
	hypertrophic cardiomyopathy	247	200	1.014932	2.67E-06	-1.80739
	cardiovascular disease	1242	837	1.042153	2.87E-06	0.301511
	edema	856	598	1.075588	3.19E-06	0.808122
	polycystic ovary syndrome	409	275	1.056427	3.56E-06	1.788854
	inflammatory infiltrate	217	126	1.130889	5.05E-06	1.133893

(predicted downstream direction of the pathway) are presented. Zebrafish exposed to 10 µg/L citalopram had disruptions in transcripts related to mechanical hyperalgesia, pain, inflammatory pain, and respiratory hypersensitivity while zebrafish in the 1000 µg/L treatment had altered disease networks that included obstructive hypertrophic cardiomyopathy, allergic asthma, fatigue, Diamond-Blackfan anemia, atopic dermatitis, and hypertrophic cardiomyopathy. Overall, there were 999 disease networks predicted to be regulated by citalopram ($p<0.05$). There were 509 gene networks for disease that were shared in fish treated with 10 µg/L or 1000 µg/L citalopram, equaling a 34.2% overlap (Fig. 1).

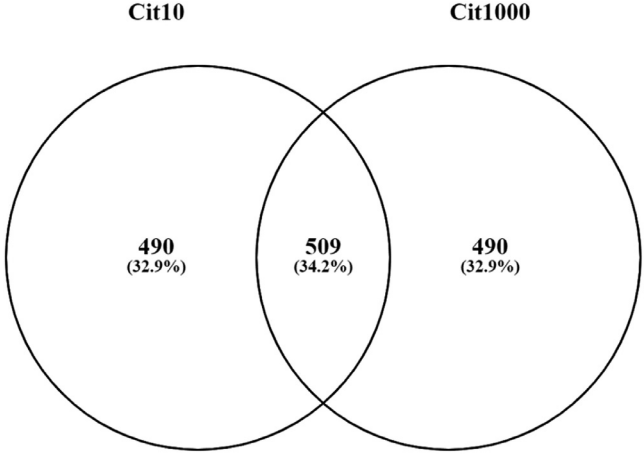

Fig. 1. Overlap in disease networks with 10 µg/L (Cit10) and 1000 µg/L (Cit 1000) citalopram.

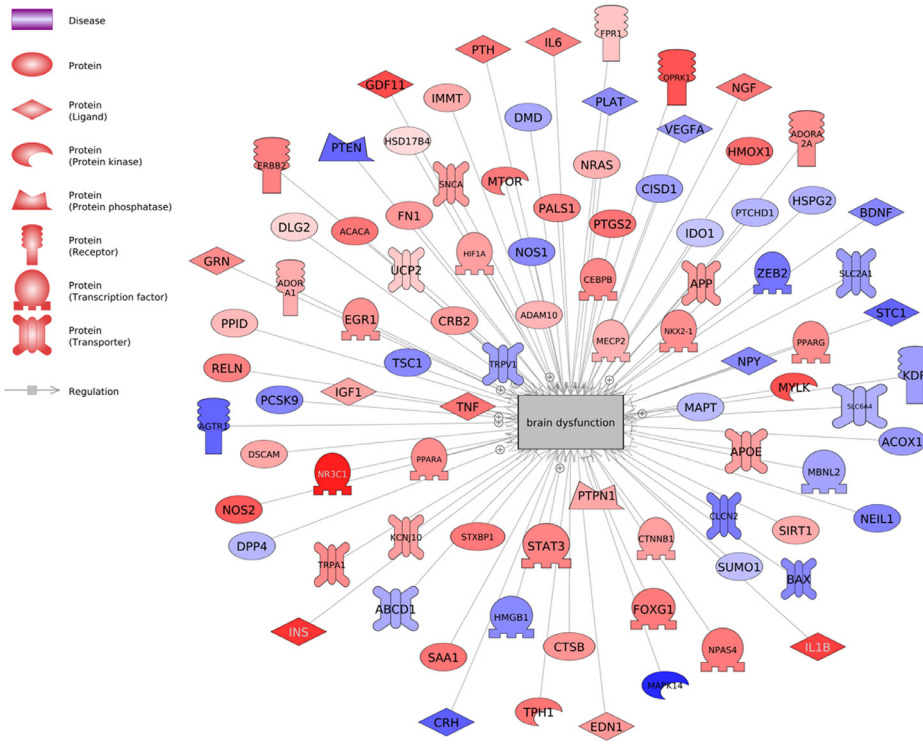

Fig. 2. A gene network in fish for brain dysfunction following exposure to 10 µg/L citalopram. If a transcript is colored red, then the gene is up-regulated relative to the control. If the transcript is colored green, then the gene is down-regulated relative to the control. Such networks indicate how genes may interact in the larval fish. Abbreviations of genes are described in Supplemental Data.

In Fig. 2, genes related to brain dysfunction are presented following exposure to 10 µg/L citalopram. Several transcripts were link to brain dysfunction and these genes included prostaglandin-endoperoxide synthase 2, microtubule associated protein tau, cathepsin B, and dystrophin among others. Similarly, genes related to cardiac dysfunction following exposure to 1000 µg/L citalopram are presented in Fig. 3. In addition, transcripts related to cardiac dysfunction were regulated in the dataset and included lysyl oxidase, myosin heavy chain 6, catalase, and SET nuclear proto-oncogene among others. Using literature and databases that describe gene interactions, molecular networks (clinical and disease networks) were constructed to understand the effects of citalopram.

4. Experimental Design, Materials and Methods

Zebrafish toxicity assays followed recommendations found in the OECD guideline 236 [5] with some modification. Fertilized zebrafish embryos (n=15-20) were placed into 25 mL beakers containing 10 mL sterile ERM. Fish were distributed in a randomized and staggered fashion among beakers. Fish husbandry has been described previously by us [2]. Treatment groups included ERM (negative control), 10 µg/L, and 1000 µg/L citalopram (n=4 beakers/treatment). Survival rates and the presence of deformity were recorded over 7-days. At the termination of the experiment, zebrafish larvae were euthanized in buffered MS-222 and rapidly frozen in liquid nitrogen. Samples were kept at -80°C until the RNA was processed for RNA-seq.

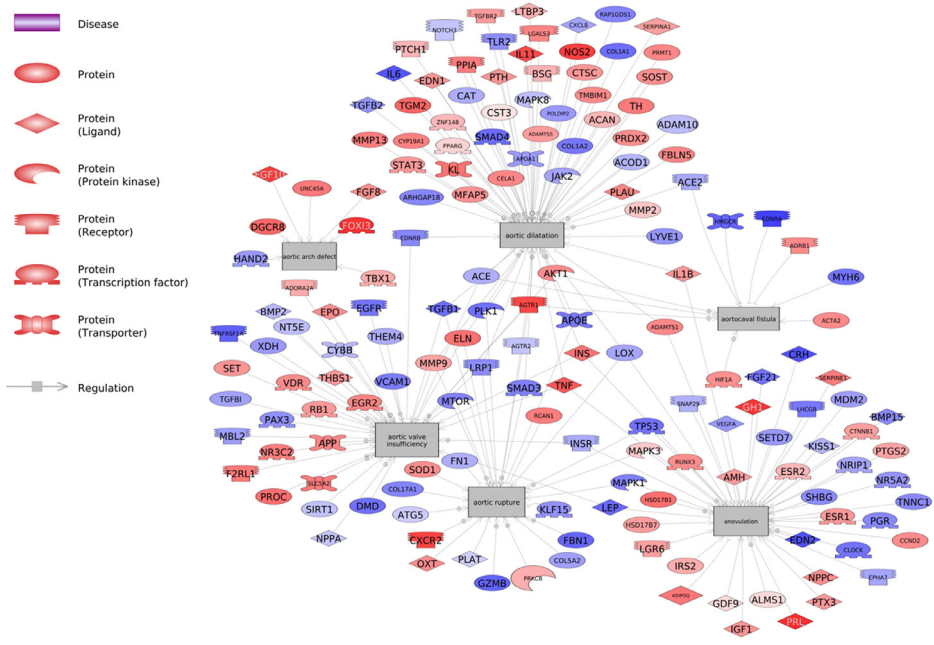

Fig. 3. A gene network in fish for cardiac dysfunction following exposure to 1000 µg/L citalopram. If a transcript is colored red, then the gene is up-regulated relative to the control. If the transcript is colored green, then the gene is down-regulated relative to the control. Such networks indicate how genes may interact in the larval fish. Abbreviations of genes are described in Supplemental Data.

RNA for library preparation was extracted from zebrafish larvae and quality was evaluated as that outlined in [1,2]. A total of 12 RNA samples were prepared for RNA-seq library construction (RNA Integrity Numbers >7). Experimental groups included fish from the ERM controls (n=4), 10 µg/L citalopram (n=4), and 1000 µg/L citalopram (n=4). The beakers were considered biological replicates. Sequencing libraries and RNA-seq were conducted by Novogene Corporation (Beijing, China). The analysis and processing of transcriptome data is outlined in [1,2,4]. The mRNAs were purified, and libraries prepped using the NEBNext Poly(A) mRNA Magnetic Isolation protocol (catalog # E7490, New England Biolabs) and NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina® (catalog #E7760, New England Biolabs). Individually prepared libraries were pooled by equimolar concentrations and sequenced using a NovoSeq 6000 instrument (150 bp paired end reads) (Illumina Inc., CA, USA). Data processing and alignment to the zebrafish genome has been described [2,6]. Transcript levels were estimated using FPKM (Fragments Per Kilobase of transcript sequence per Millions base pairs sequenced). Pathway Studio (Elsevier, V12) [2,7] was used to generate interaction networks.

Sub-network enrichment analysis (SNEA) queried expression data for associations to clinical endpoints and diseases by identifying differentially expressed transcriptome networks using gene-gene relationships derived from experiments and literature. This method has been described [1,7]. Data for subnetworks are presented in Supplemental Data. To identify differentially expressed gene networks, a permutation algorithm was employed using the complete set of transcriptome data. A randomized distribution of expression values was calculated. Comparisons were then made between the “query data” and the background distribution. Differences in subnetworks from the normal background were tested using a Mann–Whitney U-Test. A significance value (p-value) was calculated to determine whether a particular subnetwork was enriched more so than change, based on the background distribution of subnetworks created through permutations.

Limitations

- As our study only determined citalopram's effects on fish after 7 days of exposure, further studies analysing the impacts of chronic citalopram exposure are warranted.

Ethics Statement

All experimental data were collected within ethical guidelines and the Institutional Animal Care and Use Committee of University of Florida approved all experiments (UF IACUC#201708562).

Data Availability

GSE217875 (Original data) (NCBI Gene Expression Omnibus).

CRediT Author Statement

Kira J. Kazi: Investigation, Formal analysis; **Cole D. English:** Investigation, Formal analysis; **Emma Ivantsova:** Writing – original draft, Writing – review & editing; **Christopher L. Souders II:** Supervision, Investigation, Formal analysis; **Christopher J. Martyniuk:** Supervision, Writing – review & editing, Formal analysis.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dib.2024.110756.

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