radiation

MDPI

Article

BRIDE v2: A Validated Collection of Genes Involved in the Mammalian Brain Response to Low-Dose Ionizing Radiation

Christos Karapiperis [1,2], Dimitrios Vasileiou [1], Lefteris Angelis [2] and Christos A. Ouzounis [1,2,*]

[1] Chemical Process and Energy Resources Institute, Centre for Research and Technology Hellas, 57001 Thessalonica, Greece
[2] School of Informatics, Aristotle University of Thessalonica, 54124 Thessalonica, Greece
* Correspondence: cao@csd.auth.gr

Simple Summary: The impact of low-dose ionizing radiation on the mammalian brain is a topic of great interest, not only because of our everyday exposure to low radiation doses but also due to the growing focus on long-haul space flights. We report the redesign of a gene-centric data collection on a cloud infrastructure, thus eliminating the need for specific software plugins and improving both maintenance for developers and access for users. The BRIDE resource (version 2) contains 3174 unique gene records and approximately 50,000 links to other data resources, further supporting research into the effects of low-dose ionizing radiation on the mammalian brain.

Abstract: There is significant interest in the response of the mammalian brain to low-dose ionizing radiation (LDIR), mainly examined by gene or protein expression, with applications in radiation safety on Earth, the atmosphere and outer space. Potential associations of molecular-level responses with sensory or cognitive defects and neurodegenerative diseases are currently under investigation. Previously, we have described a light-weight approach for the storage, analysis and distribution of relevant datasets, with the platform BRIDE. We have re-implemented the platform as BRIDE v2 on the cloud, using the bioinformatics infrastructure ELIXIR. We connected the annotated list of 3174 unique gene records with modern omics resources for downstream computational analysis. BRIDE v2 is a cloud-based platform with capabilities that enable researchers to extract, analyze, visualize as well as export the gene collection. The resource is freely available online at <http://bride-db.eu>.

Keywords: low-dose ionizing radiation (LDIR); mammalian brain; database; cloud computing; open data

Citation: Karapiperis, C.; Vasileiou, D.; Angelis, L.; Ouzounis, C.A. BRIDE v2: A Validated Collection of Genes Involved in the Mammalian Brain Response to Low-Dose Ionizing Radiation. *Radiation* **2022**, *2*, 311–317. https://doi.org/10.3390/radiation2040024

Academic Editor: Gabriele Multhoff

Received: 19 March 2022
Accepted: 10 October 2022
Published: 12 October 2022

1. Introduction

Exposure to low-dose ionizing radiation (LDIR) is an important public health factor, with long-term consequences for human well-being [1]. Common situations for LDIR exposure relate to medical diagnostic procedures [2] and frequent air travel [3]. More unusual settings involve specific professional groups and range anywhere from nuclear power stations to space travel [4]. It is estimated that our annual LDIR exposure has increased in just one generation six-fold, from 0.5mSv in 1980 to 3mSv today [5]. Particular emphasis has been given to the molecular mechanisms of LDIR response beyond dosimetry [6]. With omics technologies, it is expected that we can better understand the genetic variations or expression patterns relevant for LDIR response, to improve radiation protection [7]. Earlier considerations can now be addressed with precise measurements at the genomic, transcriptomic and proteomic levels [8]. The planning of long-haul space flight missions has also invigorated the field and spawned renewed interest [9].

Multiple systems have been profiled with omics technologies, including human skin [10], heart tissue [11] and stem cells [12]. Of primary concern, however, is the effect of LDIR on the brain, both for impairing cognitive function and the long-term consequences

such as neurodegenerative disease [13]. Identifying molecular markers that can be used as proxies for dosimetry is also a key factor in this research, in particular the mammalian brain [14]. Beyond gene expression responses and the quest for potential protein biomarkers, microRNAs might also be involved [15], as well as various epigenetic effects [16]. Despite progress, omics profiling of LDIR in mammalian tissues is still at its infancy [17].

As little is known about the cerebrovascular system and the brain, it is important to record gene information for brain-specific LDIR response within a broader context, to validate existing data and guide future experimentation. The BRIDE resource was launched six years ago, with rather limited infrastructure [18]. We now relaunch the original collection as BRIDE v2 on the cloud, with additional and more modern tools that can facilitate research into this domain. BRIDE v2 follows the initial philosophy of BRIDE [18], in particular a gene-centric view for the curation of relevant genes found to respond to LDIR in the mammalian brain.

2. Materials and Methods

2.1. Design and Content Overview

We have re-implemented BRIDE following the same design principles as in v1 [18], with a slight update of the original tabs and in particular the PC-Viz tool, now replaced by a GeneMania client call [19]. We opted for a light-weight approach to data integration [20] as previously reported [18], using responsive design principles for a variety of screens and devices. The documentation for each entry has been extended and now includes additional fields (Figure 1). While the collection does not represent by itself an instance of the big data domain [21], the implied and/or extended datasets for each gene record are significant; 3174 unique records, with an average of 15–20 links per record, the collection points to over 50,000 static or dynamic data frames.

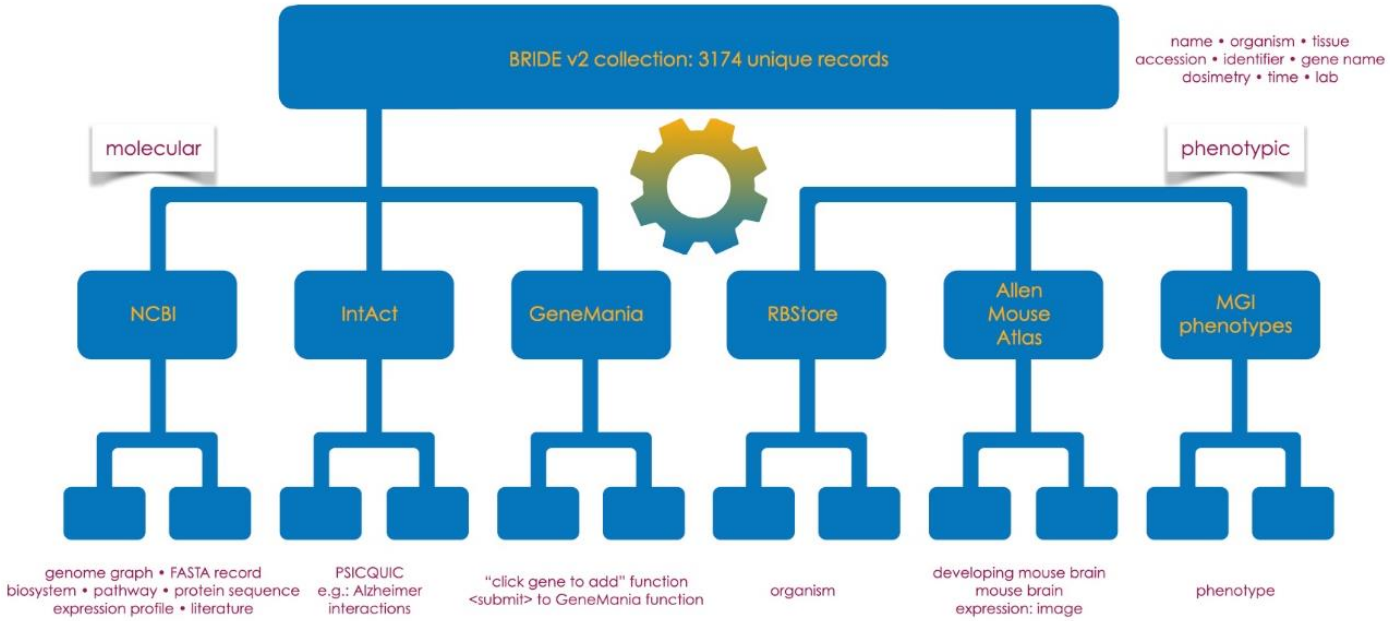

Figure 1. Simplified view of functionality with contextual tools listed under each tab section.

The basic BRIDE data front-end design has not been significantly altered, maintaining the unification and relationship links for the detection of the identity and associations of each gene, respectively [22], yet the actual tools that serve those queries have been slightly modified, as well as the underlying, back-end architecture (see Section 2.2). For example, the PathwayCommons tool PC-Viz has been replaced by GeneMania [19], as a more convenient and comprehensive solution. Dose–time records are also provided in each case, as well as tissue and organism (species). The effort aims at further supporting

activities for systems biology and omics experiments [23] in the field of LDIR mammalian brain response.

2.1.1. Design Details

As stated previously [18], we have compiled information for genes involved in the mammalian response to LDIR response, validated from the literature and omics results from the CEREBRAD project. The unification links [22] connect gene records to the UniProt knowledge base [24], both for identifiers and accession numbers. Links to the relevant publications are also provided at the main entry point. Using the NCBI tab, more links including relationship links [22] are given for genomic location, pathways [discontinued in March 2022] and gene expression profiles [25]. The same strategy is used for the IntAct database of protein interactions [26] and a selection function for GeneMania [19]. Finally, rich links to relevant RBStore experiment-centric records, the Allen Mouse Atlas [27] anatomy and gene expression records and MGI phenotypes, where available, [28] are also provided for completeness (Figure 1).

2.1.2. Content Details

In the v2 re-implementation, some unification links have been redesigned, as data providers have changed the API details; we now reproduce the entire dataset through the new APIs to ensure proper connection with external databases. The data have been imported into a PostgreSQL database. All user queries and choices target the database which returns results through a web browser. BRIDE v2 supports access via all modern browsers and mobile devices, without the need of any plugin installation. The full dataset is available in JSON format for download by end users—seen at the bottom of the page at all levels of access or tabs. The open nature of the dataset encourages potential extensions that may capture additional details from the original publications, such as type of irradiation, linear energy transfer (LET) or phenotypic information.

2.2. System Architecture

The BRIDE v2 platform implementation is based exclusively on AWS cloud services, in contrast to v1, which was based on a 3-tier architecture with MS® Azure Cloud and SQL [18] (no longer available). The services for this implementation and the system architecture are shown (Figure 2). The design philosophy of the system is based on the serverless computing model, with AWS Lambda which has revolutionized the application landscape. The function-as-a-service approach lets users deploy cloud applications without the need of a 24/7 active server. Instead of hosting an entire application on a server, we simply need to upload an individual function to AWS Lambda and call it using one of the many triggers available to initiate a function call.

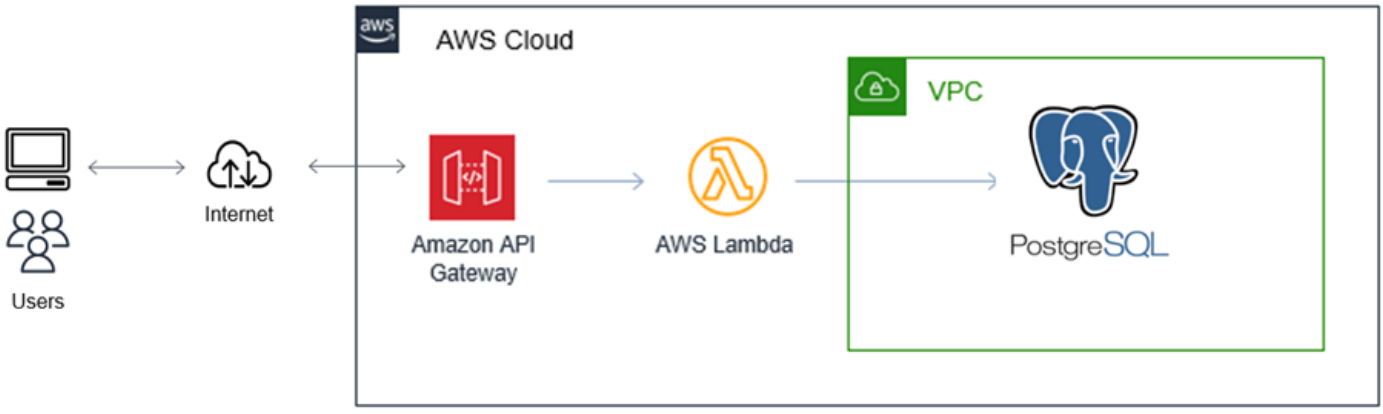

Figure 2. BRIDE serverless architecture.

AWS Lambda provides a stand-alone execution environment for individual functions written in Python. Thus, we can significantly reduce the total costs and the hardware maintenance needs. Unfortunately, the programmer has no control over the environment, and needs to manipulate more complex patterns to ensure proper functionality, specifically orchestrating and organizing the functions, so that they can work in a distributed fashion on available data. AWS supports PostgreSQL as a fully managed database service with Amazon Relational Database Service (RDS). PostgreSQL is an open-source database that supports both SQL and JSON queries. The Amazon API Gateway is a fully managed service to create, publish, maintain, monitor, and secure APIs at any scale. APIs act as the 'front door' for applications to access data, business logic or functionality from back-end services. This API easily accepts and processes up to hundreds of thousands of concurrent API calls and is very well suited for integration with AWS Lambda. The BRIDE v2 front-end has been developed using jsGrid, which is a lightweight client-side data grid control based on jQuery. It supports basic grid operations like inserting, filtering, editing, deleting, paging and sorting. jsGrid is flexible and allows customization of its appearance and components. With this approach, we ensure a minimal interface which presents all the available information without the need for complex navigation and wasteful resource management.

3. Results and Discussion

3.1. Data Consumption

Users can access records in BRIDE v2 with simple text queries, sort functionality and other search capabilities, e.g., a combination of the above, as following: first filter by text, then sort entries. Examples of the interface are provided in a pictorial manner (Figure 3).

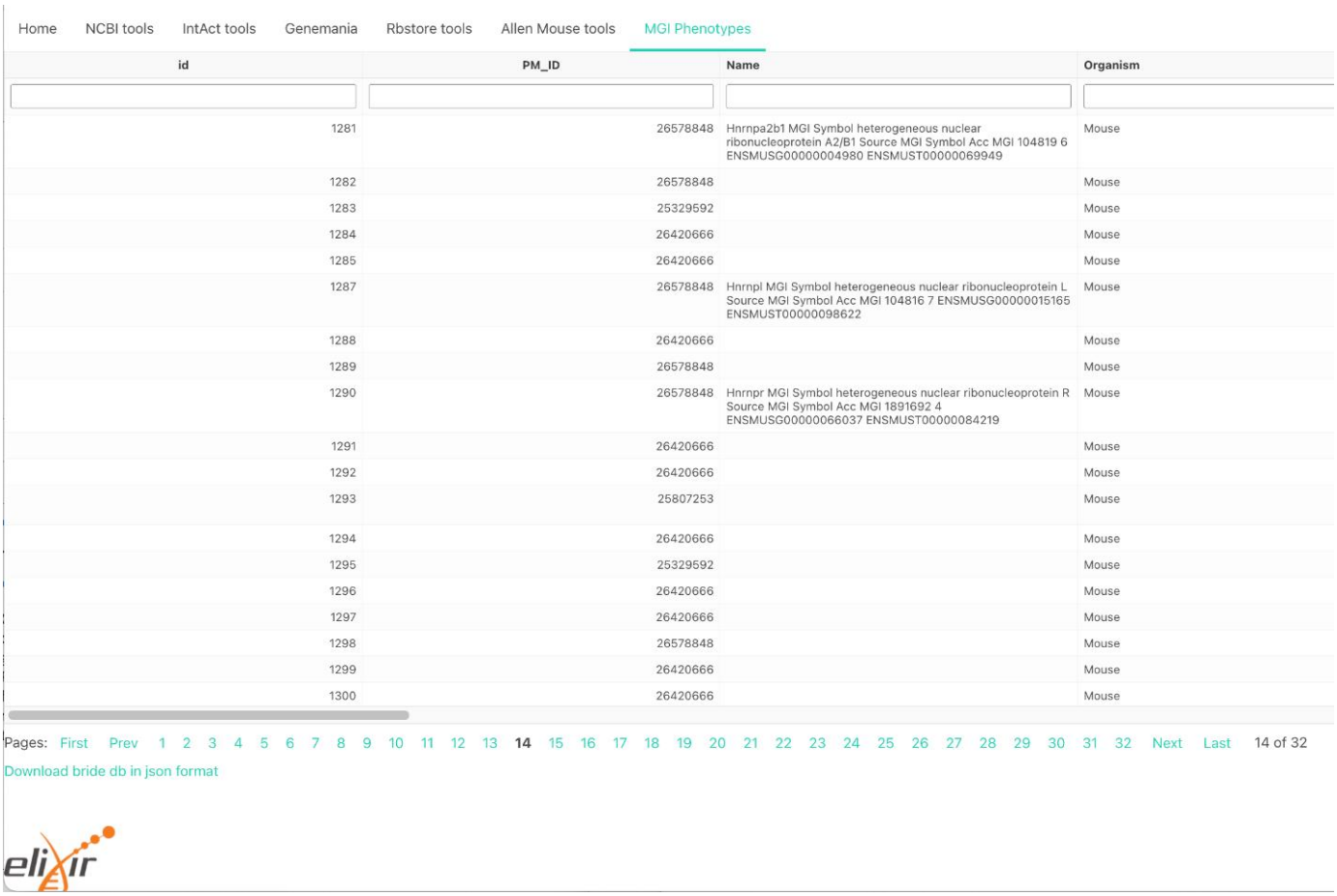

Figure 3. Views for the front-end of BRIDE v2.

At all levels, the download functionality is provided at the bottom of any page.

The BRIDE v2 collection is identical to the previously published list, namely 3174 records, using gene names as handles, plus the tissue–dose–time tuple (after irradiation). In other words, time refers to the time-period from irradiation to measurement. As previously reported, 95% of entries correspond to protein-coding genes expressed in the brain of *Mus musculus*. The additional genes are kept as they are reported in the same studies, documented by the corresponding PubMed identifier (PMID). Amongst the records that derive from four major publications, there are also a small number of unpublished instances (154 in total). Manually curated records (165 in total) are also included [18], and further curation efforts are envisaged.

With ~16 links per record, there are over 50,000 active links to other tools and databases (Table 1), thus creating a dense network of connections from BRIDE to some of ELIXIR's core data resources [29] and others. Users are able to generate dynamic links with the Genemania tool [19]: more than one gene can (and should) be added to the query string and submitted to Genemania, in order to predict functional associations of the selected genes.

Table 1. Links for each record of BRIDE v2 to tools and databases.

Provider	Section	Type	Results
NCBI	Graph	Unification Link	web page
	Fasta	Unification Link	web page
	Biosystems	Unification Link	web page
	Pathway	Unification Link	web page
	Protein	Unification Link	web page
	Geo Profile	Unification Link	web page
	PIE	Unification Link	web page
IntAct	PSICQUIC	Unification Link	web page
	Alzheimer db	Unification Link	web page
	Interactions	Unification Link	web page
Genemania	Network Visualizer	Relationship Link	web page
Rb Store	Organism	Unification Link	web page
Allen Mouse Brain	Mouse Brain Experiments	Unification Link	web page
	Developing Mouse Brain Experiments	Unification Link	web page
	Expression Mask Image	Unification Link	image file
MGI Phenotypes	Phenotypes	Unification Link	web page

Of the total number of entries, 1965 (62%) refer to radiation doses $\leq$1Gy, thus making the collection particularly relevant for LDIR research.

3.2. Utility and Discussion

The re-implementation of BRIDE as a new version provides an updated resource for relevant genes known to be affected by LDIR in the mouse brain and a toolkit for further analyses. We have upgraded the previous design due to changes both in the data content/specifications as well as the plugin-free serverless architecture options that are now available. We maintain the choices for platform usability and portal access and make the entire dataset available to the scientific community in JSON format. Further integration with other relevant resources and better connection to ELIXIR bioinformatics platforms remain a near-future prospect.

3.3. Availability and Requirements

BRIDE can be accessed with a web browser at <http://bride-db.eu/>. Data downloads are available in JSON format.

4. Conclusions

BRIDE is a knowledge broker for LDIR brain research and in particular systems radiobiology and omics. As is typical in databases, only positive cases are recorded i.e., genes that are known to be involved in LDIR response. Negative cases, i.e., genes not involved in LDIR response are much harder to capture as negative assertions. Further experimental measurements might augment the current count of 3174 records. Comparative genomics of the available content across other mammalian species is also a future prospect of great interest. Our implementation uses a simple serverless model, making all recorded data available to the community. BRIDE will hopefully find uses as a bioinformatics tool for the exposomics of the mammalian brain to LDIR.

Author Contributions: C.K., D.V. and C.A.O. designed, implemented and tested the database system. L.A. and C.A.O. coordinated and supervised the research and development. All authors read and approved the final manuscript.

Funding: The early development of BRIDE has been wholly supported by the collaborative European project CEREBRAD (grant # 295552), within the 7th EU framework programme, Nuclear Fission and Radiation Protection. C.A.O. acknowledges support by the project Elixir-GR (grant # MIS 5002780), implemented under the action "Reinforcement of the Research and Innovation Infrastructure," funded by the Operational Program Competitiveness, Entrepreneurship, and Innovation (NSRF 2014-2020) and co-financed by Greece and the European Union (European Regional Development Fund).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article.

Acknowledgments: We thank all CEREBRAD partners for their contributions.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mullenders, L.; Atkinson, M.; Paretzke, H.; Sabatier, L.; Bouffler, S. Assessing cancer risks of low-dose radiation. *Nat. Cancer* **2009**, *9*, 596–604. [CrossRef]
2. Einstein, A.J. Medical imaging: The radiation issue. *Nat. Rev. Cardiol.* **2009**, *6*, 436–438. [CrossRef]
3. De Angelis, G.; Caldora, M.; Santaquilani, M.; Scipione, R.; Verdecchia, A. Radiation exposure of civilian airline crew members and associated biological effects due to the atmospheric ionizing radiation environment. *Phys. Med.* **2001**, *17* (Suppl. 1), 258–260.
4. Bonner, W.M. Low-dose radiation: Thresholds, bystander effects, and adaptive responses. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 4973–4975. [CrossRef] [PubMed]
5. Thompson, G. Unmasking the truth: The science and policy of low-dose ionizing radiation. *Bull. At. Sci.* **2012**, *68*, 44–50. [CrossRef]
6. Feinendegen, L.E.; Pollycove, M.; Sondhaus, C.A. Responses to Low Doses of Ionizing Radiation in Biological Systems. *Nonlinearity Biol. Toxicol. Med.* **2004**, *2*, 143–171. [CrossRef] [PubMed]
7. Kempf, S.J.; Azimzadeh, O.; Atkinson, M.J.; Tapio, S. Long-term effects of ionising radiation on the brain: Cause for concern? *Radiat. Environ. Biophys.* **2013**, *52*, 5–16. [CrossRef]
8. Nussbaum, R.H.; Kohnlein, W. Inconsistencies and open questions regarding low-dose health effects of ionizing radiation. Environ. *Health Perspect.* **1994**, *102*, 656–667. [CrossRef]
9. Cucinotta, F.A.; Schimmerling, W.; Wilson, J.W.; Peterson, L.E.; Badhwar, G.D.; Saganti, P.B.; Dicello, J.F. Space Radiation Cancer Risks and Uncertainties for Mars Missions. *Radiat. Res.* **2001**, *156 Pt 2*, 682–688. [CrossRef]
10. Goldberg, Z.; Schwietert, C.W.; Lehnert, B.; Stern, R.; Nami, I. Effects of low-dose ionizing radiation on gene expression in human skin biopsies. *Int. J. Radiat. Oncol. Biol. Phys.* **2004**, *58*, 567–574. [CrossRef] [PubMed]
11. Azimzadeh, O.; Scherthan, H.; Sarioglu, H.; Barjaktarovic, Z.; Conrad, M.; Vogt, A.; Calzada-Wack, J.; Neff, F.; Aubele, M.; Buske, C.; et al. Rapid proteomic remodeling of cardiac tissue caused by total body ionizing radiation. *Proteomics* **2011**, *11*, 3299–3311. [CrossRef] [PubMed]

12. Squillaro, T.; Galano, G.; De Rosa, R.; Peluso, G.; Galderisi, U. The effect of low-dose ionizing radiation on stem cell biology: A contribution to radiation risk. *Stem Cells* **2018**, *36*, 1146–1153. [CrossRef]
13. Loganovsky, K. Do low doses of ionizing radiation affect the human brain? *Data Sci. J.* **2009**, *8*, BR13–BR35. [CrossRef]
14. Verheyde, J.; Benotmane, M.A. Unraveling the fundamental molecular mechanisms of morphological and cognitive de-fects in the irradiated brain. *Brain Res. Rev.* **2007**, *53*, 312–320. [CrossRef]
15. Lee, E.-S.; Won, Y.J.; Kim, B.-C.; Park, D.; Bae, J.-H.; Park, S.-J.; Noh, S.J.; Kang, Y.-R.; Choi, S.H.; Yoon, J.-H.; et al. Low-dose irradiation promotes Rad51 expression by down-regulating miR-193b-3p in hepatocytes. *Sci. Rep.* **2016**, *6*, 25723. [CrossRef]
16. Tharmalingam, S.; Sreetharan, S.; Kulesza, A.V.; Boreham, D.R.; Tai, T.C. Low-Dose Ionizing Radiation Exposure, Oxidative Stress and Epigenetic Programming of Health and Disease. *Radiat. Res.* **2017**, *188*, 525–538. [CrossRef]
17. Sokolov, M.; Neumann, R. Global Gene Expression Alterations as a Crucial Constituent of Human Cell Response to Low Doses of Ionizing Radiation Exposure. *Int. J. Mol. Sci.* **2015**, *17*, 55. [CrossRef] [PubMed]
18. Karapiperis, C.; Kempf, S.J.; Quintens, R.; Azimzadeh, O.; Vidal, V.L.; Pazzaglia, S.; Bazyka, D.; Mastroberardino, P.G.; Scouras, Z.G.; Tapio, S.; et al. Brain Radiation Information Data Exchange (BRIDE): Integration of experimental data from low-dose ionising radiation research for pathway discovery. *BMC Bioinform.* **2016**, *17*, 212. [CrossRef] [PubMed]
19. Warde-Farley, D.; Donaldson, S.L.; Comes, O.; Zuberi, K.; Badrawi, R.; Chao, P.; Franz, M.; Grouios, C.; Kazi, F.; Lopes, C.T.; et al. The GeneMANIA prediction server: Biological network integration for gene prioritization and predicting gene function. *Nucleic Acids Res.* **2010**, *38* (Suppl. 2), W214–W220. [CrossRef]
20. Philippi, S. Light-weight integration of molecular biological databases. *Bioinformatics* **2003**, *20*, 51–57. [CrossRef] [PubMed]
21. Marx, V. Biology: The big challenges of big data. *Nature* **2013**, *498*, 255–260. [CrossRef] [PubMed]
22. Karp, P.D. Database links are a foundation for interoperability. *Trends Biotechnol.* **1996**, *14*, 273–279. [CrossRef]
23. Philippi, S.; Köhler, J. Addressing the problems with life-science databases for traditional uses and systems biology. *Nat. Rev. Genet.* **2006**, *7*, 482–488. [CrossRef] [PubMed]
24. UniProt Consortium. UniProt: A hub for protein information. *Nucleic Acids Res.* **2015**, *43*, D204–D212. [CrossRef]
25. NCBI Resource Coordinators. Database resources of the National Center for Biotechnology Information. *Nucleic Acids Res.* **2014**, *42*, D7–D17. [CrossRef]
26. Orchard, S.; Ammari, M.; Aranda, B.; Breuza, L.; Briganti, L.; Broackes-Carter, F.; Campbell, N.H.; Chavali, G.; Chen, C.; Del-Toro, N.; et al. The MIntAct project—IntAct as a common curation platform for 11 molecular interaction databases. *Nucleic Acids Res.* **2014**, *42*, D358–D363. [CrossRef]
27. Jones, A.R.; Overly, C.C.; Sunkin, S.M. The Allen Brain Atlas: 5 years and beyond. *Nat. Rev. Neurosci.* **2009**, *10*, 821–828. [CrossRef]
28. Smith, C.L.; Eppig, J.T. The mammalian phenotype ontology: Enabling robust annotation and comparative analysis. *WIREs Syst. Biol. Med.* **2009**, *1*, 390–399. [CrossRef]
29. Drysdale, R.; Cook, C.E.; Petryszak, R.; Baillie-Gerritsen, V.; Barlow, M.; Gasteiger, E.; Gruhl, F.; Haas, J.; Lanfear, J.; Lopez, R.; et al. The ELIXIR Core Data Resources: Fundamental infrastructure for the life sciences. *Bioinformatics* **2020**, *36*, 2636–2642. [CrossRef]