PerturbDB: A Database of Huntington's Disease Perturbation Studies
https://www.hdinhd.org/

Viktoria Andreeva[3], Richard A Blevins[2], Irina Murasheva[3], Kabenla Armah[3], Chuck Borromeo[3], Liliana Menalled[1], David Howland[1], Dan Felsenfeld[1], Vahri Beaumont[1], Jeff Aaronson[1]

[1] CHDI Management/CHDI Foundation, Princeton, NJ, USA. [2] Bridlewood Consulting LLC, Flower Mound, TX, USA. [3] Rancho Biosciences LLC, San Diego, CA, USA.

Abstract

PerturbDB is a database of Huntington's disease (HD) perturbation studies incorporating methods, outcomes, and experimental details from >10,000 experiments curated from >1,200 publications and CHDI study reports. In addition to maintaining provenance, several classes of experimental metadata have been curated, collectively describing the nature of the: a) HD model; b) perturbation; and c) readout/results. Wherever possible, metadata are standardized according to existing ontologies and custom vocabularies. HD models are characterized as either in vitro, in vivo, ex vivo, or in silico and organisms in scope include human, rodent, worm, fly and others. A perturbation is defined broadly as any type of intervention, e.g., pharmacological, genetic, lifestyle, etc. applied to an HD model. Readouts are described relative to the phenotype of the HD model without perturbation. Where applicable, directionality is assigned to each result, indicating whether the perturbation improves or worsens the HD phenotype. PerturbDB is available within HDinHD (Huntington's Disease in High Definition; hdinhd.org) as an integrated component within the HD Explorer tool [1]. PerturbDB expands and replaces the more narrowly scoped Therapeutic Interventions (TI) studies section previously available within HD Explorer. Additionally, the broader offering will augment all pre-existing TI studies with outcome data for each readout.

PerturbDB enables rapid data mining of thousands of HD perturbation experiments to help understand how perturbations of a single gene across a spectrum of interventional paradigms impact the HD phenotype. The integration of PerturbDB within HD Explorer places these perturbations results within a greater HD experimental context, further facilitating interpretation and hypothesis generation.

Perturbation Experiment

A perturbation experiment is defined as one model and one perturbation described in a single publication or report. PerturbDB mostly focuses on phenotypic readouts, e.g. behavioral tests in animal models, or aggregation and toxicity in cell culture models. Generally, gene/protein expressions are outside of scope for PerturbDB except Htt levels. A single source, publication or report may include multiple experiments if several perturbations were studied, and a single experiment may have multiple readouts.

Sources of Perturbation Experiments

Source Category	Number
Publications (PubMed)	1,205
CHDI Reports	66
Preprints (bioRxiv)	4

Models

HD models are characterized as either in vitro, in vivo, ex vivo, or in silico and organisms in scope range across those described in the literature. Details about the model, such as cell line, animal strain, or cell type, are collected alongside additional experimental metadata, such as number of Q repeats in mHtt, and type of mHtt used (e.g., full length or exon 1 fragment).

Model Type	Model Name	Number of Experiments	
In vitro	Cell Culture	4,437	79 cell lines 22 primary cell types
Ex vivo	Brain Slices	110	
In vivo	Mice In Vivo	2,863	43 HD mouse lines and AAV, LV or chemically induced
	C. Elegans	1,836	
	Drosophila	866	
	Yeast	270	
	Rat In Vivo	87	2 HD rat lines and AAV, LV or chemically induced
	Human	45	
	Zebrafish In Vivo	23	
	Sheep In Vivo	2	1 HD sheep line
	Dictyostelium	2	
	Pig In Vivo	1	
In silico	GWAS	117	
Total		**10,659**	

Perturbations

A perturbation is defined broadly as any type of intervention applied to an HD model. In PerturbDB, the most common perturbation category is Knockdown via Gene Delivery followed by Small Molecule treatments.

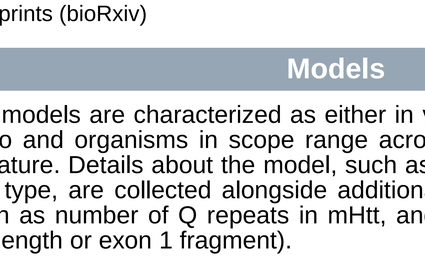
Perturbation Category	Perturbation Effect	Number of Experiments
Gene Delivery	Knockdown	6,269
	Overexpression	732
	Dominant Negative	107
	Constitutively Active	33
	Gain of Function	2
	Loss of Function	1
Small Molecule		1,908
Genetic Cross	Loss of Function	449
	Overexpression	275
	Knockdown	217
	Knockout	183
	Gain of Function	72
	RNAi	61
	Conditional Knockout	12
	Constitutively Active	1
HD Modifier Gene		117
Peptide Delivery		88
Protein Delivery		84
Gene Editing	Knockout	24
	Conditional Knockout	3
Antibody Delivery		11
Mixed		6
Diet		2
Cell-Based		2

Readouts

Results are described relative to the phenotype of the HD model without perturbation.

Model Type	Readout Type	Number of Readouts
In vivo	Motor Behavior	3,686
	Toxicity	2,185
	HD Disease Symptoms (Ataxia, Gliosis, Seizures, etc.)	960
	Aggregation	892
	Survival	566
	Body Weight	462
	Htt Level, Clearance or Modification	219
	Cognitive	219
	Other Physiological Functions	176
	Stress Response	72
	Neuronal Functions	47
	Behavior	41
	MRI	40
	Autophagy	33
	Psychiatric-Cognitive	32
	CAG Repeat Stability	11
	Other Cell Processes	4
	Pain Response	3
In vitro	Aggregation	1,712
	Toxicity	1,580
	Htt Level, Clearance or Modification	1,481
	Neuronal Functions	216
	Autophagy or Mitophagy	134
	Other Cell Processes	77
	CAG Repeat Stability	24
In silico	HD Factors	122
Ex vivo	Neuronal Functions	85
	Toxicity	21
	Aggregation	8
	Htt Level	2
Total		**15,110**

HD Explorer



PerturbDB is integrated within HDinHD's HD Explorer tool at https://www.hdinhd.org/

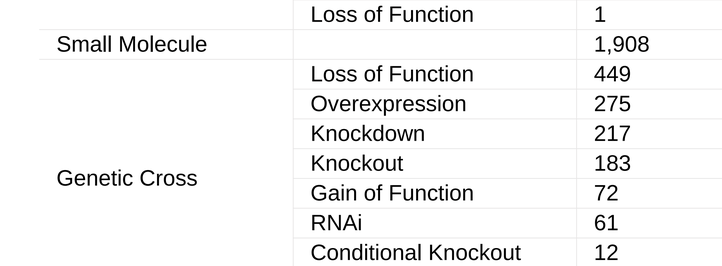
Therapeutic Intervention Merger

The original HD Explorer release in Apr-2021 included Therapeutic Intervention (TI) studies, focusing on in vivo behavior treatment studies [1]. The TI section has now been retired as all TI experiments are now contained within the larger PerturbDB. Additionally, PerturbDB augments all pre-existing TI studies with outcome data for each readout, and the Treatment Arms tab in study drill down includes additional experimental metadata.

Grid Overview

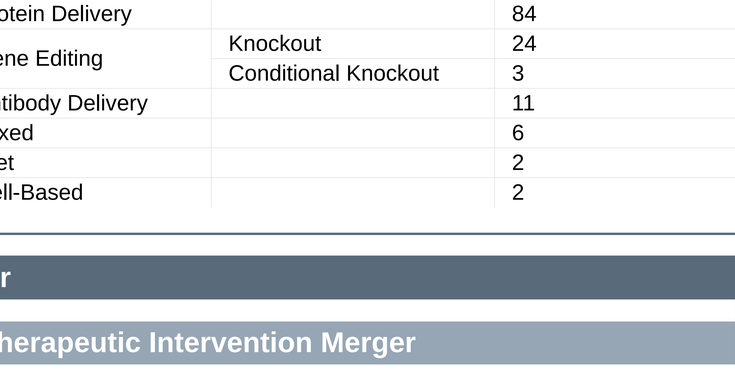
The Grid view presents a list of available experiments and key metadata for them: source, target gene symbol, summary, model, treatment and perturbation. Values in each column can be sorted or filtered using Excel-like controls in the column headers.

Clicking on the left corner icon opens a facet menu allowing users to filter experiments on additional fields: Treatment Category, Perturbation Type, Readout Category, Readout, and Improve/Worsen HD Phenotype.



Individual Experiment View

Selecting an individual experiment opens a drill down view to explore experimental details, which are presented in 3 sections: Source, Model and Perturbation. The Model tab provides information on the HD model used in the selected experiment. The Perturbation tab provides details of the perturbation, including target and pharmacology, as well as Readout results.



Conclusions and Future Directions

PerturbDB enables rapid data mining of thousands of HD perturbation experiments to understand how perturbations of a single gene across a spectrum of interventional paradigms impact the HD phenotype. The integration of PerturbDB within HD Explorer places these perturbations results within a greater HD experimental context, further facilitating interpretation and hypothesis generation. Integration of PerturbDB in the HD Explorer allows quickly identify all Perturbation experiments published for a gene of interest, filter on other parameters like model or readout and quickly find results of this experiments.

We are currently curating outcome data for each arm of a large set of in vivo studies currently represented in PerturbDB. This will enable users to understand the effect of dosing and other experimental parameters on outcomes. We anticipate regular updates to PerturbDB in order to incorporate the emerging literature. We are planning to develop summary views that collate results across similar (e.g., shared treatment) sets of publications and reports.

Acknowledgements

PerturbDB is funded and developed by CHDI Foundation, Inc., a nonprofit biomedical research organization exclusively dedicated to collaboratively developing therapeutics that will substantially improve the lives of those affected by Huntington's disease. Colleagues at Rancho BioSciences contributed data curation, data modeling and data engineering support, and Bridlewood Consulting contributed systems and software engineering support. The pilot system that inspired the current PerturbDB was developed by Jim Wang while working as a consultant for CHDI Foundation [2].

References

1. Aaronson J et al., *J Huntington's Dis* 2021,10(3):405-412. doi: 10.3233/JHD-210491
2. Wang JKT et al., *Frontiers in Neuroscience* 2017,11:149.