Caracterización clínica, asesoramiento genético y análisis genético molecular del gen HTT en núcleos familiares en riesgo para eh en el Departamento del Atlántico y otras poblaciones del Caribe Colombiano

Nombres y apellidos

Javier Antonio Yáñez Torregrosa

Código estudiantil:

2014210556124

Trabajo de Investigación presentado como requisito para optar el título de:

Magíster en Genética

Tutor(es):

Zuleima Isabel Yáñez Torregrosa

RESUMEN

La Enfermedad de Huntington de Huntington (EH) es un trastorno neurodegenerativo autosómico dominante causado por la expansión del triplete CAG en el gen *HTT* (4p16.3), que produce una progresiva alteración motora, cognitiva y psiquiátrica. Aunque está reconocida como una enfermedad huérfana en Colombia, persisten profundas brechas en diagnóstico molecular, acceso a asesoramiento genético y atención especializada, especialmente en el Caribe colombiano, donde existen poblaciones históricamente afectadas y con transmisión intrafamiliar sostenida.

El objetivo de este estudio fue caracterizar clínicamente a los individuos en riesgo, evaluar sus condiciones socio epidemiológicas y realizar el análisis molecular del gen *HTT* para determinar la distribución de repeticiones CAG, integrando además un proceso formal de asesoramiento genético dirigido a familias de los departamentos del Atlántico y Magdalena. Se incluyeron 59 participantes pertenecientes a 13 núcleos familiares con antecedente confirmado o presunto de EH.

La caracterización clínica permitió identificar manifestaciones motoras, cognitivas y psiquiátricas consistentes con fases tempranas y avanzadas de la enfermedad, coherentes con la literatura según la cual los síntomas pueden iniciarse décadas antes del diagnóstico definitivo. Asimismo, se documentaron síntomas neuropsiquiátricos premotores, cuya presencia temprana puede anticipar la expansión patológica en personas presintomáticas.

El componente socio epidemiológico evidenció vulnerabilidad estructural en las familias evaluadas: materiales de vivienda de bajo costo, hacinamiento, exposición a zonas de riesgo, empleos informales, limitaciones económicas y barreras de acceso al sistema de salud. Estos hallazgos son consistentes con estudios previos en comunidades afectadas del Caribe colombiano y explican en parte la continuidad silenciosa de la enfermedad entre generaciones.

El análisis molecular se realizó mediante PCR y evaluación de electroferogramas, clasificando los alelos en categorías internacionalmente aceptadas: normales (≤26 CAG), intermedios (27–35 CAG), penetrancia reducida (36–39 CAG) y patológicos (≥40 CAG). Se identificaron casos con alelos expandidos, con inestabilidad intergeneracional compatible con el fenómeno de anticipación, y se confirmó la presencia de alelos intermedios que podrían contribuir al mantenimiento de la mutación en la población.

El asesoramiento genético se desarrolló conforme a las guías internacionales, abordando la toma de decisiones autónomas, las implicaciones emocionales y los riesgos reproductivos. Este proceso permitió mejorar la comprensión del patrón autosómico dominante, reducir la incertidumbre emocional y favorecer la adherencia a rutas de seguimiento neurológico. No obstante, se identificaron barreras importantes para la atención: ausencia de servicios de genética en la región, desconocimiento general sobre la herencia, estigma sociocultural y falta de preparación para afrontar el diagnóstico presintomático.

Este estudio constituye una aproximación integral que combina evaluación clínica, análisis socio habitacional, caracterización genética molecular y asesoramiento genético en comunidades del Caribe colombiano. Sus resultados aportan evidencia esencial para fortalecer rutas de atención en enfermedades neurodegenerativas, orientar decisiones en salud pública y fundamentar programas locales de diagnóstico temprano y reducción del riesgo reproductivo. Además, establece una base sólida para investigaciones futuras que profundicen en la prevalencia regional, el comportamiento intergeneracional de la mutación y los determinantes sociales que condicionan la evolución de la enfermedad.

Palabras clave: Enfermedad de Huntington; asesoramiento genético; repeticiones CAG; análisis molecular; Caribe colombiano.

ABSTRACT

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat in the *HTT* gene, leading to progressive motor, cognitive, and psychiatric decline. Although HD is officially recognized as a rare disease in Colombia, significant gaps remain in molecular diagnosis, genetic counseling, and specialized clinical care, especially in the Caribbean region, where several high-risk families have been historically identified.

This study conducted clinical characterization, socio epidemiological assessment, and CAG repeat molecular analysis in 59 individuals from 13 families with confirmed or suspected HD in the departments of Atlántico and Magdalena. Clinical findings revealed motor and neuropsychiatric features consistent with early and advanced stages of the disease. Socio epidemiological evaluations showed structural vulnerability, limited access to health services, and socioeconomic constraints affecting disease management.

Molecular analysis identified normal, intermediate, reduced penetrance, and fully penetrant alleles, supporting intergenerational instability and anticipation. Genetic counseling followed international protocols, improving understanding of inheritance, emotional preparedness, and reproductive decision-making.

This integrative approach provides essential evidence for improving diagnostic pathways, public health strategies, and genetic counseling services for HD in the Colombian Caribbean and establishes a foundation for future research.

Key Words: Huntington's disease; genetic counseling; CAG repeats; molecular analysis; Colombian Caribbean

REFERENCIAS BIBLIOGRÁFICAS

1. Huntington T, Macdonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell. 1993;72(6).
2. Cardoso F. Huntington Disease and Other Choreas. Vol. 27, Neurologic Clinics. 2009.
3. Devadiga SJ, Bharate SS. Recent developments in the management of Huntington's disease. Vol. 120, Bioorganic Chemistry. 2022.
4. Medina A, Mahjoub Y, Shaver L, Pringsheim T. Prevalence and Incidence of Huntington's Disease: An Updated Systematic Review and Meta-Analysis. Vol. 37, Movement Disorders. 2022.
5. Medina Escobar A, Pringsheim T, Gautreau S, Rivera-Duarte JD, Amorelli G, Cornejo-Olivas M, et al. Epidemiology of Huntington's disease in Latin America: A Systematic Review and Meta-Analysis. Mov Disord. 2024 Nov;39(11):1907–21.
6. Walker RH, Gatto EM, Bustamante ML, Bernal-Pacheco O, Cardoso F, Castilhos RM, et al. Huntington's disease-like disorders in Latin America and the Caribbean. Vol. 53, Parkinsonism and Related Disorders. 2018.
7. Daza B, Cajaffa RH, Arteta BJH, et al. Estudio Neuroepidemiológico en Juan de Acosta (Atlántico-Colombia) Julio de 1989 a Julio de 1991. Acta Medica Colombiana. 1992:17:324.
8. Echeverría E. El desarrollo social en la comunidad de Juan de Acosta afectada por la enfermedad de Huntington. Atlántico (Colombia): Documento institucional; 2009.
9. Campo M, Baute L. Procesos humanitarios en comunidades afectadas por la Enfermedad de Huntington en la Región Caribe Colombiana. Fundación Colombiana de Comunidades Vulnerables de Colombia (FUNCOVULC). 2013.
10. Ramos AR, Paiva T, Almeida L. Huntington’s disease: Premotor phase. Neurodegener Dis. 2017;17(6):313-22.
11. Kachian ZR, Cohen-Zimerman S, Bega D, Gordon B, Grafman J. Suicidal ideation and behavior in Huntington's disease: Systematic review and recommendations. Vol. 250, Journal of Affective Disorders. 2019.
12. Varela Londoño LE, Giraldo Mora CV, León Gañan J, Arias Valencia MM. La enfermedad de Huntington: una difícil relación entre los enfermos y el derecho a la salud en Colombia. Revista Ciencias de la Salud. 2021;19(2).

13. Oosterloo M, Touze A, Byrne LM, Achenbach J, Aksoy H, Coleman A, et al. Clinical Review of Juvenile Huntington's Disease. J Huntingtons Dis. 2024 Jul 2;13(2):149–61.

14. Congreso de la República de Colombia. Ley 1392 de 2010. Gaceta oficial 2010.

15. Congreso de Colombia. Ley 1438 de 2011. Congreso de Colombia. 2011;4.

16. Protocolo de Vigilancia en salud pública. Enfermedades Huérfanas - Raras. 2024 Aug.

17. Ministerio de Salud y de Protección Social. Resolución 0023 de 2023. Colombia; Jan 4, 2023 p. 1–42.

18. Instituto Nacional de Salud (INS). Informe de Evento de Enfermedades Huérfanas. Periodo epidemiológico XII de 2024. 2024.

19. Jiang A, Handley RR, Lehnert K, Snell RG. From Pathogenesis to Therapeutics: A Review of 150 Years of Huntington's Disease Research. Vol. 24, International Journal of Molecular Sciences. 2023.

20. Corte Constitucional de Colombia. Sentencia C-055 de 2022. Colombia. 2022;(i).

21. Andhale R, Shrivastava D. Huntington's Disease: A Clinical Review. Cureus. 2022 Aug 27;

22. Nance MA. Genetics of Huntington disease. In 2017. p. 3–14.

23. Bastepe M, Xin W. Huntington Disease: Molecular Diagnostics Approach. Curr Protoc Hum Genet. 2015 Oct 6;87(1).

24. Stoker TB, Mason SL, Greenland JC, Holden ST, Santini Huntington's disease: diagnosis and management. Pract Neurol. 2022 H, Barker RA. Feb;22(1):32–41.

25. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol. 2011 Jan;10(1):83–98.

26. Gusella JF, Lee JM, Macdonald ME. Huntington's disease: Nearly four decades of human molecular genetics. Vol. 30, Human Molecular Genetics. 2021.

27. Sathasivam K, Neueder A, Gipson TA, Landles C, Benjamin AC, Bondulich MK, et al. Aberrant splicing of HTT generates the pathogenic exon 1 protein in Huntington disease. Proc Natl Acad Sci U S A. 2013;110(6).

28. Morigaki R, Goto S. Striatal vulnerability in huntington's disease: Neuroprotection versus neurotoxicity. Vol. 7, Brain Sciences. 2017.

29. Serranilla M, Pressey JC, Woodin MA. Restoring Compromised Cl- in D2 Neurons of a Huntington's Disease Mouse Model Rescues Motor

Disability. The Journal of Neuroscience. 2024 Dec 11;44(50):e0215242024.

30. Lee JM, Correia K, Loupe J, Kim KH, Barker D, Hong EP, et al. CAG Repeat Not Polyglutamine Length Determines Timing of Huntington's Disease Onset. Cell. 2019;178(4).

31. Pearson CE, Tam M, Wang YH, Montgomery SE, Dar AC, Cleary JD, et al. Slipped-strand DNAs formed by long (CAG)-(CTG) repeats: Slipped-out repeats and slip-out junctions. Nucleic Acids Res. 2002;30(20).

32. Cubo E, Martinez-Horta SI, Santalo FS, Descalls AM, Calvo S, Gil-Polo C, et al. Clinical manifestations of homozygote allele carriers in Huntington disease. Neurology. 2019;92(18).

33. Lee JM, Ramos EM, Lee JH, Gillis T, Mysore JS, Hayden MR, et al. CAG repeat expansion in Huntington disease determines age on onset in a fully dominant fashion. Neurology. 2012;78(10).

34. Yescas P, Rasmussen A, Ochoa A, Macias R, Ruiz I, Suastegui R. Homozygosity in Huntington's disease: new ethical dilemma caused by molecular diagnosis. Clin Genet. 2002;61(6).

35. Papadopoulou AS, Gomez-Paredes C, Mason MA, Taxy BA, Howland D, Bates GP. Extensive Expression Analysis of Htt Transcripts in Brain Regions from the zQ175 HD Mouse Model Using a QuantiGene Multiplex Assay. Sci Rep. 2019;9(1).

36. Hughes AC, Mort M, Elliston L, Thomas RM, Brooks SP, Dunnett SB, et al. Identification of novel alternative splicing events in the huntingtin gene and assessment of the functional consequences using structural protein homology modelling. J Mol Biol. 2014;426(7).

37. Ruzo A, Ismailoglu I, Popowski M, Haremaki T, Croft GF, Deglincerti A, et al. Discovery of novel isoforms of Huntington reveals a new hominid-specific exon. PLoS One. 2015;10(5).

38. Schilling J, Broemer M, Atanassov I, Duernberger Y, Vorberg I, Dieterich C, et al. Deregulated Splicing Is a Major Mechanism of RNA-Induced Toxicity in Huntington's Disease. J Mol Biol. 2019;431(9).

39. Saudou F, Humbert S. The Biology of Huntingtin. Vol. 89, Neuron. 2016.

40. Seefelder M, Kochanek S. A meta-analysis of transcriptomic profiles of Huntington's disease patients. PLoS One. 2021;16(6 June).

41. Graham RK, Deng Y, Slow EJ, Haigh B, Bissada N, Lu G, et al. Cleavage at the Caspase-6 Site Is Required for Neuronal Dysfunction and Degeneration Due to Mutant Huntingtin. Cell. 2006;125(6).

42. Waldron-Roby E, Ratovitski T, Wang X, Jiang M, Watkin E, Arbez N, et al. Transgenic mouse model expressing the caspase 6 fragment of mutant huntingtin. Journal of Neuroscience. 2012;32(1).

43. Seefelder M, Klein FAC, Landwehrmeyer B, Fernández-Busnadiego R, Kochanek S. Huntingtin and Its Partner Huntingtin-Associated Protein 40: Structural and Functional Considerations in Health and Disease. Vol. 11, Journal of Huntington's Disease. 2022.

44. Palidwor GA, Shcherbinin S, Huska MR, Rasko T, Stelzl U, Arumughan A, et al. Detection of alpha-rod protein repeats using a neural network and application to huntingtin. PLoS Comput Biol. 2009;5(3).

45. Schaefer MH, Fontaine JF, Vinayagam A, Porras P, Wanker EE, Andrade-Navarro MA. Hippie: Integrating protein interaction networks with experiment based quality scores. PLoS One. 2012;7(2).

46. Guo Q, Huang B, Cheng J, Seefelder M, Engler T, Pfeifer G, et al. The cryo-electron microscopy structure of huntingtin. Nature. 2018;555(7694).

47. Biagioli M, Ferrari F, Mendenhall EM, Zhang Y, Erdin S, Vijayvargiya R, et al. Htt CAG repeat expansion confers pleiotropic gains of mutant huntingtin function in chromatin regulation. Hum Mol Genet. 2015;24(9).

48. Wändel P, Fredrikson S, Carlsson AC, Li X, Sundquist J, Sundquist K. Huntington's disease among immigrant groups and Swedish-born individuals: a cohort study of all adults 18 years of age and older in Sweden. Neurological Sciences. 2021;42(9).

49. Kay C, Collins JA, Wright GEB, Baine F, Miedzybrodzka Z, Aminkeng F, et al. The molecular epidemiology of Huntington disease is related to intermediate allele frequency and haplotype in the general population. American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics. 2018;177(3).

50. El Pilón. https://elpilon.com.co/costa-atlantica-segunda-region-con-mayor-numero- de-pacientes-con-mal-de-san-vito/. 2017. Costa Atlántica, segunda región con mayor numero de pacientes con ‘mal de San Vito.’

51. Consultorsalud. https://consultorsalud.com/el-mayor-numero-de-pacientes-con- huntington-esta-en-la-costa-atlantica/. 2017. El mayor número de pacientes con Huntington está en la Costa Atlántica.

52. Harper PS. The epidemiology of Huntington’s disease. Vol. 89, Human Genetics 1992.

53. Apolinário TA, Rodrigues DC, Lemos MB, Paiva CLA, Agostinho LA. Distribution of the htt gene a1 and a2 haplotypes worldwide: A systematic review. Vol. 18, Clinical Medicine and Research. 2020.

54. Warby SC, Visscher H, Collins JA, Doty CN, Carter C, Butland SL, et al. HTT haplotypes contribute to differences in Huntington disease prevalence between Europe and East Asia. European Journal of Human Genetics. 2011;19(5).

55. Baine FK, Kay C, Ketelaar ME, Collins JA, Semaka A, Doty CN, et al. Huntington disease in the South African population occurs on diverse and ethnically distinct genetic haplotypes. European Journal of Human Genetics. 2013;21(10).

56. Kay C, Tirado-Hurtado I, Cornejo-Olivas M, Collins JA, Wright G, Inca-Martinez M, et al. The targetable A1 Huntington disease haplotype has distinct Amerindian and European origins in Latin America. European Journal of Human Genetics. 2017;25(3).

57. Kay C, Collins JA, Miedzybrodzka Z, Madore SJ, Gordon ES, Gerry N, et al. Huntington disease reduced penetrance alleles occur at high frequency in the general population. Neurology. 2016 Jul 19;87(3):282 8.

58. Warby SC, Montpetit A, Hayden AR, Carroll JB, Butland SL, Visscher H, et al. CAG Expansion in the Huntington Disease Gene Is Associated with a Specific and Targetable Predisposing Haplogroup. Am J Hum Genet. 2009;84(3).

59. Falush D. Haplotype Background, Repeat Length Evolution, and Huntington’s Disease. The American Journal of Human Genetics. 2009 Dec;85(6):939 42.

60. Lee JM, Gillis T, Mysore JS, Ramos EM, Myers RH, Hayden MR, et al. Common SNP-based haplotype analysis of the 4p16.3 Huntington disease gene region. Am J Hum Genet. 2012;90(3).

61. Li XY, Li HL, Dong Y, Gao B, Cheng HR, Ni W, et al. Haplotype analysis encompassing HTT gene in Chinese patients with Huntington's disease. Eur J Neurol. 2020;27(2).

62. Blum D, Chern Y, Domenici MR, Buée L, Lin CY, Rea W, et al. The Role of Adenosine Tone and Adenosine Receptors in Huntington's Disease. J Caffeine Adenosine Res. 2018;8(2).

63. Koch ET, Raymond LA. Dysfunctional striatal dopamine signaling in Huntington's disease. Vol. 97, Journal of Neuroscience Research. 2019.

64. Rosas-Arellano A, Estrada-Mondragón A, Maniellero C, Tejeda-Guzmán C, Castro M. The adjustment of γ-aminobutyric acidA tonic subunits in Huntington's disease: From transcription to translation to synaptic levels into the neostriatum. Vol. 13, Neural Regeneration Research. 2018.

65. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989;12(10).

66. Galvan L, André VM, Wang EA, Cepeda C, Levine MS. Functional differences between direct and indirect striatal output pathways in Huntington's disease. Vol. 1, Journal of Huntington's Disease. 2012.

67. Augood SJ, Faull RLM, Love DR, Emson PC. Reduction in enkephalin and substance P messenger RNA in the striatum of early grade Huntington's disease: A detailed cellular in situ hybridization study. Neuroscience. 1996;72(4).

68. Jamwal S, Kumar P. Insight Into the Emerging Role of Striatal Neurotransmitters in the Pathophysiology of Parkinson's Disease and Huntington's Disease: A Review. Curr Neuropharmacol. 2018;17(2).
69. Carmo C, Maia L, Lopes C, Rego AC. Mitochondrial Dysfunction in Huntington's Disease. In 2018. p. 59–83.
70. Dubinsky JM. Towards an Understanding of Energy Impairment in Huntington's Disease Brain. Vol. 6, Journal of Huntington's Disease. 2017.
71. Puigivell M, Saavedra A, Pérez-Navarro E. Cognitive dysfunction in Huntington's disease: mechanisms and therapeutic strategies based on BDNF. Brain Pathology. 2016;26(6).
72. Walker FO. Huntington's disease. The Lancet. 2007 Jan;369(9557):218–28.
73. Rosas HD, Salat DH, Lee SY, Zaleta AK, Hevelone N, Hersch SM. Complexity and heterogeneity: What drives the ever-changing brain in Huntington's disease? In: Annals of the New York Academy of Sciences. 2008.
74. Valadão PAC, Santos KBS, Ferreira e Vieira TH, Macedo e Cordeiro T, Teixeira AL, Guatimosim C, et al. Inflammation in Huntington's disease: A few new twists on an old tale. Vol. 348, Journal of Neuroimmunology. 2020.
75. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, et al. Huntington disease. Nat Rev Dis Primers. 2015 Apr;23;1(1):15005.
76. Ghosh R, Tabrizi SJ. Clinical features of huntington's disease. In: Advances in Experimental Medicine and Biology. 2018.
77. Paulsen JS, Langbehn DR, Stout JC, Aylward E, Ross CA, Nance M, et al. Detection of Huntington's disease decades before diagnosis: The Predict-HD study. J Neurol Neurosurg Psychiatry. 2008;79(8).
78. Tabrizi SJ, Scahill RI, Owen G, Durr A, Leavitt BR, Ross RA, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. Lancet Neurol. 2013;12(7).
79. Van Duijn E, Kingma EM, Van Der Mast RC. Psychopathology in verified Huntington's disease gene carriers. Journal of Neuropsychiatry and Clinical Neurosciences. 2007;19(4).
80. Paulsen JS, Ready RE, Hamilton JM, Mega MS, Cummings JL. Neuropsychiatric aspects of Huntington's disease. J Neurol Neurosurg Psychiatry. 2001;71(3).

81. Reininghaus E, Lackner N. Relationship satisfaction and sexuality in Huntington's disease. In: Handbook of Clinical Neurology. 2015.

82. Grimaldi A, Veneziani I, Culicetto L, Quartarone A, Lo Buono V. Risk Factors and Interventions for Suicide in Huntington's Disease-A Systematic Review. J Clin Med. 2024 Jun 12;13(12):3437.

83. Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. American Journal of Psychiatry. 2005;162(4).

84. McGarry A, McDermott MP, Kieburtz K, Fung WLA, McCusker E, Peng J, et al. Risk factors for suicidality in Huntington disease: An analysis of the 2CARE clinical trial. Neurology. 2019;92(14).

85. Park S, Colwell CS. Do disruptions in the circadian timing system contribute to autonomic dysfunction in Huntingon’s disease? Vol. 92, Yale Journal of Biology and Medicine. 2019.

86. Van der Burg JMM, Weydt P, Landwehrmeyer GB, Aziz NA. Effect of Body Weight on Age at Onset in Huntington Disease. Neurol Genet. 2021;7(4).

87. Losekoot M, Van Belzen MJ, Seneca S, Bauer P, Stenhouse SAR, Barton DE. EMQN/CMGS best practice guidelines for the molecular genetic testing of huntington disease. European Journal of Human Genetics [Internet]. 2013;21(5):480 6. Available from: http://dx.doi.org/10.1038/ejhg.2012.200

88. Jou YS, Myers RM. Evidence from antibody studies that the CAG repeat in the huntington disease gene is expressed in the protein. Hum Mol Genet. 1995;4(3).

89. Andrew SE, Goldberg YP, Theilmann J, Zeisler J, Hayden MR. A CCG repeat polymorphism adjacent to the CAG repeat in the Huntington disease gene: implications for diagnostic accuracy and predictive testing. Hum Mol Genet. 1994 Jan 1;3(1):65 7.

90. Pêcheux C, Mouret JF, Dürr A, Agid Y, Feingold J, Brice A, et al. Sequence analysis of the CCG polymorphic region adjacent to the CAG triplet repeat of the HD gene in normal and HD chromosomes. J Med Genet. 1995;32(5).

91. Pramanik S, Basu P, Gangopadhaya PK, Sinha KK, Jha DK, Sinha S, et al. Analysis of CAG and CCG repeats in Huntingtin gene among HD patients and normal populations of India. European Journal of Human Genetics. 2000;8(9).

92. De Luca A, Morella A, Consoli F, Fanelli S, Thibert JR, Statt S, et al. A Novel Triplet-Primed PCR Assay to Detect the Full Range of Trinucleotide CAG Repeats in the Huntingtin Gene (HTT). Int J Mol Sci. 2021 Feb 8;22(4):1689.

93. Losekoot M, van Belzen MJ, Seneca S, Bauer P, Stenhouse SAR, Barton DE. EMQN/CMGS best practice guidelines for the molecular genetic testing of Huntington disease. European Journal of Human Genetics. 2013 May 19;21(5):480 6.

94. Margolis RL, Ross CA. Diagnosis of Huntington Disease. Clin Chem. 2003 Oct 1;49(10):1726 32.

95. Bird TD. Outrageous Fortune: The Risk of Suicide in Genetic Testing for Huntington Disease. The American Journal of Human Genetics. 1999 May;64(5):1289 92.

96. Creighton S, Almqvist EW, MacGregor D, Fernandez B, Hogg H, Beis J, et al. Predictive, pre-natal and diagnostic genetic testing for Huntington's disease: The experience in Canada from 1987 to 2000. Clin Genet. 2003;63(6).

97. Reed SC. A short history of genetic counseling. Soc Biol. 1974 Dec 23;21(4):332 9.

98. Nance MA. Genetic counseling and testing for Huntington's disease: A historical review. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2017 Jan 13;174(1):75 92.

99. Goldman JS. Predictive genetic counseling for neurodegenerative diseases: Past, present, and future. Cold Spring Harb Perspect Med. 2020;10(7).

100. Dufrasne S, Roy M, Galvez M, Rosenblatt DS. Experience over fifteen years with a protocol for predictive testing for Huntington disease. Mol Genet Metab. 2011;102(4).

101. Groves M. The highly anxious individual presenting for Huntington disease-predictive genetic testing: the psychiatrist's role in assessment and counseling. In 2017. p. 99 105.

102. Alon I, Bussod I, Ravitsky V. Mapping ethical, legal, and social implications (ELSI) of preimplantation genetic testing (PGT). J Assist Reprod Genet. 2024;41(5).

103. Huibers AK Van T Spijker A. The autonomy paradox: Predictive genetic testing and autonomy: Three essential problems. Patient Educ Couns. 1998;35(1).

104. Roberts MC, Dotson WD, DeVore CS, Bednar EM, Bowen DJ, Ganiats TG, et al. Delivery of cascade screening for hereditary conditions: A scoping review of the literature. Health Aff. 2018;37(5).

105. Srinivasan S, Won NY, Dotson WD, Wright ST, Roberts MC. Barriers and facilitators for cascade testing in genetic conditions: a systematic review. Vol. 28, European Journal of Human Genetics. 2020.

106. Sobel SK, Cowan DB. Impact of genetic testing for Huntington disease on the family system. Am J Med Genet. 2000;90(1).

107. Tillerås KH, Kjoelaas SH, Dramstad E, Feragen KB, von der Lippe C. Psychological reactions to predictive genetic testing for Huntington's disease: A qualitative study. J Genet Couns. 2020;29(6).

108. Gargiulo M, du Montcel ST, Jutras MF, Herson A, Cazeneuve C, Durr A. A liminal stage after predictive testing for Huntington disease. J Med Genet. 2017;54(8).

109. Migliore S, Jankovic J, Squitieri F. Genetic Counseling in Huntington's Disease: Potential New Challenges on Horizon? Front Neurol. 2019 Apr 30;10.

110. Asociación Española Corea Huntington. https://www.e-huntington.es/opciones-reproductivas-en-la-enfermedad-de-huntington/ Planificación Familiar. Opciones Reproductivas en la Enfermedad de Huntington (Parte 2).

111. Asuragen®. AmplideX® PCR/CE HTT. Protocol Guide. Austin, TX, USA.; 2018. p. 1–28.

112. Fuminaya A; García E; Gonzalez; Plata; Rodriguez. CALIDAD DE VIDA EN FAMILIAS CON ENFERMEDAD DE HUNTINGTON EN EL DEPARTAMENTO DEL ATLÁNTICO (1). [Trabajo no Publicado, Universidad Simón Bolívar]. 2023 Nov 21;1–59.

113. Apolinário TA, da Silva I dos S, Agostinho L de A, Paiva CLA. Investigation of intermediate CAG alleles of the HTT gene in the general population of Rio de Janeiro, Brazil, in comparison with a sample of Huntington disease-affected families. Mol Genet Genomic Med. 2020 Apr 17;8(4).

114. Ruiz de Sabando A, Urrutia Lafuente E, Galbete A, Ciosi M, García Amigót F, García Solaesa V, et al. Spanish HTT gene study reveals haplotype and allelic diversity with possible implications for germline expansion dynamics in Huntington disease. Hum Mol Genet. 2023 Mar 6;32(6):897–906.

115. Aziz NA, van Belzen MJ, Coops ID, Belfroid RDM, Roos RAC. Parent-of-origin differences of mutant HTT CAG repeat instability in Huntington's disease. Eur J Med Genet. 2011 Jul;54(4):e413–8.

116. Wheeler VC, Persichetti F, McNeil SM, Mysore JS, Mysore SS, MacDonald ME, et al. Factors associated with HD CAG repeat instability in Huntington disease. J Med Genet. 2007 Aug 23;44(11):695–701.

117. Mroczek M. Comment on: "Somatic CAG repeat instability in intermediate alleles of the HTT gene and its potential association with a clinical phenotype" by Ruiz de Sabando et al. European Journal of Human Genetics. 2024 Jul 7;32(7):745–6.

118. Savitt D, Jankovic J. Clinical phenotype in carriers of intermediate alleles in the huntingtin gene. J Neurol Sci. 2019 Jul;402:57 61.

119. Epping EA, Kim JI, Craufurd D, Brashers-Krug TM, Anderson KE, McCusker E, et al. Longitudinal Psychiatric Symptoms in Prodromal Huntington’s Disease: A Decade of Data. American Journal of Psychiatry. 2016 Feb;173(2):184 92

120. Raschka T, Li Z, Gaßner H, Kohl Z, Jukic J, Marxreiter F, et al. Unraveling progression subtypes in people with Huntington's disease. EPMA Journal. 2024 Jun 1;15(2):275–87.

121. Podvin S, Reardon HT, Yin K, Mosier C, Hook V. Multiple clinical features of Huntington's disease correlate with mutant HTT gene CAG repeat lengths and neurodegeneration. Vol. 266, Journal of Neurology. Dr. Dietrich Steinkopff Verlag GmbH and Co. KG; 2019. p. 551–64.

122. Pagan F, Torres-Yaghi Y, Altshuler M. The diagnosis and natural history of Huntington disease. In: Handbook of Clinical Neurology. Elsevier B.V.; 2017. p. 63–7.

123. Campo Oviedo M del C, Baute Gamez LE. Grupos vulnerables, la responsabilidad del Estado de garantizarles el derecho a la salud: Huntington en comunidades de la región Caribe de Colombia. Perfiles de las Ciencias Sociales. 2016 Jul–Dec;4(7):56–99. Universidad Juárez Autónoma de Tabasco (UJAT)