Researchers estimate risk of transmission of Huntington's disease to offspring among male carriers

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Researchers from Boston University School of Medicine (BUSM) have quantified the probability of a male who carries a "high normal" variant of the Huntington's Disease (HD) gene having a child who develops the disease. Although thought to be a very rare event, the probability has never been estimated using current information and disease guidelines. The findings, appear on-line in the *American Journal of Medical Genetics*, may be useful during prenatal genetic counseling.

Huntington disease (HD) is a hereditary neurodegenerative disorder that arises from expansion of a CAG trinucleotide repeat on chromosome 4. Individuals with a variant of at least 36 CAG repeats will likely develop HD in their lifetime. Most individuals have a variant below 27 CAG repeats and are not at risk for the disease nor are they at risk of passing on the disease to their children. However, although individuals with a variant between 27 and 35 CAG repeats (called high normal) are not at risk of developing HD, males may pass an expanded CAG repeat onto their children making the child at risk of developing HD.

While several studies suggest that male carriers of high normal alleles have a low probability of transmitting an expanded HD allele in the penetrant range, few studies have attempted to estimate this probability.

The researchers estimated the conditional probability of an offspring inheriting an expanded allele from a father with a high normal allele by

applying probability definitions and rules to estimates of HD incidence, paternal birth rate, frequency of no family history of HD, and frequency of high normal alleles in the general population. "The estimated probability that a male high normal allele carrier will have an offspring who develops HD ranges from 1/6,241 to 1/951," said lead author Audrey Hendricks, a research assistant and biostatistics doctoral student at BUSM and Boston University School of Public Health.

According to the researchers, the proportion of males who have a high normal allele is less than three percent. "Using our maximum probability estimate of 1/951, we see that over 30,000 men would need to be gathered to find one man with a high normal allele who has a child who develops HD," explained Hendricks.

"Even with our effort to provide a conservative estimate, our estimate for the maximum probability suggests that expansion rates are rare. However, it provides a baseline to assist genetic counselors and high normal allele carriers with family planning," she added.

Source: Boston University Medical Center