Interpretation of genomic regulatory variation in the human brain and Parkinson's disease by integrating deep learning with single-cell multi-omics

A Data Management Plan created using DMPonline.be

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Project abstract:

The combination of whole-genome sequencing with matching single-cell multi-omics data provides unprecedented opportunities to unravel the impact of genomic variation on gene expression and cell state. In this project, we will use deep learning models and enhancer-based gene regulatory network inference to model enhancers and link them to target genes, applied to human substantia nigra (SN) and cingulate gyrus (CG) brain regions. Next, we will leverage the availability of fully phased whole genome sequences for a cohort of donors to statistically test the effects of genetic variation on chromatin accessibility and gene expression in different cell types of CG and SN. These results will be then integrated to prioritize variants with potential effects on gene regulation in the human brain, with subsequent experimental validation of a subset of selected enhancer variants..

To our knowledge, a combined framework that integrates statistical QTL mapping, allelic imbalance, deep learning, and GRN inference has not yet been applied to any human tissue, at the scale of our proposal. This unique data resource along with the novel computational strategies, will allow us to study gene regulation in the human brain at unprecedented resolution, and with a direct application to a complex disease. This approach should significantly improve our understanding of the functional effects of non-coding genetic variation and could lead to improved polygenic risk scores for Parkinson's disease.

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learning with single-cell multi-omics			

DPIA

DPIA

Have you performed a DPIA for the personal data processing activities for this project?

• Not applicable

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learning with single-cell multi-omics
GDPR

GDPR

Have you registered personal data processing activities for this project?

• Not applicable

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Application DMP

Questionnaire

Describe the datatypes (surveys, sequences, manuscripts, objects ...) the research will collect and/or generate and /or (re)use. (use up to 700 characters)

The research will generate:

- Sequencing data (>100 TB): whole genome sequencing, single-nucleus ATAC and RNA sequencing for a cohort of donors (PD and control)
- · Algorithms and scripts
- Models
- Manuscripts

In addition, we might reuse some of the publicly available datasets of single-cell RNA-seq data, single-cell ATAC-seq data, and whole genome sequences.

Based on the results of WP1-WP2, additional validation datasets will be generated including enhancer-reporter assays and MPRA in vivo (in the mouse brain, spatial MPRA) or/and in vitro (differentiated neurons / microglia derived from human induced pluripotent stem cells or human embryonic stem cells)

Specify in which way the following provisions are in place in order to preserve the data during and at least 5 years after the end of the research? Motivate your answer. (use up to 700 characters)

Responsible persons: Olga Sigalova (researcher), Stein Aerts (Group Leader)

DURING the research:

- Data and scripts will be stored on KU Leuven and on the Flemish Supercomputer Center servers, with daily on-site backup and mirroring
- All samples will be stored as appropriate

AFTER the research:

- Manuscripts will be published on BioRxiv and in open access journals
- Software and scripts will be published on Github
- Models will be archived in Kipoi.org
- Single-cell data will shared in GEO/ArrayExpress as count data, and the raw sequencing data will be archived under restricted access (DAC) in EGA. Intermediate analysis files will be kept on KU Leuven servers for 5 years
- All samples will be stored as appropriate

What's the reason why you wish to deviate from the principle of preservation of data and of the minimum preservation term of 5 years? (max. 700 characters)

not applicable

Are there issues concerning research data indicated in the ethics questionnaire of this application form? Which specific security measures do those data require? (use up to 700 characters)

Our study involves the creation of data derived from the postmortem human brain samples. Samples were obtained as part of the ASAP consortium, ethical approval obtained at the start of the project (EC Research S-number: S64966).

Which other issues related to the data management are relevant to mention? (use up to 700 characters)

not applicable

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FWO DMP (Flemish Standard DMP)

1. Research Data Summary

List and describe all datasets or research materials that you plan to generate/collect or reuse during your research project. For each dataset or data type (observational, experimental etc.), provide a short name & description (sufficient for yourself to know what data it is about), indicate whether the data are newly generated/collected or reused, digital or physical, also indicate the type of the data (the kind of content), its technical format (file extension), and an estimate of the upper limit of the volume of the data.

				Only for digital data	Only for digital data	Only for digital data	Only for physical data
Dataset Name	Description	New or reused	Digital or Physical	Digital Data Type	Digital Data format	Digital data volume (MB/GB/TB)	Physical volume
		Please choose from the following options: • Generate new data • Reuse existing data	Please choose from the following options: Digital Physical	Compiled/aggregated dataSimulation data	Please choose from the following options: • .por, .xml, .tab, .csv,.pdf, .txt, .rtf, .dwg, .gml,	Please choose from the following options: • <100MB • <1GB • <100GB • <1TB • <5TB • <10TB • <50TB • <50TB • >50TB	
WGS	long-read whole genome sequencing (ONT) of postmortem human brain samples from the cohort of donors (PD and control)	new	Digital	Experimental	- Raw: pod5 data. Aligned: BAM (or CRAM) files - VCF files - metadata: textual data(.rtf, .xml, .txt)	>50TB	
snATAC- seq	single-nucleus ATAC sequencing (10x Genomics sn-multiome and sn-ATAC) of human substantia nigra and cingulate cortex (matching cohort with WGS)	new	Digital	Experimental	- Raw: binary base call format (.bcl) - textual data: FASTQ file (.fastq, zipped as .gz) - metadata: textual data(.rtf, .xml, .txt)	>50TB	

snRNA-seq	substantia nigra and cingulate cortex (matching cohort with WGS)		Digital	Experimental	- Raw: binary base call format (.bcl) - textual data: FASTQ file (.fastq, zipped as .gz)- metadata: textual data(.rtf, .xml, .txt)	<50TB	
deepCC / deepSN	genetic variation in human cingulate cortex and substantia nigra	new (based on existing code base in the host lab)	Digital	Derived and compiled data	python (.py) files and notebooks (.ipynb)	<1Gb	
regulatory variants scoring algorithm	models to predict functional effects of genetic variation by integration of statistical (QTL/allele imbalance) and deep learning approaches Lenti-MPRA	new (based on existing software)	Digital	Derived and compiled data	- analysis scripts and notebooks (.py, .ipynb, .R, .sh) - textual data (.txt, .csv)	<1Gb	
MPRA libraries	and AAV- MPRA plasmid libraries	new	physical	Biological and chemical samples			~200 µl per sample
neuronal and microglial MPRA	bulk and single-cell MPRA (sequencing) of selected enhancers in human brain cells (differentiated cells in vitro)	new	Digital	Experimental measurement	- Raw: binary base call format (.bcl) - textual data: FASTQ file (.fastq, zipped as .gz) -metadata: textual data (.rtf, .xml, .txt)	<1TB	

spatial MPRA	MRPA (sequencing) to determine enhancer activity with spatial resolution in the mouse brain		เเวเซเเลเ	Experimental measurement	- Raw: binary base call format (.bcl) - textual data: FASTQ file (.fastq, zipped as .gz) -metadata: textual data (.rtf, .xml, .txt)	<1TB	
Microscopy images	microscopy images from enhancer reporter assays and spatial MPRA	new	II Jigitai	Experimental measurement	nd2, tiff, png	<1TB	

If you reuse existing data, please specify the source, preferably by using a persistent identifier (e.g. DOI, Handle, URL etc.) per dataset or data type:

The project is mostly based on the new data generated in the host lab. Published brain dataset might be reused at the later stages of the project for the comparison and interpretation of the results

Are there any ethical issues concerning the creation and/or use of the data (e.g. experiments on humans or animals, dual use)? Describe these issues in the comment section. Please refer to specific datasets or data types when appropriate.

- Yes, human subject data
- · Yes, animal data

Our study involves the creation of data derived from the postmortem human brain samples. Samples were obtained as part of the ASAP consortium, ethical approval obtained at the start of the project (EC Research S-number: S64966).

Some validation experiments will be conducted on mice. We will seek approval from the Ethical Committee for Animal Experimentation before their initiation.

Will you process personal data? If so, briefly describe the kind of personal data you will use in the comment section. Please refer to specific datasets or data types when appropriate.

• Yes

We obtained some personal data for the human samples from the biobanks (Banner Sun Health, USA; Edinbrugh, UK; QSBB, UK), including age, race, gender, and disease status. All personal data was anonymised.

Does your work have potential for commercial valorization (e.g. tech transfer, for example spin-offs, commercial exploitation, ...)? If so, please comment per dataset or data type where appropriate.

• Yes

potential for identification of new drug targets for PD treatments

Do existing 3rd party agreements restrict exploitation or dissemination of the data you (re)use (e.g. Material/Data transfer agreements/ research collaboration agreements)? If so, please explain in the comment section to what data they relate and what restrictions are in place.

• Yes

Our agreement with ASAP obliges open science approaches when disseminating any data. In addition, we have material transfer agreements with multiple biobanks (QSBB, Banner, Edinbrugh) that may restrict the dissemination of data within certain contexts.

Are there any other legal issues, such as intellectual property rights and ownership, to be managed related to the data you (re)use? If so, please explain in the comment section to what data they relate and which restrictions will be asserted.

No

currently there are no legal issues with regard to IP rights and ownership

2. Documentation and Metadata

Clearly describe what approach will be followed to capture the accompanying information necessary to keep data understandable and usable, for yourself and others, now and in the future (e.g., in terms of documentation levels and types required, procedures used, Electronic Lab Notebooks, README.txt files, Codebook.tsv etc. where this information is recorded).

Data will be accompanied by documentation containing all contextual and descriptive features of the research data, which allow to understand and (re)use the data. This includes data collection methods, protocols, and code explanation. Documentation is stored at the study- and the data-level, providing data provenance from the original source data to specific datasets linked to publications. Data will be generated following standardized protocols. Clear and detailed descriptions of these protocols will be stored in our lab protocol database and electronic laboratory notebook (E-notebook) and published along with the results, eg. on protocols.io (https://www.protocols.io/workspaces/aertslab/publications). Algorithms, scripts and software usage will be documented,e.g. using Jupyter Notebooks. Internally, we use git.aertlab.org to save and version the scripts. When scripts, algorithms and software tools are finalized, they will be additionally described in manuscripts and on GitHub (seewww.github.com/aertslab for our previous scripts and tools). Metadata will be documented by the research and technical staff at the time of data collection and analysis, by taking careful notes in the E-notebook and/or in hard copy lab notebooks that refer to specific datasets.

All datasets will be accompanied by metadata that is stored in our electronic lab notebook and in our central samplesheet. We have scripts that process the metadata, for example to obtain all fastq files of a certain project.

Digital files will be named following a standard procedure, so that all the name of all files in a given dataset will be in the same format.

Raw data is named as:

SEQUENCER_NAME_YYYYMMDD/PROJECT__CUAL__NAME_*:

- SEQUENCER_NAME: e.g. NovaSeq6000, NextSeq2000
- YYYYMMDD: Sequencing date
- PROJECT: 3 character project code
- CUAL: 6 character Globally Unique, Correctable, and Human-Friendly Sample Identifier for Comparative Omics Studies (generated with: https://github.com/johnchase/cual-id: cual-id)
 - NAME: descriptive sample name

To allow long term access and use of research data will be stored or converted to open file formats as much as possible.

- Containers: TAR, ZIP
- databases: XML, CSV, JSON
- Statistics: DTA, POR, SAS, SAV
- Images: TIFF, JPEG 2000, PNG, GIF
- Tabular data: CSV, TXT
- Text: XML, PDF/A, HTML, JSON, TXT, RTF
- Sequencing data: FASTA, FASTQ

We use controlled vocabularies or ontologies when applicable to provide unambiguous meaning, for example:

- Gene Onotology: molecular function, cellular component, and biological role of RNA seq
- ENSEMBL or NBCI identifiers: gene identity
- HUGO Gene Nomenclature Committee: names and symbol of human genes
- Mouse Genome Informatics: names and symbol of mouse genes
- FlyBase: names and symbol of Drosophila genes
- Chicken Gene Nomenclature Committee: names and symbol of chicken genes
- UniProt protein accessions: protein identity

Will a metadata standard be used to make it easier to find and reuse the data? If so, please specify (where appropriate per dataset or data type) which metadata standard will be used. If not, please specify (where appropriate per dataset or data type) which metadata will be created to make the data easier to find and reuse.

Yes

Metadata will be documented by the research and technical staff at the time of data collection and analysis, by taking careful notes in the electronic laboratory notebook (E-notebook) and/or in hard copy lab notebooks that refer to specific datasets. All datasets will be accompanied by a README.txt file containing all the associated metadata, which will include the following elements:

- Title: free text
- Creator: Last name, first name, organization
- Date and time reference
- Subject: Choice of keywords and classifications
- Structure: internal structure of the dataset, or the meaning of abbreviations (not necessary when it is clear from the in-file documentation).
- Description: Text explaining the content of the data set and other contextual information needed for the correct interpretation of the data, the software(s) (including version number) used to produce and to read the data, the purpose of the experiment, etc.
- Format: Details of the file format,
- Resource Type: data set, image, audio, etc.
- Identifier: DOI (when applicable)
- Access rights: closed access, embargoed access, restricted access, open access.

Additionally, we will closely monitor MIBBI (Minimum Information for Biological and Biomedical Investigations) for metadata standards more specific to our data type.

For specific datasets, additional metadata will be associated with the data file as appropriate.

3. Data storage & back-up during the research project

Where will the data be stored?

Digital data

Primary storage for active digital files is on KU Leuven servers. KU Leuven offers fast ("J-drive) and slower ("L-drive") storage that allows reading/writing/modification of non-confidential, confidential, and strictly confidential data. KU Leuven further offers the ManGO platform for storage and management of large volumes of active research data. This platform allows secure storage, manual and automated metadata coupling, data workflows, and file sharing.

- Algorithms, scripts and software: All the relevant algorithms, scripts and software code will be stored on the lab GitHub account (https://github.com/aertslab).
- Omics data: omics data generated during the project will be stored on KU Leuven servers or on the ManGO platform. Upon publication, all sequences supporting a manuscript will be made publicly available via repositories such as:
 - ASAP collaborative network cloud platform
 - EGA (WGS, snRNA, snATAC)
- Personal data of human subjects will be stored on a dedicated KU Leuven secure server (Digital vault).
- Upon publication, all sequences supporting a manuscript will be made publicly available via repositories such as the GenBank database or the European Nucleotide Archive (nucleotide sequences from primers / new genes / new genomes), NCBI Gene Expression Omnibus (microarray data / RNA-seq data / CHIPseq data), the Protein Database (for protein sequences), or the EBI European Genome-phenome Archive (for human (epi)genome and transcriptome sequences).

Physical samples

- Tissue samples: Tissues will be stored locally in the laboratory.
- Vectors: As a general rule at least two independently obtained clones will be preserved for each vector, both under the form of purified DNA (in -20°C freezer) and as a bacterial glycerol stock (-80°C). All published vectors and the associated sequences will be sent to the non-profit plasmid repository Addgene, which will take care of vector storage and shipping upon request.
- Cell lines: Newly created human cell lines will be stored locally in the laboratory in liquid nitrogen storage and will be deposited in the UZ Leuven-KU Leuven Biobank. Other human cell lines will be stored locally in liquid nitrogen cryostorage of the laboratory when actively used for experiments. Animal cell lines will be stored in liquid nitrogen cryostorage of the laboratory.

How will the data be backed up?

KU Leuven drives are backed-up according to the following scheme:

- data stored in manGO: Snapshots are made at regular intervals (hourly, daily and monthly) in case data needs to be recovered. The data itself is synchronized on two separate hardware storage systems, each 6 PB large, located at Leuven and at Heverlee (ICTS). The data is protected against calamities at either site by synchronizing it in real-time at hardware level.
- data stored on the "L-drive" is backed up daily using snapshot technology, where all incremental changes in respect of the previous version are kept online; the last 14 backups are kept.
- data stored on the "J-drive" is backed up hourly, daily (every day at midnight) and weekly (at midnight between Saturday and Sunday); in each case the last 6 backups are kept.
- data stored on the digital vault is backed up using snapshot technology, where all incremental changes in respect of the previous version are kept online. As standard, 10% of the requested storage is reserved for backups using the following backup regime: an hourly backup (at 8 a.m., 12 p.m., 4 p.m. and 8 p.m.), the last 6 of which are kept; a daily backup (every day) at midnight, the last 6 of which are kept; and a weekly backup (every week) at midnight between Saturday and Sunday, the last 2 of which are kept.

Is there currently sufficient storage & backup capacity during the project? If yes, specify concisely. If no or insufficient storage or backup capacities are available, then explain how this will be taken care of.

• Yes

KU Leuven servers offer sufficient storage for active data (J/L-drive, ManGO) and archived data (K-drive). Required data-storage volumes can be easily scaled up.

How will you ensure that the data are securely stored and not accessed or modified by unauthorized persons?

The buildings on our campus are restricted by badge system so only employees are allowed in and visitors are allowed under supervision after registration.

Access to the "L-drive", "J-drive", and ManGO servers is possible only through using a KU Leuven user-id and password, and user rights only grant access to their own data, or data that was shared to them. Data in these drives are mirrored in the second ICTS datacenter for business continuity and disaster recovery so that a copy of the data can be recovered within an hour.

Access to the digital vault is possible only through using a KU Leuven user-id and password, and user rights only grant access to the data in their own vault. Sensitive data transfer will be performed according to the best practices for "Copying data to the secure environment" defined by KU Leuven. The operating system of the vault is maintained on a monthly basis, including the application of upgrades and security patches. The server in the vault is managed by ICTS, and only ICTS personnel (bound by the ICT code of conduct for staff) have administrator/root rights. A security service monitors the technical installations continuously, even outside working hours. Only the PI and medical team members will be granted access to the server to deposit private data. The PI and medical team members will be the only responsible for linking patient information and/or samples, and will strictly respect confidentiality.

What are the expected costs for data storage and backup during the research project? How will these costs be covered?

- -The costs of digital data storage are as follows: 569,2€/5TB/Year for the "L-drive", 519€/TB/Year for the "J-drive", and 35€/TB/Year for the ManGO platform. Data storage and backup costs are included in general lab costs.
- -Maintaining a mouse colony alive costs about 1,200 euro per year (for 6 cages), excluding the costs of genotyping. When no experiment is planned with a particular mouse strain, and in compliance with the 3R's rule (https://www.nc3rs.org.uk), cryopreservation will thus be used to safeguard the strain, prevent genetic drift, loss of transgene and potential infections or breeding problems. Cryopreservation of sperm/embryos costs about 500 to 700 euro per genotype, plus a minimal annual storage fee (25 euro per strain for 250 to 500 embryos). Frozen specimen are kept in two separate liquid nitrogen tanks at two different sites on campus. When necessary, the costs of revitalization from cryopreserved sperm/embryos are about 1,100/600 euro.

4. Data preservation after the end of the research project

Which data will be retained for at least five years (or longer, in agreement with other retention policies that are applicable) after the end of the project? In case some data cannot be preserved, clearly state the reasons for this (e.g. legal or contractual restrictions, storage/budget issues, institutional policies...).

According to KU Leuven RDM policy, relevant research data will be preserved on the university's servers for a minimum of 10 years. Such

data include data that are at the basis of a publication, that can only be generated or collected once, that are generated as a result of a substantial financial or personal effort, or are likely to be reused within the research unit or in wider contexts.

Where will these data be archived (stored and curated for the long-term)?

data submitted to the databases

As a general rule all research outputs (data, documentation, and metadata) related to publications will be made openly accessible, whenever possible via existing platforms that support FAIR data sharing (www.fairsharing.org). We aim at communicating our results in top journals that require full disclosure upon publication of all included data, either in the main text, in supplementary material or in a separate data repository.

Other research data will be archived on KU Leuven servers as described above.

What are the expected costs for data preservation during the expected retention period? How will these costs be covered?

-The costs of digital data storage are as follows: 569,2€/5TB/Year for the "K-drive" and the "L-drive", 519€/TB/Year for the "J-drive", and 35€/TB/Year for the ManGO platform. Data storage and backup costs are included in general lab costs.

5. Data sharing and reuse

Will the data (or part of the data) be made available for reuse after/during the project? In the comment section please explain per dataset or data type which data will be made available.

- Yes, in an Open Access repository
- Yes, in a restricted access repository (after approval, institutional access only, ...)
- Datasets and metadata generated from **human omics** will be deposited under restricted access on the European Genome Phenome Archive (EGA), where they will be assigned a unique and persistent identifier.
- Computational workflows, models, and metadata will be stored on platforms such as Github, Kipoi, and Zenodo with proper versioning.
- To ensure data findability, links and references these datasets, workflows and modes will be included in the data availability statements of the associated publication.

If access is restricted, please specify who will be able to access the data and under what conditions.

Access to restricted access dataset (such as human omics datasets) is governed by the Data Access Committees of KU Leuven / UZ Leuven or VIB.

Are there any factors that restrict or prevent the sharing of (some of) the data (e.g. as defined in an agreement with a 3rd party, legal restrictions)? Please explain in the comment section per dataset or data type where appropriate.

- Yes, Privacy aspects
- Yes, Intellectual Property Rights
- Human omics data are considered sensitive personal data, and are are only made available on restricted access repositories such as the European Genome Phenome Archive (EGA). Access to these datasets is under control of a Data Access Committee.
- The researchers involved and the IP team of the VIB TechTransfer Office shall make the necessary arrangements in order to maintain an embargo on the public access of research data, at least until the essential steps in securing intellectual property (e.g. the filing of a patent application) have been taken. As such the IP protection does not withhold the research data from being made public. In the case a decision is taken to file a patent application it will be planned so that publications need not be delayed.

Where will the data be made available? If already known, please provide a repository per dataset or data type.

- Upon publication, datasets and metadata generated from animal omics will be stored in public repositories such as Zenodo or the NCBI Gene Expression Omnibus, where they will receive a unique and persistent identifier.
- Datasets and metadata generated from human omics will be deposited under restricted access on the ASAP platform and on the European Genome Phenome Archive (EGA), where they will be assigned a unique and persistent identifier.
- Computational workflows, models, and metadata will be stored on platforms such as Github, Kipoi, and Zenodo with proper versioning.
- protocols will be deposited on protocols.io.

When will the data be made available?

All research outputs (data, documentation, code, and associated metadata) will be made openly accessible at the latest at the time of publication. No embargo will be foreseen unless imposed e.g. by pending publications, potential IP requirements – note that patent application filing will be planned so that publications need not be delayed - or ongoing projects requiring confidential data. In those cases, datasets will be made publicly available as soon as the embargo date is reached.

Which data usage licenses are you going to provide? If none, please explain why.

Data is typically available under a Creative Commons CC0 1.0 Universal (CC0 1.0) Public Domain Dedication, a Creative Commons Attribution (CC-BY), or an ODC Public Domain Dedication and Licence, with a material transfer agreement when applicable. Software and code usually are available under a GNU General Public License or an Academic Non-commercial Software License.

Do you intend to add a PID/DOI/accession number to your dataset(s)? If already available, you have the option to provide it in the comment section.

Yes

What are the expected costs for data sharing? How will these costs be covered?

It is the intention to minimize data management costs by implementing standard procedures e.g. for metadata collection and file storage and organization from the start of the project, and by using free-to-use data repositories and dissemination facilities whenever possible. Data management costs will be covered by the laboratory budget.

6. Responsibilities

Who will manage data documentation and metadata during the research project?

The researcher (Olga Sigalova) and collaborators from the lab (Koen Theunis, Gert Hulselmans, Alexandra PanČíková, Julie De Man)

Who will manage data storage and backup during the research project?

The researcher (Olga Sigalova) and collaborators from the lab (Koen Theunis, Gert Hulselmans, Alexandra PanČíková, Julie De Man)

Who will manage data preservation and sharing?

During the project, the researcher (Olga Sigalova) and collaborators from the lab will manage data preservation and sharing with support of Sara Salama (ASAP project manager). After the project, PI (Stein Aerts) will guarantee data preservation and sharing according to KU Leuven RDM policy

Who will update and implement this DMP?

The researcher (Olga Sigalova)

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