Classification of chemogenomic drugs' effect on HD skin fibroblasts phenotype according to patient's severity status

Noam Muchtar Ph.D. student

Under the supervision of Prof. Miguel Weil

Abstract

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder, caused by an overextension of CAG nucleotide repeats in the gene that encodes the Huntingtin protein. The mutated protein (mHTT) causes various deficiencies in the patient's cells, leading to neuron death in the striatum and disease progression. Currently, there is no cure for HD.

Previous studies were done in our laboratory using image-based HCA technology and broad analysis using primary skin fibroblasts as a model, identify differences in nuclear parameters, cell migration patterns, and mitochondrial morphology in HD compared to HC samples.

One of the challenges in HD research is that the HD cohort is heterogeneous because of different CAG repeat lengths, disease duration, and other factors.

Deepening the knowledge and understanding of the phenotype differences between the HD stages in patients' cells is highly important for future development of personalized medicine for HD, as well as to improve HD diagnosis and create potential drug treatment accuracy for the patient's disease stage. Therefore, in this work, we focus on expanding the already established cell phenotypic characterization of the HD group using novel image-based high-content analysis and trying to classify the patients into the appropriate disease sub-group based on the patient's fibroblasts phenotype and their respective known clinical parameters (such as CAP score calculation). Next, the main aim is to investigate the effect of different chemogenomic drugs (with known molecular drug targets) on patient's fibroblasts phenotype, based on the patient's disease severity. This goal may promote a severity-based drug screening platform for HD that may improve the ability to adjust the appropriate (yet unavailable) treatment for HD patients in the future.

So far, new preliminary phenotypic experiments have shown differences between the HC and the different HD subgroups in the lysosome and the mitochondria. In a recently published work, we have shown severity-based mitochondrial dynamics differences in HD using custom image based high-content analysis and machine learning tools.