



Polymorphisms in the oxytocin receptor and their association with apathy and impaired social cognition in Huntington's disease

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Abstract

Background Huntington's disease (HD) is a neurodegenerative disorder characterized by cognitive, motor, and neuropsychiatric manifestations. Oxytocin is a neuropeptide studied for its role as a neuromodulator regulating multiple behaviors linked to social cognition. Genetic variation of oxytocin receptor (OXTR) might interact in the etiology and development of several impaired social behaviors. Our aim was to study OXTR polymorphisms and their relationship with apathy and social cognition in HD.

Methods *OXTR* was sequenced in 21 cases and 22 controls. We assessed apathy, anxiety, depression, and irritability (Hospital Anxiety and Depression Scale-Snaith Irritability scale, HADS-SIS) and social cognition (Ekman 60 faces test), motor symptoms and functionality with the total functional capacity (TFC), and the Unified HD rating Scale (UHDRS).

Results We identified ten variants in *OXTR*. Three variants were classified as possibly damaging (p.Arg40Gly) or probably damaging (p.Leu46Pro, p.Thr102Asn). Subjects carrying the wild-type genotype of the synonymous variant p.Val45 showed a significantly lower score in the HADS-SIS scale, related to lower irritability ($p=0.013$). The only subject carrying the heterozygous genotype of the synonymous variant p.Leu62 showed a significantly higher score on Ekman scale, compared to wild-type ($p=0.049$); however, this finding was not confirmed after bootstrapping.

Conclusion Variations in *OXTR* could have a relevant role in the correct development of social and cognitive functions. Future approaches will include the molecular study of p.Arg40Gly, p.Leu46Pro, and p.Thr102Asn to confirm their pathogenicity, as well as the validation of the influence of p.Val45 and p.Leu62 variants for their involvement in irritability and social cognition in HD.

Keywords Huntington's disease · Oxytocin receptor · Polymorphisms

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Introduction

Huntington's disease (HD) is neurodegenerative disorder caused by a pathological expansion of a CAG repeat (≥ 36 repeats) that encodes the huntingtin gene (HTT), characterized by cognitive, motor, and neuropsychiatric manifestations. Among the different cognitive domains impaired in HD, social cognition is one of the most impacted at an early stage. It was previously described a decrease in social cognition, specifically in the recognition of emotions, like fear and anger, even in pre-symptomatic phases of the disease, and this finding has been related to the duration of the disease, severity of motor symptoms, age, and number of CAG repeats [1].

Oxytocin is a neuropeptide produced in the supraoptic and paraventricular nuclei of the hypothalamus and released by neurohypophysis into the circulation, being involved in the peripheral effects of parturition and lactation. Oxytocin is also studied for its role as a neuromodulator regulating multiple behaviors linked to social cognition [2]. Several studies revealed that oxytocin improves different features such as stress, anxiety, and facial emotion recognition [3].

Genetic alterations of oxytocin receptor (OXTR), coded by *OXTR*, might interact in the etiology and development of several mental disorders [3], along with associations with a differential response related to social behaviors [4]. There is some evidence in autism that certain polymorphisms in *OXTR* can be associated with behavioral alterations [5]. *OXTR* rs53576 wild-type allele is commonly associated with better social-emotional behavior [6]. Moreover, rs53576

and rs2254298 polymorphisms seemed to be significantly involved in the psychopathology of disruptive behavior, depression, anxiety, eating disorder, and borderline personality disorder [7]. In short, although there is some evidence of hypothalamic degeneration in HD, it is not known whether this leads to oxytocinergic dysfunction in HD and its association with neuropsychiatric manifestations. Our aim was to study *OXTR* polymorphisms and their relationship with apathy and social cognition in HD.

Materials and methods

This is a multicenter, cross-sectional, observational, case-control study approved by the Research Ethics Committee of Health Area of Burgos and Soria (Spain). From January 2019 to January 2020, we included symptomatic HD outpatients with larger allele > 36 CAG repeats within HTT and with a Unified Huntington's Disease Rating Scale (UHDRS) motor subscale score > 4 , who provided written informed consent. Sex and age-matching controls were recruited principally from the partners, spouses, or caregivers of the HD group with no clinical evidence or family history of HD.

We assessed apathy [Apathy Evaluation Scale-Clinician (AES)], anxiety, depression, and irritability [Hospital Anxiety and Depression Scale-Snaith Irritability scale], and social cognition [Ekman 60 faces test], motor symptoms and functionality with the Total functional capacity (TFC), and the Unified HD rating Scale (UHDRS).

Table 1 Main demographic and clinical characteristics of the study population

Variable	Patients	Controls	<i>p</i> Value
Sex			0.758
Men	9 (40.9)	9 (47.4)	
Women	13 (59.1)	10 (52.6)	
Age	58.1 $\pm$ 9.7	52.0 $\pm$ 9.7	0.052
BMI	25.4 $\pm$ 3.6	25.4 $\pm$ 3.9	0.958
CAG repetitions	43 (40.7; 45.0)	-	-
Disease duration	5.5 (3.0; 10.0)	-	-
Antidopaminergic treatment	9 (40.9)	0 (0.0)	0.002
Antidepressive treatment	10 (45.5)	2 (10.5)	0.019
UHDRS-motor score	26.00 (17.75; 38.50)	-	-
TFC score	11.00 (9.75; 13.00)	-	-
HADS-anxiety score	4.00 (2.75; 7.25)	5.00 (2.00–10.00)	0.360
HADS-depression score	4.00 (2.00; 8.00)	5.00 (2.00; 7.00)	0.920
HADS-SIS score	4.00 (1.00; 5.25)	4.00 (1.00; 6.00)	0.850
Ekman total score	38.0 (30.0; 44.0)	54.0 (51.0; 56.0)	< 0.001
Apathy evaluation scale	33.50 (28.00; 41.25)	20.00 (18.00; 25.00)	< 0.001

Values are shown as count (%), mean $\pm$ standard deviation or median (interquartile range). Abbreviation: BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HADS-SIS, Hospital Anxiety and Depression Scale-Snaith Irritability scale; TFC, total functional capacity; UHDRS, Unified Huntington Disease rating Scale

Table 2 Apathy, anxiety, depression, irritability, social cognition, and motor symptoms and functionality scales according to different OXTR genotypes

Variant	Genotype	UDHRS-motor score	TFC score	HADS-anxiety score	HADS-depression score	HADS-SIS score	Ekman total score	Apathy evaluation Scale
p.Ala4	Wild-type homozygous	24 (17.5; 37.5) (n = 21)	11 (9.5; 13) (n = 21)	4.5 (2.2; 8.0) (n = 40)	5.0 (2.0; 7.0) (n = 40)	4.0 (1.0; 5.75) (n = 40)	46.0 (38.0; 53.7) (n = 40)	27.0 (19.2; 35.0) (n = 40)
	Patients	24 (17.5; 37.5) (n = 21)	11 (9.5; 13) (n = 21)	4.0 (2.5; 6.5) (n = 21)	4.0 (2.0; 8.0) (n = 21)	4.0 (1.0; 5.5) (n = 21)	38.0 (30.0; 44.0)* (n = 21)	35.5 (29.5; 41.5)* (n = 21)
	Controls	NA	NA	5.0 (2.0; 10.0) (n = 19)	5.0 (2.0; 7.0) (n = 19)	4.0 (1.0; 6.0) (n = 19)	54.0 (51.0; 56.0) (n = 19)	20.0 (18.0; 25.0) (n = 19)
	Heterozygous	48 (n = 1)	10 (n = 1)	7 (n = 1)	3 (n = 1)	5 (n = 1)	33 (n = 1)	25 (n = 1)
	Patients	48 (n = 1)	10 (n = 1)	7 (n = 1)	3 (n = 1)	5 (n = 1)	33 (n = 1)	25 (n = 1)
	Controls	NA	NA	NA	NA	NA	NA	NA
	p Value	0.273	0.545	0.683	0.780	0.585	0.390	0.927
	Wild-type homozygous	24 (17.5; 38.5) (n = 21)	11 (9.5; 13) (n = 21)	5.0 (2.0; 8.0) (n = 39)	5.0 (2.0; 7.0) (n = 39)	4.0 (1.0; 5.0) (n = 39)	45.0 (35.0; 53.0) (n = 39)	28.0 (19.0; 35.0) (n = 39)
	Patients	24 (17.5; 38.5) (n = 21)	11 (9.5; 13) (n = 21)	4.0 (2.5; 7.5) (n = 21)	4.0 (2.0; 8.0) (n = 21)	4.0 (1.0; 5.5) (n = 21)	38.0 (30.0; 44.0)* (n = 21)	35.0 (29.5; 41.5)* (n = 21)
	Controls	NA	NA	5.0 (2.0; 8.5) (n = 18)	5.0 (2.0; 7.0) (n = 18)	3.5 (1.0; 5.2) (n = 18)	53.5 (51.0; 56.0) (n = 18)	20.0 (18.0; 25.0) (n = 18)
p.Glu24Asp	Heterozygous	38 (n = 1)	11 (n = 1)	7.5 (4.0; NA) (n = 2)	4.0 (2.0; NA) (n = 2)	7.5 (3.0; NA) (n = 2)	48.5 (43.0; NA) (n = 2)	20.0 (20.0; 20.0) (n = 2)
	Patients	38 (n = 1)	11 (n = 1)	4.0 (n = 1)	2.0 (n = 1)	3.0 (n = 1)	43.0 (n = 1)	20.0 (n = 1)
	Controls	NA	NA	11.0 (1)	6.0 (1)	12.0 (1)	54.0 (1)	20.0 (1)
	p Value	0.545	0.909	0.412	0.790	0.351	0.705	0.295
	Wild-type homozygous	25.0 (17.7; 37.2) (n = 14)	11.0 (9.7; 13.0) (n = 14)	4.5 (2.0; 10.0) (n = 28)	5.0 (2.0; 7.7) (n = 28)	4.0 (1.0; 6.0) (n = 28)	45.5 (40.0; 53.7) (n = 28)	27.0 (19.0; 34.2) (n = 28)
	Patients	25.0 (17.7; 37.2) (n = 14)	11.0 (9.7; 13.0) (n = 14)	4.0 (2.0; 8.5) (n = 14)	5.0 (2.7; 8.0) (n = 14)	4.0 (2.5; 6.0) (n = 14)	40.0 (29.7; 44.0)* (n = 14)	33.5 (30.2; 43.7)* (n = 14)
	Controls	NA	NA	6.5 (1.7; 11.0) (n = 14)	5.5 (2.0; 7.0) (n = 14)	3.5 (0.7; 6.2) (n = 14)	53.5 (50.0; 56.0) (n = 14)	19.5 (18.0; 25.2) (n = 14)
	Heterozygous	28.0 (11.5; 48.0) (n = 8)	12.0 (7.75; 13.0) (n = 8)	5.0 (3.0; 6.5) (n = 13)	3.0 (1.0; 7.0) (n = 13)	3.0 (1.5; 4.0) (n = 13)	45.0 (31.5; 54.0) (n = 13)	25.0 (21.5; 35.0) (n = 13)
	Patients	28.0 (11.5; 48.0) (n = 8)	12.0 (7.75; 13.0) (n = 8)	4.0 (3.0; 6.5) (n = 8)	2.5 (1.0; 6.7) (n = 8)	2.5 (1.0; 4.7) (n = 8)	34.0 (30.0; 43.2)* (n = 8)	33.5 (25.7; 35.7)* (n = 8)
	Controls	NA	NA	5.0 (3.0; 7.0) (n = 5)	5.0 (1.5; 7.0) (n = 5)	4.0 (2.0; 4.0) (n = 5)	55.0 (52.0; 57.0) (n = 5)	21.0 (18.0; 23.5) (n = 5)
p.Ala37Asp	p Value	0.570	0.868	0.772	0.177	0.446	0.750	0.923
	Wild-type homozygous	28.0 (19.0; 38.0) (n = 19)	11.0 (9.0; 13.0) (n = 19)	4.0 (2.0; 8.0) (n = 37)	4.0 (2.0; 6.5) (n = 37)	4.0 (1.0; 5.5) (n = 37)	44.0 (36.5; 53.5) (n = 37)	26.0 (19.0; 33.5) (n = 37)
	Patients	28.0 (19.0; 38.0) (n = 19)	11.0 (9.0; 13.0) (n = 19)	3.0 (2.0; 5.0) (n = 19)	4.0 (2.0; 7.0) (n = 19)	4.0 (1.0; 5.0) (n = 19)	38.0 (30.0; 43.0)* (n = 19)	32.0 (28.0; 42.0)* (n = 19)
	Controls	NA	NA	5.0 (2.0; 10.2) (n = 18)	5.0 (2.0; 6.2) (n = 18)	3.5 (1.0; 6.0) (n = 18)	53.5 (51.0; 56.0) (n = 18)	19.5 (18.0; 23.5) (n = 18)
	Heterozygous	7.0 (5.0; NA) (n = 3)	13.0 (10; NA) (n = 3)	7.5 (4.7; 8.0) (n = 4)	7.5 (4.0; 9.5) (n = 4)	4.5 (3.2; 9.5) (n = 4)	51.5 (37.5; 55.7) (n = 4)	30.0 (25.0; 35.0) (n = 4)
	Patients	7.0 (5.0; NA) (n = 3)	13.0 (10; NA) (n = 3)	7.0 (4.0; NA) (n = 3)	8.0 (3.0; NA) (n = 3)	5.0 (3.0; NA) (n = 3)	51.0 (33.0; NA) (n = 3)	35.0 (25.0; NA) (n = 3)
	Controls	NA	NA	8.0 (1)	7.0 (1)	4.0 (1)	57.0 (1)	25.0 (1)
	p Value	0.265	0.408	0.294	0.133	0.255	0.457	0.457
	Wild-type homozygous	28.0 (19.0; 38.0) (n = 19)	11.0 (9.0; 13.0) (n = 19)	4.0 (2.0; 8.0) (n = 37)	4.0 (2.0; 6.5) (n = 37)	4.0 (1.0; 5.5) (n = 37)	44.0 (36.5; 53.5) (n = 37)	26.0 (19.0; 33.5) (n = 37)
	Patients	28.0 (19.0; 38.0) (n = 19)	11.0 (9.0; 13.0) (n = 19)	3.0 (2.0; 5.0) (n = 19)	4.0 (2.0; 7.0) (n = 19)	4.0 (1.0; 5.0) (n = 19)	38.0 (30.0; 43.0)* (n = 19)	32.0 (28.0; 42.0)* (n = 19)
p.Arg40Gly	Controls	NA	NA	5.0 (2.0; 10.2) (n = 18)	5.0 (2.0; 6.2) (n = 18)	3.5 (1.0; 6.0) (n = 18)	53.5 (51.0; 56.0) (n = 18)	19.5 (18.0; 23.5) (n = 18)
	Heterozygous	7.0 (5.0; NA) (n = 3)	13.0 (10; NA) (n = 3)	7.5 (4.7; 8.0) (n = 4)	7.5 (4.0; 9.5) (n = 4)	4.5 (3.2; 9.5) (n = 4)	51.5 (37.5; 55.7) (n = 4)	30.0 (25.0; 35.0) (n = 4)
	Patients	7.0 (5.0; NA) (n = 3)	13.0 (10; NA) (n = 3)	7.0 (4.0; NA) (n = 3)	8.0 (3.0; NA) (n = 3)	5.0 (3.0; NA) (n = 3)	51.0 (33.0; NA) (n = 3)	35.0 (25.0; NA) (n = 3)
	Controls	NA	NA	8.0 (1)	7.0 (1)	4.0 (1)	57.0 (1)	25.0 (1)
	p Value	0.265	0.408	0.294	0.133	0.255	0.457	0.457

Table 2 (continued)

Variant	Genotype	UDHRS-motor score	TFC score	HADS-anxiety score	HADS-depression score	HADS-SIS score	Ekman total score	Apathy evaluation Scale
p.Val45	Wild-type homozygous	24.0 (18.0; 37.0) (n = 11)	13.0 (11.0; 13.0) (n = 11)	3.0 (2.0; 8.0) (n = 23)	3.0 (2.0; 6.0) (n = 23)	2.0 (0.0; 5.0) (n = 23)	45.0 (40; 54.0) (n = 23)	25.0 (19.0; 32.0) (n = 23)
	Patients	24.0 (18.0; 37.0) (n = 11)	13.0 (11.0; 13.0) (n = 11)	3.0 (2.0; 5.0) (n = 11)	3.0 (2.0; 6.0) (n = 11)	3.0 (0.0; 4.0) (n = 11)	40.0 (34.0; 44.0)* (n = 11)	32.0 (28.0; 42.0)* (n = 11)
	Controls	NA	NA	5.0 (1.5; 10.7) (n = 12)	3.0 (2.0; 9.0) (n = 12)	1.5 (0.2; 5.7) (n = 12)	53.5 (51.2; 56.0) (n = 12)	19.0 (18.0; 24.5) (n = 12)
	Heterozygous	31.0 (17.0; 38.0) (n = 7)	11.0 (10.0; 12.0) (n = 7)	7.0 (4.0; 8.0) (n = 11)	6.0 (3.0; 8.0) (n = 11)	5.0 (4.0; 9.0) (n = 11)	43.0 (33.0; 54.0) (n = 11)	25.0 (20.0; 35.0) (n = 11)
	Patients	31.0 (17.0; 38.0) (n = 7)	11.0 (10.0; 12.0) (n = 7)	5.0 (4.0; 8.0) (n = 7)	5.0 (3.0; 8.0) (n = 7)	5.0 (4.0; 9.0)** (n = 7)	38.0 (30.0; 43.0)* (n = 7)	32.0 (25.0; 36.0)* (n = 7)
	Controls	NA	NA	8.0 (3.5; 10.2) (n = 4)	6.0 (2.2; 6.7) (n = 4)	6.0 (2.5; 11.0) (n = 4)	54.5 (51.7; 56.5) (n = 4)	19.5 (18.2; 23.7) (n = 4)
	Mutated homozygous	29.5 (8.5; 46.0) (n = 4)	8.0 (5.5; 12.0) (n = 4)	4.0 (2.0; 6.0) (n = 7)	5.0 (3.0; 8.0) (n = 7)	4.0 (1.0; 4.0) (n = 7)	47.0 (30.0; 52.0) (n = 7)	28.0 (22.0; 49.0) (n = 7)
	Patients	29.5 (8.5; 46.0) (n = 4)	8.0 (5.5; 12.0) (n = 4)	3.50 (0.7; 10.7) (n = 4)	5.5 (1.5; 13.2) (n = 4)	2.0 (1.0; 4.5) (n = 4)	30.0 (28.5; 46.5) (n = 4)	42.0 (29.7; 60.2) (n = 4)
	Controls	NA	NA	4.0 (2.0; NA) (n = 3)	5.0 (5.0; NA) (n = 3)	4.0 (4.0; NA) (n = 3)	51.0 (47.0; NA) (n = 3)	22.0 (21.0; NA) (n = 3)
	<i>p</i> Value	0.991	0.213	0.389	0.307	0.013	0.687	0.423
p.Leu46Pro	Wild-type homozygous	24.0 (17.5; 35.0) (n = 17)	11.0 (9.5; 13.0) (n = 17)	4.5 (2.2; 8.0) (n = 24)	3.5 (2.0; 7.7) (n = 24)	3.5 (1.0; 5.7) (n = 24)	42.0 (31.2; 51.0) (n = 24)	31.0 (23.0; 35.7) (n = 24)
	Patients	24.0 (17.5; 35.0) (n = 17)	11.0 (9.5; 13.0) (n = 17)	4.0 (2.5; 6.5) (n = 17)	4.0 (2.0; 8.0) (n = 17)	4.0 (1.0; 5.50) (n = 17)	38.0 (30.0; 43.5)* (n = 17)	32.0 (29.5; 39.5)* (n = 17)
	Controls	NA	NA	5.0 (2.0; 8.0) (n = 7)	2.0 (1.0; 7.0) (n = 7)	2.0 (1.0; 6.0) (n = 7)	53.0 (51.0; 57.0) (n = 7)	19.0 (18.0; 25.0) (n = 7)
	Heterozygous	29.5 (9.2; 45.2) (n = 4)	12.0 (10.2; 13.0) (n = 4)	7.5 (2.5; 10.2) (n = 10)	6.0 (2.7; 8.5) (n = 10)	3.5 (0.0; 5.2) (n = 10)	51.5 (40.7; 54.2) (n = 10)	23.0 (18.7; 32.7) (n = 10)
	Patients	29.5 (9.2; 45.2) (n = 4)	12.0 (10.2; 13.0) (n = 4)	5.5 (3.2; 7.7) (n = 4)	5.5 (3.2; 7.7) (n = 4)	4.5 (3.2; 5.7) (n = 4)	40.5 (33.2; 50.7) (n = 4)	30.0 (20.5; 40.2) (n = 4)
	Controls	NA	NA	9.0 (1.0; 12.2) (n = 6)	6.0 (1.5; 10.75) (n = 6)	0.5 (0.0; 5.2) (n = 6)	53.0 (49.0; 55.2) (n = 6)	20.0 (18.0; 26.7) (n = 6)
	Mutated homozygous	56 (n = 1)	7 (n = 1)	4.0 (2.0; 6.0) (n = 7)	5.0 (2.0; 6.0) (n = 7)	4.0 (3.0; 7.0) (n = 7)	54.0 (47.0; 56.0) (n = 7)	21.0 (19.0; 26.0) (n = 7)
	Patients	56 (n = 1)	7 (n = 1)	0.0 (n = 1)	2.0 (n = 1)	0.0 (n = 1)	28.0 (n = 1)	55.0 (n = 1)
	Controls	NA	NA	4.5 (2.7; 7.2) (n = 6)	5.0 (3.5; 6.2) (n = 6)	4.0 (3.7; 8.2) (n = 6)	55.0 (50.0; 56.2) (n = 6)	20.5 (18.7; 23.0) (n = 6)
	<i>p</i> Value	0.321	0.373	0.519	0.578	0.652	0.082	0.166
p.Leu54	Wild-type homozygous	26.0 (17.7; 38.5) (n = 22)	11.0 (9.7; 13.0) (n = 22)	4.5 (2.2; 8.0) (n = 40)	4.5 (2.0; 7.0) (n = 40)	4.0 (1.0; 5.7) (n = 40)	44.5 (35.7; 53.7) (n = 40)	27.0 (19.2; 35.0) (n = 40)
	Patients	26.0 (17.7; 38.5) (n = 22)	11.0 (9.7; 13.0) (n = 22)	4.0 (2.7; 7.2) (n = 22)	4.0 (2.0; 8.0) (n = 22)	4.0 (1.0; 5.2) (n = 22)	38.0 (30.0; 44.0)* (n = 22)	33.5 (28.0; 41.25)* (n = 22)
	Controls	NA	NA	5.0 (2.0; 10.2) (n = 18)	5.0 (2.0; 6.2) (n = 18)	3.5 (1.0; 6.0) (n = 18)	54.0 (51.0; 56.0) (n = 18)	19.5 (18.0; 25.0) (n = 18)
	Heterozygous	NA	NA	6.0 (n = 1)	7.0 (n = 1)	4.0 (n = 1)	51.0 (n = 1)	22.0 (n = 1)
	Patients	NA	NA	NA	NA	NA	NA	NA
	Controls	NA	NA	6.0 (n = 1)	7.0 (n = 1)	4.0 (n = 1)	51.0 (n = 1)	22.0 (n = 1)
	<i>p</i> Value	NA	NA	0.732	0.537	0.878	0.780	0.732

Table 2 (continued)

Variant	Genotype	UDHRS-motor score	TFC score	HADS-anxiety score	HADS-depression score	HADS-SIS score	Ekman total score	Apathy evaluation Scale
p.Leu62	Wild-type homozygous	26.0 (17.7; 38.5) (n = 22)	11.0 (9.7; 13.0) (n = 22)	4.5 (2.2; 8.0) (n = 40)	4.5 (2.0; 7.0) (n = 40)	4.0 (1.0; 5.0) (n = 40)	44.5 (35.7; 53.0) (n = 40)	25.5 (19.2; 35.0) (n = 40)
	Patients	26.0 (17.7; 38.5) (n = 22)	11.0 (9.7; 13.0) (n = 22)	4.0 (2.7; 7.2) (n = 22)	4.0 (2.0; 8.0) (n = 22)	4.0 (1.0; 5.2) (n = 22)	38.0 (30.0; 44.0)* (n = 22)	33.5 (28.0; 41.2)* (n = 22)
	Controls	NA	NA	5.0 (2.0; 8.5) (n = 18)	5.0 (2.0; 6.2) (n = 18)	3.5 (1.0; 5.2) (n = 18)	53.5 (51.0; 56.0) (n = 18)	19.5 (18.0; 23.5) (n = 18)
	Heterozygous	NA	NA	13.0 (n = 1)	12.0 (n = 1)	6.0 (n = 1)	58.0 (n = 1)	31.0 (n = 1)
	Patients	NA	NA	NA	NA	NA	NA	NA
	Controls	NA	NA	13.0 (n = 1)	12.0 (n = 1)	6.0 (n = 1)	58.0 (n = 1)	31.0 (n = 1)
	<i>p</i> Value	NA	NA	0.098	0.146	0.390	0.049	0.829
	Wild-type homozygous	28.0 (17.5; 39.0) (n = 21)	11.0 (9.5; 13.0) (n = 21)	4.5 (2.2; 8.0) (n = 40)	5.0 (2.0; 7.0) (n = 40)	4.0 (1.0; 5.0) (n = 40)	46.0 (35.7; 53.7) (n = 40)	25.5 (19.2; 34.2) (n = 40)
	Patients	28.0 (17.5; 39.0) (n = 21)	11.0 (9.5; 13.0) (n = 21)	4.0 (2.5; 7.5) (n = 21)	4.0 (2.0; 8.0) (n = 21)	4.0 (1.0; 5.0) (n = 21)	38.0 (30.0; 44.0)* (n = 21)	32.0 (28.0; 41.5)* (n = 21)
	Controls	NA	NA	5.0 (2.0; 10.0) (n = 19)	5.0 (2.0; 7.0) (n = 19)	4.0 (1.0; 6.0) (n = 19)	54.0 (51.0; 56.0) (n = 19)	20.0 (18.0; 25.0) (n = 19)
p.Val120	Heterozygous	21.0 (n = 1)	12.0 (n = 1)	5.0 (n = 1)	4.0 (n = 1)	9.0 (n = 1)	38.0 (n = 1)	38.0 (n = 1)
	Patients	21.0 (n = 1)	12.0 (n = 1)	5.0 (n = 1)	4.0 (n = 1)	9.0 (n = 1)	38.0 (n = 1)	38.0 (n = 1)
	Controls	NA	NA	NA	NA	NA	NA	NA
	<i>p</i> Value	0.727	0.818	0.878	0.927	0.146	0.537	0.341
	Wild-type homozygous	26.0 (17.2; 39.5) (n = 20)	11.0 (9.2; 13.0) (n = 20)	4.0 (2.0; 8.0) (n = 37)	5.0 (2.0; 7.0) (n = 37)	4.0 (1.0; 6.0) (n = 37)	45.0 (38.0; 53.5) (n = 37)	26.0 (19.5; 35.0) (n = 37)
	Patients	26.0 (17.2; 39.5) (n = 20)	11.0 (9.2; 13.0) (n = 20)	3.5 (2.2; 7.7) (n = 20)	4.0 (2.0; 7.7) (n = 20)	4.0 (1.0; 5.7) (n = 20)	39.0 (30.7; 44.0)* (n = 20)	33.5 (28.0; 41.7)* (n = 20)
	Controls	NA	NA	6.0 (2.0; 10.5) (n = 17)	6.0 (2.0; 7.0) (n = 17)	4.0 (1.0; 6.0) (n = 17)	54.0 (51.0; 56.0) (n = 17)	20.0 (18.0; 25.0) (n = 17)
	Heterozygous	27.0 (22.0; NA) (n = 2)	12.0 (11.0; NA) (n = 2)	5.0 (4.2; 5.0) (n = 4)	3.5 (1.2; 7.2) (n = 4)	3.5 (2.2; 4.0) (n = 4)	41.5 (29.2; 56.0) (n = 4)	26.5 (18.7; 35.0) (n = 4)
	Patients	27.0 (22.0; NA) (n = 2)	12.0 (11.0; NA) (n = 2)	5.0 (5.0; 5.0) (n = 2)	4.5 (1.0; NA) (n = 2)	3.5 (3.0; NA) (n = 2)	29.5 (29.0; NA) (n = 2)	34.0 (32.0; NA) (n = 2)
	Controls	NA	NA	4.5 (4.0; NA) (n = 2)	3.5 (2.0; NA) (n = 2)	3.0 (2.0; NA) (n = 2)	55.0 (53.0; NA) (n = 2)	19.5 (18.0; NA) (n = 2)
p.Val45	<i>p</i> Value	1.000	0.554	0.816	0.626	0.816	0.849	0.849

Data are expressed by median (interquartile range). Abbreviation: BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; HADS-SIS, Hospital Anxiety and Depression Scale-Snaith Irritability scale; TFC, total functional capacity; UHDRS, Unified Huntington Disease rating Scale; NA, not available

* $p < 0.001$ versus controls for each genotype group

** $p < 0.05$ among patients with different p.Val45 genotype

Genomic DNA was extracted from peripheral blood (E.Z.N.A.® Blood DNA Kit, Omega Bio-tek, Norcross, USA) and quantified using a NanoDrop 2000 (Thermo Fisher Scientific, Darmstadt, Germany). Polymerase chain reaction (PCR) was performed with 20 ng of DNA and primers specific for the coding regions of *OXTR* (NM_000916.4; Supplementary Table 1). DNA sequencing was performed in LGC's sequencing laboratories (Berlin, Germany) on an

ABI3730 XL Sequencer. Sequencing reads were analyzed using Mutation Surveyor software v5.1.2. We used public database dbSNP to identify known and novel polymorphisms and Polyphen-2 algorithm to predict the functional significance of an allele replacement from its individual features by Naïve Bayes classifier trained using supervised machine-learning [8]. Allele frequencies for European

populations (Iberian population in Spain) were obtained from the Genome Aggregation Database.

Analyses were performed with IBM-SPSS 21 software. The normal distribution of the variables was analyzed using the Kolmogorov–Smirnov test. Descriptive analysis of the participants' characteristics was performed in terms of frequencies (percentage), mean/median values with the corresponding standard deviation or interquartile range, as appropriate, and 95% confidence intervals (CI). Group comparisons between HD and control participants and different genotypes were assessed by χ^2 and the Mann–Whitney U test, respectively. p Values and 95% CIs for score differences between different genotypes groups were computed using bootstrapping (with replacement) with 999 iterations.

Results

A total of 41 individuals were included, 22 HD patients and 19 controls. Main demographic and clinical characteristics are shown in Table 1. Patients showed significantly higher percentage of antidopaminergic and antidepressants consumption, compared to controls. Likewise, patients showed significantly higher AES score and lower Ekman score, compared to controls, which reflect higher apathy and lower social cognition features.

We identified ten variants in the *OXTR* gene, seven of which were novel (Supplementary Table 2). Three variants were classified as possibly damaging (p.Arg40Gly) or probably damaging (p.Leu46Pro, p.Thr102Asn) by Polyphen-2 algorithm (Supplementary Table 2); however, the allele frequencies did not differ significantly between patients and control subjects (Table 2).

Comparing the scores of UHDRS, TFC, HADS, Ekman, and AES scales among the discovered *OXTR* variants, we found that subjects carrying the wild-type genotype of the synonymous variant p.Val45 showed a significantly lower score in the HADS-SIS scale, which is related to lower irritability ($p=0.013$). Moreover, the only subject carrying the heterozygous genotype of the synonymous variant p.Leu62 showed a significantly higher score on Ekman scale, compared to wild-type subjects ($p=0.049$); however, this finding was not confirmed after bootstrapping.

Discussion

In early stages of HD, a reduction of oxytocin-expressing neurons in the hypothalamus was observed, suggesting a role of oxytocin in the different neuropsychiatric manifestations of HD [9]. Histopathological studies have also found the presence of neuronal inclusions of mutated huntingtin in the hypothalamus

and a decrease in neurons expressing hypothalamic oxytocin and vasopressin by 45% and 24%, respectively, corroborating hypothalamic dysfunction in HD [10]. Our results are in line with these previous findings since HD patients showed altered Ekman scale scores compared to patients.

According to our knowledge, this is the first study to find several *OXTR* variations that could affect apathy and social cognition in HD. Polymorphisms in the oxytocin receptor could have a relevant role in the correct development of social and cognitive functions. However, the associations found in our study warrant further confirmation since the variants categorized as damaging/probably damaging did not influence apathy or social cognition. However, synonymous variants, whose role in *OXTR* gene expression needs to be further studied, did influence apathy or social cognition scales. Future approaches will include the molecular study of the p.Arg40Gly, p.Leu46Pro, and p.Thr102Asn variants to confirm their pathogenicity, as well as the validation of the influence of the synonymous p.Val45 and p.Leu62 variants for their involvement in irritability and social cognition in HD.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10072-022-06226-1>.

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Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethical approval and Informed consent This study was approved by the Research Ethics Committee of Health Area of Burgos and Soria (Spain) (Ceim 1973). Data were collected only for participants who signed the informed consent after full explanation of the procedure.

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