Clinical manifestations of intermediate allele carriers in Huntington disease

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Résumé en anglais	OBJECTIVE: There is controversy about the clinical consequences of intermediate alleles (IAs) in Huntington disease (HD). The main objective of this study was to establish the clinical manifestations of IA carriers for a prospective, international, European HD registry. METHODS: We assessed a cohort of participants at risk with <36 CAG repeats of the huntingtin (HTT) gene. Outcome measures were the Unified Huntington's Disease Rating Scale (UHDRS) motor, cognitive, and behavior domains, Total Functional Capacity (TFC), and quality of life (Short Form-36 [SF-36]). This cohort was subdivided into IA carriers (27-35 CAG) and controls (<27 CAG) and younger vs older participants. IA carriers and controls were compared for sociodemographic, environmental, and outcome measures. We used regression analysis to estimate the association of age and CAG repeats on the UHDRS scores. RESULTS: Of 12,190 participants, 657 (5.38%) with <36 CAG repeats were identified: 76 IA carriers (11.56%) and 581 controls (88.44%). After correcting for multiple comparisons, at baseline, we found no significant differences between IA carriers and controls for total UHDRS motor, SF-36, behavioral, cognitive, or TFC scores. However, older participants with IAs had higher chorea scores compared to controls ($p = 0.001$). Linear regression analysis showed that aging was the most contributing factor to increased UHDRS motor scores ($p = 0.002$). On the other hand, 1-year follow-up data analysis showed IA carriers had greater cognitive decline compared to controls ($p = 0.002$). CONCLUSIONS: Although aging worsened the UHDRS scores independently of the genetic status, IAs might confer a late-onset abnormal motor and cognitive phenotype. These results might have important implications for genetic counseling. CLINICALTRIALSGOV IDENTIFIER: NCT01590589.
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