Key Summary of Conference Abstract

HTT CAG Repeat Length Variation in Huntington Disease (HD) Patients: Experience From a US Reference Laboratory

Background

- Huntington disease (HD) is a rare, fatal neurodegenerative disease caused by an expansion of a trinucleotide (CAG) repeat in the huntingtin gene (*HTT*).
- Longer CAG-repeat lengths have been associated with earlier ages of symptom onset,[1] but larger studies in more nationally representative populations are warranted.
- **Objective:** In this study, investigators examined CAG-repeat lengths in specimens from patients of varying ages submitted for *HTT* testing at a large US reference laboratory.

Methods

- The study included consecutive specimens from patients with suspected HD.
- Specimens were submitted to Athena/Quest Diagnostics for *HTT* analysis.
  - For adults, CAG-repeat length was analyzed by PCR. For homozygous juvenile patients, length was analyzed by Southern blot.
- Patient age at testing was assumed as the age of symptom onset.
- The relationship of CAG-repeat length and age of symptom onset was analyzed using polynomial regression.

Results

- Specimens represented 5 age groups: <18 years old (3%), 18 to 30 (10%), 31 to 50 (34%), 51 to 70 (39%), and >70 (14%).
- Of the 26,037 specimens analyzed, 11,390 (44%) had CAG-repeat lengths indicating HD.
  - Reduced penetrance alleles were identified in 605. Expansions on both *HTT* alleles were identified in 34.
  - CAG-repeat lengths of 40 to 45 were identified in 73%; lengths of 46 to 50 were identified in 16%.
- CAG-repeat length was inversely associated with age of symptom onset (*P* <0.001).
  - CAG-repeat lengths >70 were identified in 35% (n=58) of patients <18 years but in <0.1% (n=7) of older patients (*P* <0.001).
  - Almost all patients >50 years had CAG repeat lengths ≤50 (5,649 of 5,650, 99.9%).

Conclusions

- CAG-repeat lengths of 40 to 50 were the most frequently identified pathogenic *HTT* alleles.
- Long CAG-repeat expansions were common in younger patients (<18 years of age) but rare in those >50.

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Authors

Sat Dev Batish,[1] Marc Meservey,[1] Farnoosh Haji-Sheikhi,[2] Elise Nedzweckas,[1] Zhenyuan Wang,[1] Vivekananda Datta,[2] Thomas Mullen,[2] Jeff Radcliff[2]

Affiliations

[1]Athena Diagnostics, Marlborough, MA, USA
[2]Quest Diagnostics, San Juan Capistrano, CA, USA

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Webpage

https://index.mirasmart.com/AAN2021/PDFfiles/AAN2021-002376.html

Reference

1. Jiminez-Sanchez M, Licitra F, Underwood BR, et al. Huntington's disease: mechanisms of pathogenesis and therapeutic strategies. *Cold Spring Harb Perspect Med*. 2017;7:a024240. doi: 10.1101/cshperspect.a024240

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