i2b2 DRIVING BIOLOGY PROJECT 3 HUNTINGTON'S DISEASE

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Huntington's disease (HD) is a dominant neurodegenerative disorder caused by expansion of a CAG trinucleotide repeat in the *HD* gene from about 6-35 repeats (non-HD range) to 36-100 repeats (HD range), extending a normally variable run of glutamines in the huntingtin protein. We have established genetic criteria from studies of human patients that define characteristics of the trigger mechanism (dominance, increasing severity with increased polyglutamine tract length in the non-HD and the HD range) but the biochemical nature of the trigger mechanism and the processes that lead to dysfunction and ultimate death of target neurons, such as medium spiny neurons of the striatum, remain unknown. This project aims to test the hypothesis that microarray analyses of sets of cells and tissues with HD CAG repeats that span the non-HD and HD ranges, may uncover changes in gene expression patterns that conform to the HD genetic criteria. We have generated 1) Affymetrix U133 Plus 2.0 microarray datasets for lymphoblastoid cell lines from 19 individuals, with HD repeats ranging from 18 to 50 CAGs, and 2) mouse Affymetrix MG 430 2.0 microarray datasets for brain tissues (striatum and cerebellum) from accurate genetic HD CAG knock-in mouse models with a juvenile onset (Hdh^{Q111}) or an adult onset (Hdh^{Q50}) CAG repeats. Unsupervised cluster analysis of the lymphoblastoid cell data revealed that there was discrimination of the short (nonpathogenic) repeats from those in the disease-causing range and early evidence of a genetic signature that may vary by CAG repeat length. Analyses of the mouse datasets revealed that the severe juvenile onset HD repeat resulted in a larger number of gene changes than the typical adult onset HD repeat and that gene changes are more frequent in striatum (a target tissue) than in cerebellum (spared in HD). Preliminary pathway analyses implicate alterations in a variety of important cellular processes; mitochondrial, ribosomal, RNA metabolism, protein metabolism, and transport. These data suggest that deeper analyses of these datasets may reveal pathways that change with HD CAG repeat size, providing candidates for genetic, cell biological and molecular studies of presymptomatic HD.
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