Journal of Huntington's Disease 10 (2021) 405–412
DOI 10.3233/JHD-210491
IOS Press

Short Communication

HDinHD: A Rich Data Portal for Huntington's Disease Research

Jeff Aaronson[a,*], Vahri Beaumont[a], Richard A. Blevins[b], Viktoria Andreeva[c], Irina Murasheva[c], Anastasia Shneyderman[c,1], Kabenla Armah[c], Rob Gill[c], Jian Chen[a], Jim Rosinski[a], Larry C. Park[a,2], Giovanni Coppola[d], Ignacio Munoz-Sanjuan[a] and Thomas F. Vogt[a]
[a]*CHDI Management/CHDI Foundation, Princeton, NJ, USA*
[b]*Bridlewood Consulting LLC, Flower Mound, TX, USA*
[c]*Rancho Biosciences LLC, San Diego, CA, USA*
[d]*Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA*

Pre-press 9 August 2021

Abstract. HDinHD (Huntington's Disease in High Definition; HDinHD.org) is an open online portal for the HD research community that presents a synthesized view of HD-related scientific data. Here, we present a broad overview of HDinHD and highlight the newly launched HD Explorer tool that enables researchers to discover and explore a wide range of diverse yet interconnected HD-related data. We demonstrate the utility of HD Explorer through data mining of a single collection of newly released *in vivo* therapeutic intervention study reports alongside previously published reports.

Keywords: HDinHD, Huntington's disease in high definition, data dissemination, rolipram

INTRODUCTION

Open science approaches are transforming scientific practice to enhance the availability and transparency of research. This has been exemplified by open access publishing policies, and through the use of best-practice archival community repositories such as NCBI's Gene Expression Omnibus (GEO) [1], Sequence Read Archive (SRA) [2], and PRoteomics IDEntifications (PRIDE) [3], where investigators can deposit raw and processed next-generation sequencing (NGS) and protein expression datasets for public access and review. The HD academic research community, including CHDI (Table 1), has contributed substantial amounts of valuable datasets to these repositories, ranging in character from large-scale, longitudinal molecular profiling datasets to specific compound treatment studies.

The power of such a wealth of information comes from the ability to synthesize and collectively mine this data to further catalyze research and generate new hypotheses and scientific directions, a process often requiring both significant data management and sophisticated data mining tools. In response to these challenges facing the HD research community, we developed HDinHD (HDinHD.org), a freely accessible data portal that curates available HD-related primary scientific data, shares analyses and

[1]Present address: Insilico Medicine Hong Kong Limited, Pak Shek Kok, Hong Kong

[2]Present address: Naason Science Inc., KBIO New Drug Development Center, Osong-eup, Cheongju-si, Korea

*Correspondence to: Jeff Aaronson, CHDI Management/CHDI Foundation, 155 Village Boulevard, Suite 200, Princeton, NJ 08540, USA. Tel.: +1 609 945 9616; E-mail: Jeff.Aaronson@chdifoundation.org.

ISSN 1879-6397/$35.00

Table 1
CHDI-submitted molecular profiling data to GEO and PRIDE

I. CHDI-SUBMITTED MOLECULAR PROFILING DATA FROM THE MOUSE ALLELIC SERIES

PMID	DATASET ID	# SAMPLES	AGE (MON)	GENOTYPE	TISSUE	METHOD
26909023	GSE65770	168	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Cortex	mRNA-seq
	GSE65772	167	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Liver	mRNA-seq
	GSE65774	208	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Striatum	mRNA-seq
	GSE65775	173	6	WT, Q175	Tissue Survey	mRNA-seq
	PXD003442	198	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Striatum	LC-MS/MS
29324753	GSE65769	168	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Cortex	miRNA-seq
	GSE65771	167	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Liver	miRNA-seq
	GSE65773	208	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Striatum	miRNA-seq
	GSE73505	166	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Cerebellum	miRNA-seq
	GSE73507	168	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Hippocampus	miRNA-seq
	GSE78790	96	6, 10	WT, Q20, Q50, Q92, Q140	Cerebellum	miRNA-seq
	GSE78791	96	6, 10	WT, Q20, Q50, Q92, Q140	Cortex	miRNA-seq
	GSE78792	96	6, 10	WT, Q20, Q50, Q92, Q140	Liver	miRNA-seq
	GSE78793	96	6, 10	WT, Q20, Q50, Q92, Q140	Striatum	miRNA-seq
PRE-JOURNAL SUBMISSION	GSE73468	166	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Cerebellum	mRNA-seq
	GSE73503	168	2, 6, 10	WT, Q20, Q80, Q92, Q111, Q140, Q175	Hippocampus	mRNA-seq
	GSE76738	52	6	WT, Q20, Q80, Q92, Q111, Q140, Q175	Gonadal Adipose	miRNA-seq
	GSE76752	55	6	WT, Q20, Q80, Q92, Q111, Q140, Q175	Gonadal Adipose	mRNA-seq
	GSE78270	96	6, 10	WT, Q20, Q50, Q92, Q140	Cerebellum	mRNA-seq
	GSE78272	95	6, 10	WT, Q20, Q50, Q92, Q140	Cortex	mRNA-seq
	GSE78273	93	6, 10	WT, Q20, Q50, Q92, Q140	Liver	mRNA-seq
	GSE78274	96	6, 10	WT, Q20, Q50, Q92, Q140	Striatum	mRNA-seq
	PXD005485	182	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Cortex	LC-MS/MS
	PXD005538	182	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Hippocampus	LC-MS/MS
	PXD005526	184	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Cerebellum	LC-MS/MS
	PXD005641	223	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Liver	LC-MS/MS
	PXD006302	198	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Striatum	LC-MS/MS
	PXD010957	229	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Gastrocnemius	LC-MS/MS
	PXD010958	217	2, 6, 10	WT, Q20, Q50, Q80, Q92, Q111, Q140, Q175	Heart	LC-MS/MS

II. CHDI-SUBMITTED MOLECULAR PROFILING DATA FROM OTHER HD DISEASE MODEL STUDIES

DATASET ID	# SAMPLES	AGE (MON)	GENOTYPE	TISSUE	METHOD	DESCRIPTION
GSE123657 GSE123664	95 95	6	WT, Q175, Q175 (neo-)	Striatum, Cortex, Liver	mRNA-seq miRNA-seq	Q175 KI mouse lines with and without neo cassette
PXD013771	60	1, 2, 3	WT, R6/2	Striatum	LC-MS/MS	Phosphoproteome and proteome time series
GSE152443 GSE169386	255 145	2, 6, 12 10, 19, 24	WT, Long Evans Q130	Striatum, Cerebellum, Cortex, Hippocampus	mRNA-seq	Characterization of LE Q130 KI rat line

III. CHDI-SUBMITTED MOLECULAR PROFILING DATA FROM COMPOUND TREATMENT STUDIES

DATASET ID	# SAMPLES	TREATMENT TYPE	TREATMENT	DURATION	AGE (WK)	GENOTYPE	TISSUE
GSE104064	160	HDAC Class IIa Inhibitor	CHDI-00390576	24 wk	4-28	WT, Q175	Cortex, Striatum, Tibialis, Heart, Liver
GSE104086	160	HDAC Class IIa Inhibitor	CHDI-00390576	8 wk	4–12	WT, R6/2	Cortex, Striatum, Tibialis, Heart, Liver
GSE105158	46	KMO Inhibitor	CHDI-00340246	8 wk	4–12	WT, R6/2	Cortex, Striatum
GSE106161	160	KMO Inhibitor	CHDI-00340246	6 hr	12	WT, R6/2	Cortex, Striatum, Cerebellum, Liver
GSE89505 PMID: 27916455	90	PDE10A Inhibitor	PF-02545920	34 wk	5–39	WT, hom(Q175)	Cortex, Striatum
PXD005138 PMID: 27916455	58	PDE10A Inhibitor	PF-02545920	1 hr	26	WT, Q175, hom(Q175)	Striatum

computational models derived from such data, and provides a unified forum for researchers to highlight their data, tools, know-how and insight to the community. Our aim is for HDinHD to increasingly facilitate data exploration and hypothesis generation through a continuing emphasis on experimental data integration and an evolving suite of custom browsing and data interrogation tools developed by the community.

HUNTINGTON'S DISEASE IN HIGH DEFINITION: THE HDinHD WEBSITE

HDinHD was launched in 2015 in partnership with the Coppola Lab at UCLA (https://www.semel.ucla.edu/coppola-lab) and has been iteratively developed and updated since then with new data and tools. Prospective users may register for an account directly from the homepage to gain full access. Content includes RSS feeds from HD Buzz (hdbuzz.net), HD-related literature aggregated from PubMed (https://pubmed.ncbi.nlm.nih.gov/), bioRxiv (https://www.biorxiv.org/) and medRxiv (https://www.medrxiv.org/), and an HD-related news feed. Downloads, Tools, and New in HDinHD sections are available as independent tabs from the home page.

Downloads

The Downloads area serves as a reference library, providing access to results from computational analyses and modeling projects performed by CHDI and collaborators, as well as to large compilations of curated HD experimental datasets. These resources are designed to be downloaded once, then digested by HDinHD users within their local environment, either through review of reports, pathway maps, analysis/modeling results, or through the incorporation of datasets into standard or special-purpose computational pipelines. For example, CHDI has recently released a report describing the creation of a "266 striatal gene disease signature" constructed from the Mouse Allelic Series dataset [4, 5] and validated on several external datasets. The report and supplementary material, including the disease gene signature, are available for download from HDinHD. Additionally, to provide rich functional context for HD-related gene set enrichment analysis (GSEA), CHDI has created a gene set enrichment library, HDSigDB, largely through the curation and analysis of HD and triplet-repeat expansion disease studies identified within community omics databases. HDSigDB is available for download from HDinHD in GSEA-compliant format [6] and can be easily incorporated into standard computational analysis pipelines.

Tools

The Tools area provides federated access to a set of applications developed by members of the HD research community, including: the GeM-HD Consortium [7, 8]; the Neri Brain-C Lab (https://www.ibps.upmc.fr/en/research/biological-adaptation-and-ageing/brainc); Evotec; the Khakh Lab (http://www.physiology.ucla.edu/Labs/khakh/index.htm) and the Coppola Lab. The AS Viewer is a simple single gene/protein visualization tool detailing expression pattern over time and CAG length within the Mouse Allelic Series reference dataset. CHDI has recently introduced HD Explorer, a new tool that provides a single integrated framework where researchers can discover and explore a wide range of diverse yet interconnected HD scientific data (Fig. 1). CHDI and colleagues curated and analyzed data from hundreds of HD studies spanning complementary experimental data types (e.g., HTT protein-protein interactions, therapeutic interventions, omics) using consistent methodologies and standard, controlled vocabularies. Data provenance is universally maintained, and experimental meta-data are mapped to centralized HD-specific catalogs of shared elements (e.g., mouse model, treatment, and HD gene catalogs). The rich interconnections between data

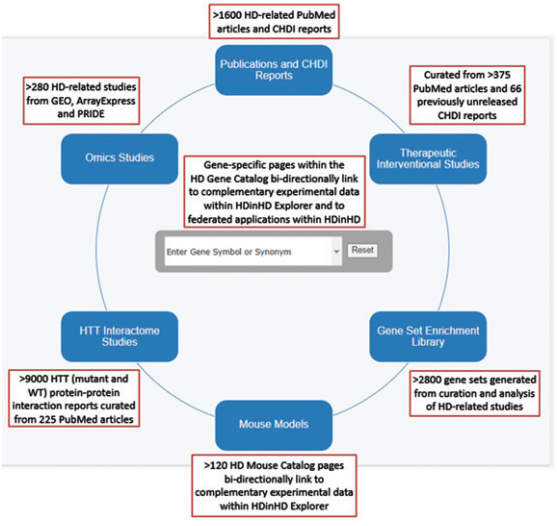

Fig. 1. HD Explorer provides multiple entry points into an integrated platform of HD experimental data.

sources, experimental data and reference catalogs allow users to pivot and identify a spectrum of both primary and experimental data related to their current inquiry. While HD Explorer is designed as an interactive tool, complete copies of component datasets are also available on the Downloads page for labs desiring batch data to facilitate internal data mining.

Therapeutic intervention studies

With the release of HD Explorer, we provide a novel resource for researchers interested in the wealth of HD therapeutic intervention studies. This new curation aims to comprehensively collate *in vivo* therapeutic studies with (largely) behavioral readouts, in a variety of HD models. It currently contains more than 375 published articles covering diverse therapeutic intervention paradigms (small molecules and biologics) in a broad range of HD model systems (yeast, fruit fly, nematode, and diverse mouse and rat models). This will continue to be updated periodically.

Users can search and filter based on several meta-data fields, including HD model system, target gene, treatment category (e.g. compound, peptide, ASO, AAV vector) and treatment name. Selecting a single data row describing a particular study will bring up a detailed view of the study. Several tabs containing the study meta-data are available, including summary of findings, PubMed abstract (if applicable), link to primary source document (and downloadable PDF if available), details of treatment arms and treatment regimen, and the HD model system used. Importantly, all target genes are linked to HD Explorer's gene catalog allowing the user to pivot and investigate all relevant experimental results on that gene captured within the HD Explorer database.

CHDI study reports

The current HDinHD release includes 66 previously unpublished and fully downloadable CHDI reports examining chronic compound dosing or genetic intervention (ASO/siRNA/AAV delivery) paradigms for improvement of behavioral deficits, in either the R6/2 (CAG repeat range constrained to 110 – 150; B6CBA-Tg(HDexon1)62Gpb/3J) or Q175 knock-in (CAG repeat range constrained to 175 – 205, B6J.129S1-Htt/190JChdi) HD mouse models, conducted under standardized husbandry, breeding and preclinical testing conditions (https://www.chdifoundation.org/wp-content/uploads/HD_Field_Guide_040414.pdf) between 2005 and 2017. Reports include a variety of a) general health measures (body weight and neurological index scores); b) motor evaluations, such as open field, rearing/climbing, rotarod, grip strength and MotorRater™ kinematic gait assessments [9]; c) fear conditioning, cued two choice swim test assessment and d) in R6/2 only, survival outcome assessment.

Between 2005 and 2010, CHDI's initial emphasis was placed on the [rapid] independent validation of interventions against a number of targets that were reported to be efficacious in HD models on at least one of these endpoints or suggested to be disease modifying in an HD context, in the published literature. These studies were conducted in a more rapid 'survey mode' in the R6/2 model, with smaller treatment arm sizes ($n = 10$–14 sex-balanced mice per arm), occasionally covering multiple compound treatment groups compared side-by-side against appropriate vehicle treatment groups. Power analysis and experimental design rationale for this staged approach is provided within these reports, with the concept that a composite weighted statistical score ($p < 0.3$) from an entire test battery would prompt a second evaluation that used treatment arm sizes with appropriate power to assess statistically significant ($p < 0.05$) treatment effects against all individual assessments employed. In later study reports (or as part of more involved programmatic testing) 'full testing mode' was employed: typically $n \geq 20$ sex-balanced mice per arm (effect size and power for many assays are published [9–11]), and was always preceded by detailed pharmacokinetic and pharmacodynamic assessments to ensure CNS target engagement.

The 'detailed view' tabs available for each study within HD Explorer's Therapeutic Intervention section enables the user to make a convenient and quick comparison of 'same target' or 'same compound' intervention studies with regard to endpoints, treatment regimens and treatment arm sizes, which assists with review when findings are in conflict or fail to reproduce across studies [12, 13]. For example, a comparative view of meta-data captured and a summary of the findings from study reports compiled using a 'Treatment' filter = rolipram, is shown (Table 2).

THE FUTURE: UPDATING AND EXPANDING THE SCOPE OF HDinHD

The HD research community continues to design, generate, and publish a diverse array of important

Table 2
Therapeutic Intervention Studies: Filter: Treatment = rolipram

Main Target Pharmacology		PDE4 inhibitor								
Treatment		Rolipram								
Reference (PMID or CHDI report)		18424161	19291221	CHDI:59	CHDI:53	CHDI:68	CHDI:69	CHDI:61	CHDI:60	21835884
Year		2008	2009	2009	2009	2010	2010	2009	2009	2011
HD Model Common Name		R6/2	R6/2	R6/2	R6/2	R6/2	R6/2	R6/2	R6/2	R6/1
Treatment Regimen	Dose (mg/kg)	1.5	1.5	0.03, 0.3	0.3, 1	0.3, 1	0.3, 1	0.03, 0.3, 1	0.03, 0.3, 1	5
	Route	ip qd	ip qd	sc qd	sc qd	sc qd	sc qd	sc	sc	ip qd
	Dosing duration (age in weeks)	4 - D	4 - 13	4.5 - D	4.5 - D	3.5 - 15	4 - D	acute	acute	10-14
	Age of mice (in weeks)	4 - D	12	4.5 - D	4.5 - D	3.5 - 15	4 - D	8	8	10-14
Endpoints										
	Group size (n)	n.a*	6-8*	20	14	20	20	10	10	4 - 15
CHDI testing mode				F	S	F	F	custom	custom	
General health	Neurological Index				○ | ○					
	Body weight	○		○ | ○	○ | ○	○ | ○	○ | ○			
	Arousal			○ | ●		● | ●	○ | ○			
Survival		●		○ | ●	○ | ●		● | ●			
Motor	OF (locomotion)		●	○ | ●	● | ●	● | ●	● | ●	○ | ● | ●	○ | ● | ●	
	Rearing (OF)			○ | ○	● | ●	● | ●	● | ●	○ | ● | ●	○ | ○ | ●	
	Rotarod		●		○ | ○					
	Grip Strength				○ | ●					
	Hindlimb clasping	●								
Cognitive	2 Choice Swim Test (2CST)			○ | ●	● | ●	● | ○	● | ●	○ | ○ | ●		
	Fear Conditioning					○ | ○	○ | ○			
	T-maze SAT									○
	Morris Water Maze									○
	Novel Object Recognition									○

D, death; S, "survey mode"; F, "full testing mode"; ip, intraperitoneal; sc, subcutaneous; qd, once daily. *24 mice were dosed per treatment arm at study start, with severe attrition of R6/2 mice over the study course. na, data not readily available. Compared to vehicle-treated HD model mice, ○ = no significant effect, ● = detrimental trend ($p = 0.06$) ● = significant detrimental effect, ● = significant beneficial effect ($p < 0.05$).

Table 2 is compiled from captured meta-data from studies readily available in the detailed view tabs or through download. **Observations:** Two publications [14, 15] reported that 1.5 mg/kg ip qd rolipram was disease modifying in the R6/2 mouse model, significantly improving survival and motor function. Chronic dosing of rolipram to R6/2 mice in CHDI studies (59, 53, 68, and 69) produced consistent findings, but did not reproduce these observations. Rolipram (0.03 mg/kg sc qd) was ineffective against all outcome measures. Rolipram (1 mg/kg sc qd) significantly worsened motor function and negatively impacted survival, but conferred a significant pro-cognitive benefit to R6/2 mice in the 2CST. Rolipram (0.3 mg/kg sc qd) partially mitigated the negative effects on survival and motor function, while retaining the positive pro-cognitive effect in the 2CST. Both the detrimental effects on locomotor function and the beneficial effects on 2CST were reproduced following a single acute administration in symptomatic R6/2 mice (CHDI studies 61 and 60), suggestive of an acute effect of the compound. Conclusions: The inability to replicate published disease modifying effects of rolipram in R6/2 mice was likely due to a combination of lesser power and non-optimized standards of care in studies conducted in [14, 15]. Outcome: CHDI continued to explore PDE4 inhibition as a potential symptomatic pro-cognitive strategy for HD patients in collaboration with Biotech partners [16]. No disease modifying potential of PDE4 inhibitors in HD patients are anticipated based on CHDI HD model studies.

omics and other studies, using both proven and emerging high-throughput technologies, such as single-cell sequencing, cell-type specific sequencing, and DNA methylation arrays. We encourage HD researchers to continue to check GEO, ArrayExpress, PRIDE, and PubMed for existing and new HD studies generated using these exciting methods.

Just as HDinHD leverages best-practice 'omics repositories, our preference is to leverage in-place community scientific applications that can provide

important analytical, visualization or reporting functionality in support of HD research. We position HDinHD as a centralized portal that highlights HD data and HD tools, and leverages the robust HD Explorer data scaffold to naturally enhance data and computing interoperability across the federated system.

Our expectation is that future improvements to HDinHD will occur organically and collaboratively with HD, informatics, and computational experts to grow a distributed yet integrated HD informatics environment. Current plans to expand HD Explorer with additional HD-centric experimental and reference data are underway. For instance, with the Therapeutics Intervention studies platform now established, CHDI remains committed to disseminating internal results to the broader community via HDinHD in as timely a manner as possible. Future planned report releases will include phenotyping reports of genetically modified crosses to HD models as well as complementary experimental studies. These will include HTT quantification studies and other relevant ancillary studies performed following terminal tissue collection or on the satellite cohorts of the behavioral studies reported here. Where applicable, treatment studies will be explicitly linked to transcriptomic and proteomic analysis that are currently represented in HD Explorer's Omics data section. In addition, we are poised to release a new HD Explorer component later this year that captures data from > 1000 HD perturbation studies described in the literature. We intend to further develop the HD Explorer's HD gene catalog as a hub with rich links to and from component applications. Our foundational driver is to grow HDinHD in response to expression of needs, and we continue to seek out community expertise and opportunities to extend HDinHD functional capabilities through growing its set of federated applications. We welcome suggestions and insights either through the Feedback link on the HDinHD website or by contacting CHDI directly.

ACKNOWLEDGMENTS

We thank the many organizations and individuals that have contributed to HDinHD application development and content. Bioinformatics Analysis: John Obenauer (Rancho Biosciences). Application Development: Sandeep Deverasetty (UCLA), Doxa Chatzopoulou (UCLA), Yining Zhao (UCLA), Leonid Ivanov (Rancho BioSciences); David Lipson. *In vivo* CROs: Psychogenics Inc., NJ, USA and Charles River Laboratories, Kuopio, Finland. Proteomics: Evotec, Hamburg, Germany. CHDI: *In vivo* Study Team: [LCP, VB, IMS], David Howland, Liliana Menalled, Roger Cachope, Vinod Khetarpal, Brenda Lager. Program Management support: Lou Ferdinand, Sharon Purcell, Oxana Lavrova, Martina Blumenthal, Todd Herbst. Technical Support: Chris Rackow. Chemistry Support: Joseph Greenstein, Celia Dominguez.

This work was funded by CHDI Foundation, a not-for-profit biomedical research organization.

CONFLICT OF INTEREST

The authors declare no competing interests.

REFERENCES

[1] Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets–update. Nucleic Acids Res. 2013; 41(Database issue):D991-5.

[2] Leinonen R, Sugawara H, Shumway M, International Nucleotide Sequence Database Collaboration. The sequence read archive. Nucleic Acids Res. 2011;39(Database issue):D19-21.

[3] Perez-Riverol Y, Csordas A, Bai J, Bernal-Llinares M, Hewapathirana S, Kundu DJ, et al. The PRIDE database and related tools and resources in 2019: Improving support for quantification data. Nucleic Acids Res. 2019;47(D1): D442-D50.

[4] Alexandrov V, Brunner D, Menalled LB, Kudwa A, Watson-Johnson J, Mazzella M, et al. Large-scale phenome analysis defines a behavioral signature for Huntington's disease genotype in mice. Nat Biotechnol. 2016;34(8):838-44.

[5] Langfelder P, Cantle JP, Chatzopoulou D, Wang N, Gao F, Al-Ramahi I, et al. Integrated genomics and proteomics define huntingtin CAG length-dependent networks in mice. Nat Neurosci. 2016;19(4):623-33.

[6] Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, et al. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet. 2003;34(3): 267-73.

[7] Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. Identification of genetic factors that modify clinical onset of Huntington's disease. Cell. 2015;162(3):516-26.

[8] Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. Electronic address: Gusella@helix.mgh.harvard.edu, et al. CAG repeat not polyglutamine length determines timing of Huntington's disease onset. Cell. 2019; 178(4):887-900 e14.

[9] Heikkinen T, Bragge T, Bhattarai N, Parkkari T, Puolivali J, Kontkanen O, et al. Rapid and robust patterns of spontaneous locomotor deficits in mouse models of Huntington's disease. PLoS One. 2020;15(12):e0243052.

[10] Menalled LB, Patry M, Ragland N, Lowden PA, Goodman J, Minnich J, et al. Comprehensive behavioral testing in the R6/2 mouse model of Huntington's disease shows no benefit

from CoQ10 or minocycline. PLoS One. 2010;5(3):e9793.
[11] Menalled LB, Kudwa AE, Miller S, Fitzpatrick J, Watson-Johnson J, Keating N, et al. Comprehensive behavioral and molecular characterization of a new knock-in mouse model of Huntington's disease: zQ175. PLoS One. 2012;7(12): e49838.
[12] Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: Why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365-76.
[13] Simmons JP, Nelson LD, Simonsohn U. False-positive psychology: Undisclosed flexibility in data collection and analysis allows presenting anything as significant. Psychol Sci. 2011;22(11):1359-66.
[14] DeMarch Z, Giampa C, Patassini S, Bernardi G, Fusco FR. Beneficial effects of rolipram in the R6/2 mouse model of Huntington's disease. Neurobiol Dis. 2008;30(3):375-87.
[15] Giampa C, Middei S, Patassini S, Borreca A, Marullo F, Laurenti D, et al. Phosphodiesterase type IV inhibition prevents sequestration of CREB binding protein, protects striatal parvalbumin interneurons and rescues motor deficits in the R6/2 mouse model of Huntington's disease. Eur J Neurosci. 2009;29(5):902-10.
[16] Sutcliffe JS, Beaumont V, Watson JM, Chew CS, Beconi M, Hutcheson DM, et al. Efficacy of selective PDE4D negative allosteric modulators in the object retrieval task in female cynomolgus monkeys (Macaca fascicularis). PLoS One. 2014;9(7):e102449.