Precise machine-learning suggests that neuronal death in HD is mainly driven by the loss of homeostatic responses

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Rationale

Although homeostasis holds great potential for neuroprotection in several neurodegenerative diseases, the global importance of homeostatic mechanisms in counteracting neurodegenerative disease has remained elusive in each case, due to difficulties associated with studying different cell types within the mammalian brain (Lee et. all 2020, Wertz et. all 2020). Recently, genomic screening technologies have been used to interrogate how specific neurons in the brain of living mice may use hundreds of genes to drive or to oppose neurodegenerative disease processes. However extracting systems level information from these complex datasets is challenging. Here, we developed **Geomic, a computational approach based on shape deformation concepts to map the dynamics of cell-type-specific molecular responses in the striatum of HD model mice**.

Source datasets

We integrated three datasets:

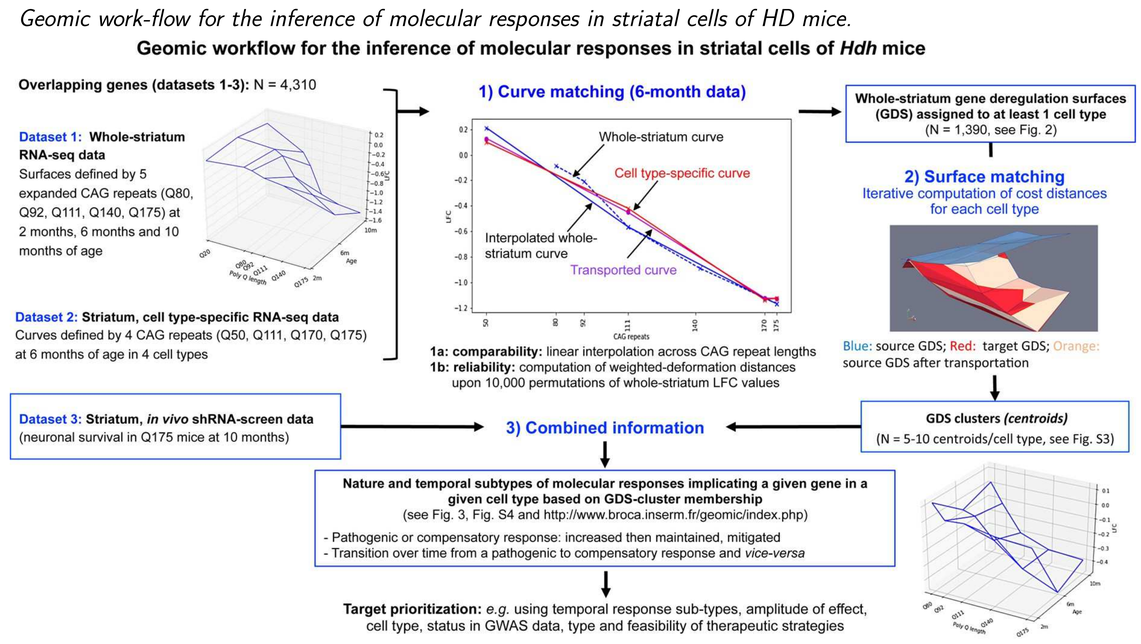
• Bulk striatal RNA of the allelic series of HD knock-in mice (Hdh mice), six CAG repeat lengths: Q20 to Q175; three age points: 2 months, 6 months, 10 months, (Langfelder et al., 2016).

• Cell-type-specific RNA-seq data encompassing four striatal cell types and five CAG repeat lengths (20, 50, 111, 170, or 175 CAG repeats) at 6 months of age (Lee et al. 2020).

• And a neuron survival dataset obtained in the Hdh-Q175 mice upon infection of the striatum with genome-wide shRNA pools subcloned into lentivirus that preferentially transfect neurons (Wertz et al. 2020).

Geomic work-flow and summary of the results

Geomic work-flow for the inference of molecular responses in striatal cells of HD mice.

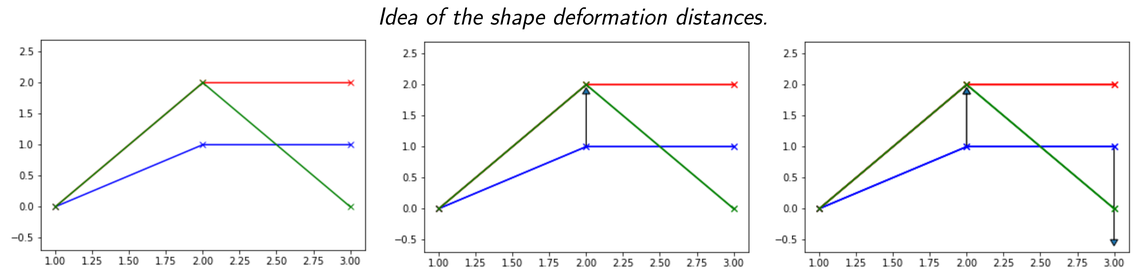


More precisely:

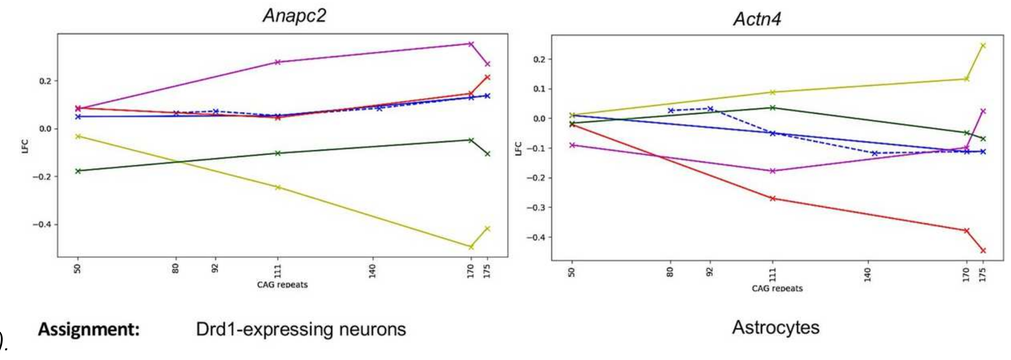
• Compute log2-to-fold change (LFC) for each gene in each data set.

• Compare the LFC-curves at 6 month to assign the whole striatum deregulation to a specific cell-type in order to assign this deregulation to one ore more cell-type.

Idea of the shape deformation distances.



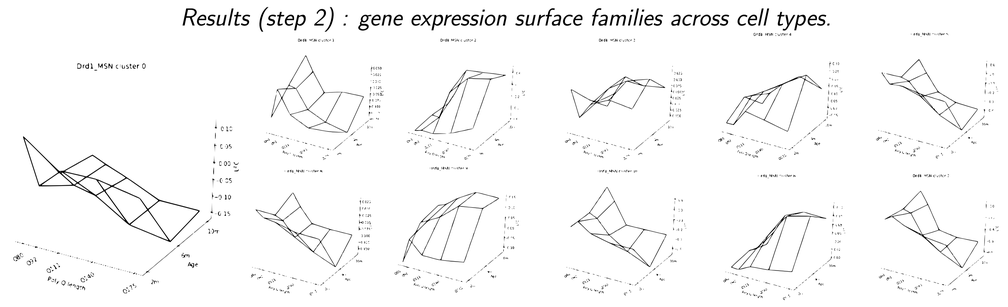
Example of whole-striatum gene-deregulation curves assigned to a specific striatal cell-type in HD knock-in mice (age: 6 month).



• Define cluster of genes deregulation surfaces for each cell-type.

• Integrate shape deformation data and shRNA-screen data in order to identify the temporal subtypes of molecular responses across striatal cell types in the HD mice.

Results (step 2) : gene expression surface families across cell types.

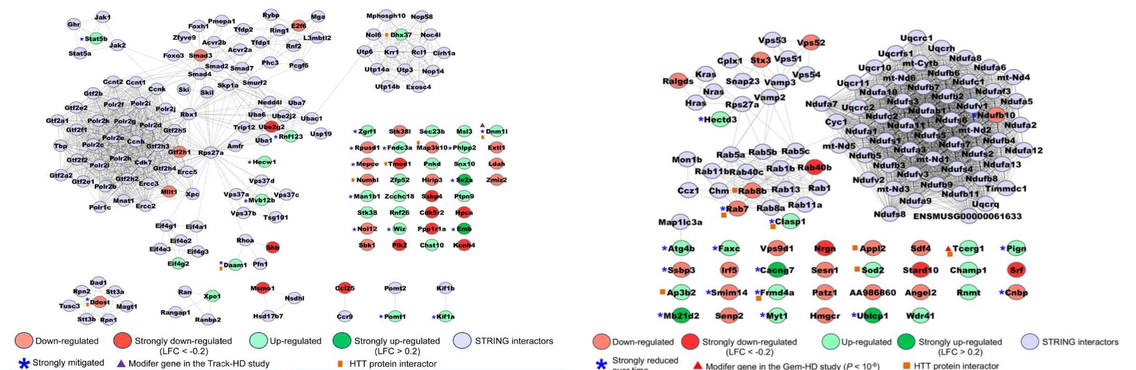


Gene-deregulation-surface centroids associated with striatal Drd1-expressing neurons.

- **Most pathogenic responses are mitigated** (Drd1-MSNs: 73%, Drd2-MSNs: 83%, and astrocytes: 64%) and that **most homeostatic responses are decreased over time** (Drd1-MSNs: 69%, Drd2-MSNs: 80%, and astrocytes: 69%).
- Strong reduction is a more frequent event in the compensatory response group (34%) compared to the pathogenic response group (25%) as observed for Drd1-MSNs, Drd2-MSNs, and astrocytes.

These findings suggest that **neuronal death in HD is mainly driven by the loss of homeostatic responses**, and not by the reinforcement of pathogenic effects, highlighting the global importance of homeostatic processes across brain cell types.

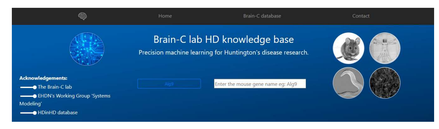
Drd1-expressing neurons of HD knock-in mice.



Pathogenic response. *Homeostatic response.*

Access to all results

Link to Geomic database here !



Link to BrainC lab database database here !

Benefits for drug discovery

Our results provide a database of future targets to probe. This database sets a precise basis for studying how to **properly re-instate brain cell compensation in HD, and possibly in other neurodegenerative diseases that share common compensatory mechanisms with HD**.

This database provides a blueprint to select the right targets for re-instating neuronal resilience, the right biomarker(s) for monitoring whether emerging drugs may engage homeostatic mechanisms for efficacy, and to use these tools in experimental models of HD. These results could provide biomarkers that **may be used in HD mice to test whether candidate drugs may protect the brain by blocking pathobiology or by increasing homeostasis, enhancing the precision of preclinical studies**.

Main points

• Geomic analysis strongly reduces data complexity, generating biologically homogeneous clusters.

• Among the compensatory responses that are increased then reduced, the alteration of endosome biogenesis and mitochondrial quality control are common disease drivers in Drd-1 neurons and striatal astrocytes: for example, *Rab7* and *Clasp1*.

• Primary targets of the combined gain of pathogenicity and loss of compensation, for example in Drd1-MSNs, include proteasome-mediated protein catabolism ($p = 5.93 \times 10^{-62}$), regulation of cell cycle ($p = 2.47 \times 10^{-5}$: e.g., G1 and G2 transitions), senescence-associated secretory phenotypes ($p = 8.32 \times 10^{-17}$), DNA repair ($p = 9.01 \times 10^{-5}$), TGF-β signaling ($p = 0.0019$), and Rab-dependent vesicle trafficking (e.g., *Rab1*, *Rac1*, *Gdi1*, *Chm*) • Several of the molecular responses identified to modulate neuronal survival in the striatum of Hdh mice may also modulate neuronal activity in HD models and/or gene expression or age-at-onset in human HD.

Finally shape deformation analysis can be applied to the analysis of omics data in a host of other diseases, notably other neurodegenerative diseases.