Abstracts

Who and Why? Requests for Presymptomatic Genetic Testing for Amyotrophic Lateral Sclerosis/Frontotemporal Dementia vs Huntington Disease

Objective We aimed to describe the population of subjects seeking presymptomatic counseling for amyotrophic lateral sclerosis and/or frontotemporal dementia (ALS/FTD) and compared them with those demanding the well-established presymptomatic test for Huntington disease (HD).

Methods We retrospectively examined the requests of a cohort of individuals at risk of familial ALS/FTD and 1 at risk of HD over the same time frame of 11 years. The individuals were seen in the referral center of our neurogenetics unit.

Results Of the 106 presymptomatic testing (PT) requests from subjects at risk of ALS/FTD, 65% were seen in the last 3 years. Over two-thirds of the subjects were at risk of carrying mutations responsible for ALS, FTD, or both. Sixty-two percent of the subjects came from families with a known hexanucleotide repeat expansion in C9ORF72. During the same period, we counseled 840 subjects at risk of HD. Subjects at risk of ALS/FTD had the presymptomatic test significantly sooner after being aware of their risk, but were older than those at risk of HD. The youngest subjects requesting the test had the highest disease load in the family (p < 0.05).

Conclusions Demands for PT for ALS/FTD have been increasingly growing, particularly since the discovery of the C9ORF72 gene. The major specificity of the genetic counseling for these diseases is the unpredictability of the clinical phenotype for most of the genes involved. Awareness of this added uncertainty does not prevent individuals from taking the test, as the dropout rate is not higher than that for HD.

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DMPK mRNA Expression in Human Brain Tissue Throughout the Lifespan

Objective Myotonic dystrophy is a multisystem disorder caused by a trinucleotide repeat expansion on the myotonic dystrophy protein kinase (DMPK) gene. To determine whether wildtype DMPK expression patterns vary as a function of age, we analyzed DMPK expression in the brain from 99 donors ranging from 5 post-conceptional weeks to 80 years old.

Methods We used the BrainSpan messenger RNA sequencing and the Yale Microarray data sets, which included brain tissue samples from 42 and 57 donors, respectively. Collectively, donors ranged in age from 5 postconceptional weeks to 80 years old. DMPK expression was normalized for each donor across regions available in both data sets. Restricted cubic spline linear regression models were used to analyze the effects of log-transformed age and sex on normalized DMPK expression data.

Results Age was a statistically significant predictor of normalized DMPK expression pattern in the human brain in the BrainSpan (p < 0.005) and Yale data sets (p < 0.005). Sex was not a significant predictor. Across both data sets, normalized wildtype DMPK expression steadily increases during fetal development, peaks around birth, and then declines to reach a nadir around age 10.

Conclusions Peak expression of DMPK coincides with a time of dynamic brain development. Abnormal brain DMPK expression due to myotonic dystrophy may have implications for early brain development.

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