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Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Comparison of the Huntington's Disease like 2 and Huntington's Disease Clinical Phenotypes

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ABSTRACT: Background: Huntington's disease like 2 (HDL2) is the most common Huntington's disease (HD) phenocopy in many countries and described as the phenocopy with the greatest resemblance to HD. The current clinical description of HDL2 is based on retrospective data. It is unknown whether HDL2 has clinical features that distinguish it from HD.

Objective: To describe the HDL2 phenotype and compare it to HD systematically.

Methods: A blinded cross-sectional design was used to compare the HDL2 (n = 15) and HD (n = 13) phenotypes. African ancestry participants underwent assessments, including the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS motor component was video recorded and evaluated by blinded experts and the inter-rater reliability calculated.

Results: Both groups were homogeneous in terms of demographics and disease characteristics. However, HDL2 patients presented three years earlier with more prominent dysarthria and dystonia. Raters could not distinguish between the two diseases with a high level of agreement. No significant differences in the TMS between HDL2 and HD were found. In both disorders, disease duration correlated with motor scores, with the exception of chorea. Psychiatric and cognitive scores were not significantly different between the groups.

Conclusions: The HDL2 phenotype is similar to HD and is initially characterized by dementia, chorea, and oculomotor abnormalities, progressing to a rigid and bradykinetic state, suggesting the UHDRS is useful to monitor disease progression in HDL2. Although HDL2 patients scored higher on some UHDRS domains, this did not differentiate between the two diseases; it may however be emerging evidence of HDL2 having a more severe clinical phenotype.

Introduction

Since its discovery,[1] Huntington disease like 2 (HDL2) has emerged as the most common Huntington disease (HD) phenocopy in patients with African ancestry.[2] In the South African black population, for every two cases diagnosed with HD there is one case diagnosed with HDL2.[3] Importantly HDL2 is the most frequent HD phenocopy in South America, the United States, and parts of Europe.[4–6]

The index HDL2 pedigree was followed in the Baltimore Huntington's Disease clinic for many years as a family believed to have HD. The HD mutation, caused by a CAG repeat expansion

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occurring in exon 1 of the *huntingtin* (HTT) gene on chromosome 4p16.3, was reported in 1993.[7] When genetic testing then became available, this African American family was tested and found not to have the HD mutation.[1] A subsequent study led to the discovery that the disease in this family was caused by a CTG expansion mutation in exon 2A of *junctophilin-3* (*JPH3*) on chromosome 16q24.3, and to the designation of the disease as HDL2.[8]

Both disorders present with movement abnormalities, progressive subcortical dementia, and psychiatric symptoms that progress to death 15 to 20 years after the onset of the disease.[1,9] However, previous reports suggested that HDL2 presents with two different phenotypes:[10] a parkinsonian, earlier-onset form without oculomotor involvement, or second, a later-onset variant that is akin to the classical HD phenotype with typical oculomotor involvement. Overall, the HDL2 phenotype has been considered to have greater parkinsonism, less dysarthria, and relatively preserved oculomotor function compared to HD.[9,11] A systematic review of 69 cases of HDL2 corroborated some of these reported findings.[12] Parkinsonism was reported in 37% of HDL2 cases. However, this was without the specific parkinsonian features of rigidity and bradykinesia being described. Previous definitions of parkinsonism have implied the presence of a tremor with other classic hypokinetic features.[14] Therefore, defining specific features of hypokinesia would allow for a more accurate description of the HDL2 phenotype. Dystonia was described in conjunction with parkinsonism and/or chorea in only 16 cases of HDL2. Dysarthria was identified in one-third of the HDL2 cases and was reported as mild to moderate. Only eight of the 19 cases in which an oculomotor exam was recorded had an abnormal oculomotor function, potentially differentiating HDL2 from HD, as early loss of oculomotor function is considered a cardinal sign in HD.[12,13] Myoclonus has been reported in four cases of HDL2.[11,15] Like HD, dementia was seen in almost all cases, chorea was the most common motor finding, and a strong negative correlation was observed between repeat length and age of onset of the disease.[12]

Descriptions of the HDL2 phenotype have consisted of small case series with limited detailed documentation of particular clinical signs being either present or absent. To date, there have been only three reports where the Unified Huntington's Disease Rating Scale (UHDRS) was used to assess HDL2 patients.[5,11,16] Therefore, the current understanding of the HDL2 phenotype remains incomplete.[12] Systematic examination of specific phenotypic features has yielded findings that were not consistent with initial reports. For instance, reports of acanthocytosis in HDL2 were not confirmed in a blinded, controlled study.[17] Furthermore, volumetric comparisons between matched HD and HDL2 subject's MRIs have demonstrated remarkable similarities, as expected from previous case series of HDL2 neuroimages. However, an exception of greater thalamic atrophy in HDL2 has been reported in a blinded study for the first time, and could potentially distinguish HDL2 from HD when using quantitative MRI image analysis.[18]

To compare the HDL2 and HD clinical phenotype systematically, we took advantage of the relatively high prevalence of HDL2 in South Africa.[2] Using standardized rating scales and video examinations by experienced clinicians that were blinded to the patients' genetic diagnosis, we developed a protocol for rating clinical phenotypes. Our results demonstrate remarkable similarities between the two disorders, and go some way to clarify the HDL2 phenotype.

Materials and Methods

Study Design

A cross-sectional design with blinded assessment was used to compare the phenotypes of patients with HDL2 (n = 15) and HD (n = 13). Patients with a genetically confirmed diagnosis of HDL2 or HD, tested at The Division of Human Genetics, National Health Laboratory Service (NHLS) in Johannesburg South Africa, were invited to enroll into an ongoing prospective study of the HDL2 phenotype as previously described.[12] HDL2 has been exclusively identified in patients with African and patients with mixed ancestry to date.[2] (Mixed ancestry individuals in South Africa are those whose gene pool is derived from one or more of the indigenous African populations [San, Khoikhoi or Bantu speaking]; European immigrants from western Europe; and/or slaves and indentured laborers from Madagascar, the Malaysian archipelago, and India.[2]) Therefore, both cohorts were restricted to these ethnic groups to avoid potential unblinding. The Human Research Ethics Committee of The University of the Witwatersrand approved this study (M140872).

Data Ascertainment

A movement disorder neurologist (DGA) interviewed all the participants and a friend/family member. The age of disease onset was defined as the age at which the subject initially experienced abnormal movements. These data were obtained from interviewing the patients and their accompanying friends/family members. They were then asked whether the initial symptom of the disease was: cognitive, psychiatric, or movement abnormality. Participants were then examined using the UHDRS Total Motor Score (TMS); the examination was recorded on video. Three raters (AA, DGA, FBR), experienced in the clinical examination of HD, independently viewed the videos, and scored the TMS for each subject. Raters were blinded to the genetic diagnosis of the patients. All TMS raters are Enroll-HD TMS certified and have at least three years' experience using the scale. After reviewing the videos, evaluators also assigned each participant a disease diagnosis of HDL2 or HD. The TMS scores were averaged among the three examiners. Patients underwent a cognitive assessment using the cognitive components of the UHDRS by an experienced neuropsychologist (AFC). A subgroup of patients could not complete cognitive components of the UHDRS due to the presence of important confounding variables on neuropsychological performance or inability to take the cognitive tests. Specifically, 11 cases were excluded; four of them presented with advanced dementia, three were human immunodeficiency virus

positive (HIV+), three were not proficient in English, and one had motor aphasia.

Data Analysis

Comparison of abnormal repeat length, age at onset, age at diagnosis, and disease duration between diseases was performed using the Wilcoxon rank sum test. Comparison of the difference between age at onset (defined as the age at which the subject initially experienced abnormal movements) and age at diagnosis between phenotypes was done using the independent samples t-test. The relationship between age at onset and abnormal repeat length, overall and by group, was determined by a General Linear Model (GLM) with age at onset as the dependent variable and abnormal repeat length and disease group, and their interaction, as the independent variables. Comparison of manifesting symptom, ethnicity, and gender between phenotypes was performed using Fisher's exact test. Inter-rater reliability (IR) analysis is discussed in the Supporting Data.

Composite motor assessment scores for each dimension were calculated by averaging the scores of the three raters. Comparison of these motor assessment dimensions and total scores, as well as the UDHRS functional assessment scores between phenotypes, were done with a GLM with the score as the dependent variable, and phenotype and disease duration as the independent variables. The phenotype-disease duration interaction was non-significant in all cases and was removed from the model. We controlled for disease duration (rather than age of onset, or repeat length) since this had the largest difference between the two phenotypes. The z-test for proportions was used to determine the accuracy of the clinician assigning the subject diagnosis as either HDL2 or HD. A 5% significance level was used.

Results

Demographic and Genetic Data

Thirteen patients with HD and 15 with HDL2 were studied from predominantly the north of South Africa (Fig. 1). In the HD group, three of the ten pedigrees each contributed two participants to the data. The HDL2 group consisted of 15 unrelated individuals. There was no significant difference between the abnormal triplet repeat length, age of disease onset, age at diagnosis, gender, ethnicity, or initial manifesting symptom between the two groups (Table 1). The median duration of disease was longer in the HD group (7y; IQR 6–8) compared to the HDL2 group (4y; IQR 3–7y; $P = 0.029$).

Age at onset (defined as the age at which the subject initially experienced abnormal movements) was strongly associated with the abnormal repeat length in both diseases ($P < 0.0001$), and the slope of the relationship varied with the disease group ($P = 0.022$). For every triplet increase in abnormal repeat length, the age at onset decreased by 3.2 years for the HD group, but by only 1.8 years for the HDL2 group (Fig. 2). The estimated delay between onset and molecular diagnosis was 6.0 ± 1.6y (95% CI) for the HD group, compared to 3.3 ± 1.5y for the HDL2 group ($P = 0.021$). This suggests that the time to present for medical assistance and diagnosis from the time of disease onset in the HDL2 patients was approximately three years earlier compared to HD patients. However, the age of disease onset is later for a given abnormal triplet repeat length in HDL2 compared to HD patients. The CAG repeat size on the normal allele has been shown to influence the age of disease onset in HD.[19] However, the age at onset was not significantly related to the normal triplet repeat length when controlling for either disease.

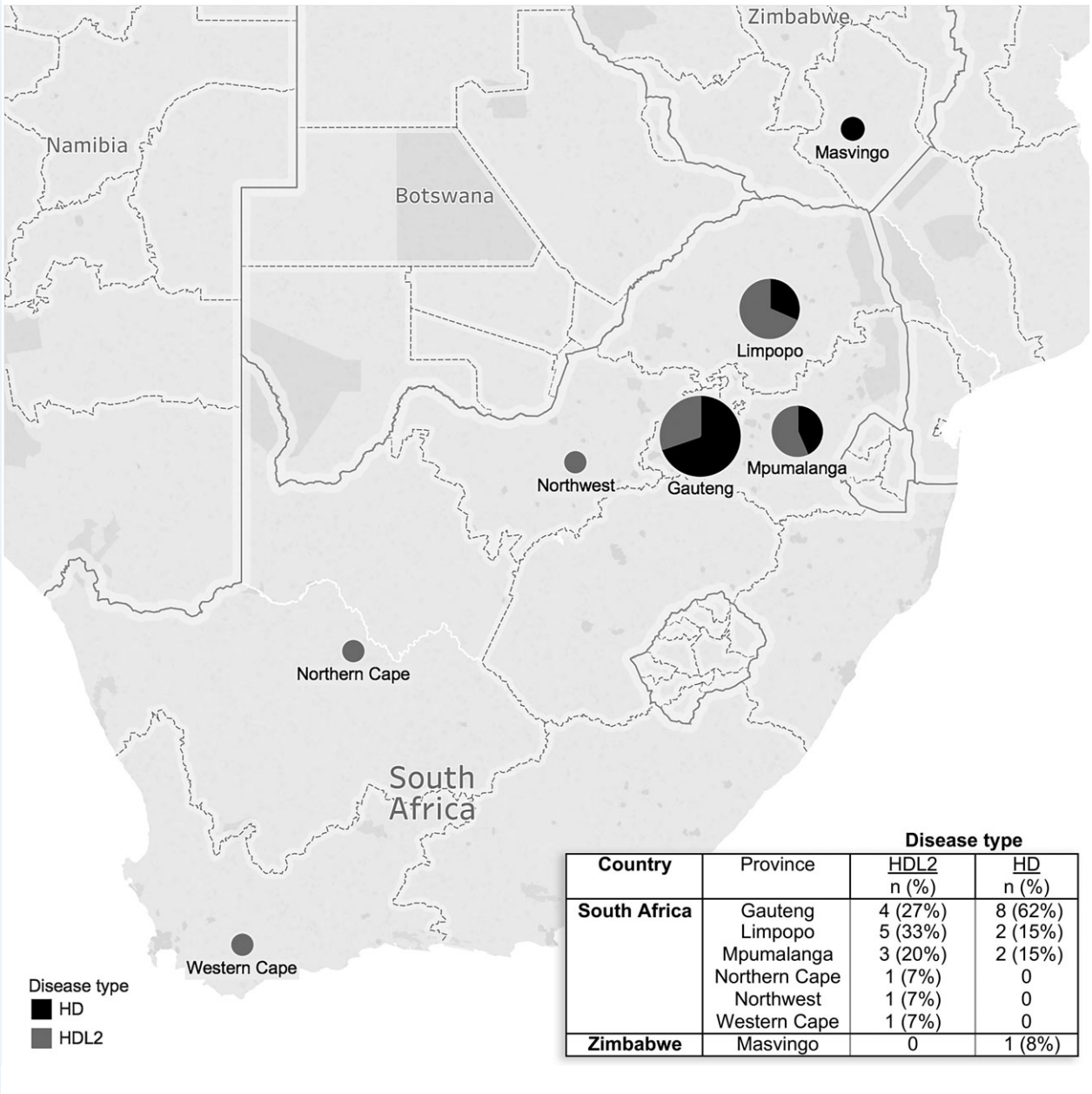
Comorbidities and Concomitant Medications

Two of the HDL2 and one of the HD patients were HIV+, and none of them had other infections. The HIV+ cases had MRI scans at the time of the study showing atrophic changes in keeping with HD. The MRIs did not show any focal lesions or HIV-associated infections. One of the HDL2 HIV+ cases had a CD4 cell count below 200 cells/μL. This subject was awaiting HIV treatment. The other two HIV+ cases had CD4 cell counts of over 500 cells/μL and were receiving antiretroviral treatment. Eight HDL2 and eight HD patients were taking dopamine antagonists. Three HD patients and none of the HDL2 group had myoclonus. Two were brothers who also had generalized seizures. Both brothers had an abnormal, expanded HD allele with a relatively long 47 triplet repeats. The disease onset was also relatively young at 23 and 28 years of age for each subject, with chorea as the manifesting symptom. However, apart from the myoclonus and seizures they did not differ significantly from the rest of the HD cases. EEG reports for both brothers were reported as generalized spike and wave discharges, and both were treated with sodium valproate. Their MRIs at the time of the study showed typical HD changes with striatal atrophy without focal brain lesions or other radiological findings that could account for the seizures. All three reported on history that the myoclonus and seizures began after the onset of HD motor symptoms.

Motor Phenotype

Across all patients, the Brennan-Prediger coefficient IR for the TMS was 0.80 (95% CI = 0.70–0.90), in the "substantial-to-almost-perfect" range, with an intraclass correlation (ICC) = 0.95, nearly identical to the standard set in the original development of the UHDRS.[20] IR ranged from moderate to near perfect for other subscores, similar to previously established standards[21] (Supporting Data).

When controlling for duration of disease, there was a significant increase in motor scores, with increased disease duration in both disease groups. The rate of increase was similar between diseases (Fig. 3). The total motor score increased by 4.4 ± 1.3 points and this did not differ significantly between disease groups ($P = 0.37$). However, for a given disease duration, the HDL2 patients had TMS scores that were higher on average, but this difference did not reach statistical significance ($P = 0.06$). In both disease groups, most individual component scores increased by an estimated



Country	Province	Disease type: HDL2 n (%)	Disease type: HD n (%)
South Africa	Gauteng	4 (27%)	8 (62%)
	Limpopo	5 (33%)	2 (15%)
	Mpumalanga	3 (20%)	2 (15%)
	Northern Cape	1 (7%)	0
	Northwest	1 (7%)	0
	Western Cape	1 (7%)	0
Zimbabwe	Masvingo	0	1 (8%)

FIG. 1. Distribution of Huntington's disease like 2 and Huntington's disease patients.
Map of Southern Africa showing the distribution of Huntington's disease like 2 and Huntington's disease patients.
Abbreviations: HD, Huntington's disease; HDL2, Huntington's disease like 2; n = number of participants.

0.2 ± 0.1 units for every year of disease ($P < 0.0001$). The chorea scores were the exception to this trend and were not higher in individuals with longer disease duration in either disease. This finding is consistent with previous reports in HD where the severity of chorea tends to plateau from the early to moderate stages of the disease.[22]

On average, the HDL2 group had worse results for the combined dystonia score (t = -2.6; $P = 0.015$), dysarthria score (t = -3.33; $P = 0.003$), and the Luria test scores (t = -3.38; $P = 0.002$) when compared to the HD group and controlling for duration of disease (Table 2A). We found no other significant differences, either overall or on any sub-score, in the TMS between the two groups.

Blinded raters' success at assigning a diagnosis of HD or HDL2 to each case was no better than chance ($P = 0.28$).

Behavior and Functional Components

All three UHDRS functional assessments demonstrated increased impairment in each disease with longer disease duration, but no

TABLE 1 *Comparison of demographic, genetic, and manifesting symptom data between Huntington's disease like 2 and Huntington's disease groups*

Demographic/genetic variable		HDL2 (n = 15) Median	HDL2 (n = 15) IQR	HD (n = 13) Median	HD (n = 13) IQR	*P* value between groups
Abnormal triplet repeat length		46	44-50	46	42-47	0.19
Disease duration (y)		4	3-7	7	6-8	**0.029**
Age at onset (y)		41	35-50	40	28-43	0.41
Age at diagnosis (y)		47	38-54	45	34-50	0.68
Years of education		12	9-15	12	12-14	0.80
		n (%)		n (%)		
Gender	Female	7 (47%)		7 (54%)		0.71
	Male	8 (53%)		6 (46%)		
Race	Black	12 (80%)		6 (46%)		0.061
	Mixed	3 (20%)		7 (54%)		
Manifesting symptom	Cognitive	3 (20%)		2 (15%)		0.57
	Movement	10 (67%)		7 (54%)		
	Psychiatric	2 (13%)		4 (31%)		

Table comparing the demographic, genetic and manifesting symptom data between HDL2 and HD groups. Note Two-tailed significance at $P < 0.05$ for *P*-value between groups with statistically significant findings noted in bold font.
Abbreviations: HD, Huntington's Disease; HDL2, Huntington's disease like 2; IQR, interquartile range; y, years.

difference between the two diseases controlling for duration of disease (Table 2B).

The behavioral component score of the UHDRS, designed to measure psychiatric symptoms in HD, did not significantly differ between the two groups and did not change with the disease duration (Table 2C).

Cognition

Cognitive scores were not significantly different between the two groups except for a higher score on the Stroop Colour-Word test for the HD patients when controlling for covariates as described ($P = 0.04$; Table 2D).

Discussion

This is the first comparison of the HDL2 and HD clinical phenotypes by blinded raters using the UHDRS. In summary, the demographic features of HD and HDL2 patients were comparable, the results support the previously described phenotypic similarity between HDL2 and HD despite their genetic differences,[1,2,12] and the diseases remain clinically indistinguishable at various points of disease duration.

When comparing the HDL2 and HD patients using the UHDRS, all four components of the scale showed similar scores. After scoring the UHDRS TMS, blinded specialists were unable to differentiate HDL2 from HD. This has important implications for clinical practice. Clinicians should consider testing for the *JPH3* mutation in patients with African ancestry with a HD phenotype but no *HTT* expansion mutation.

Dementia is a prominent feature in HDL2. Nevertheless, identifying a more refined neurocognitive profile in HDL2 has been challenging because many patients presenting with advanced disease are unable to complete comprehensive testing.[23] Although this remains to be further investigated, the present study detected no quantitative difference between HDL2 and HD except that the Stroop Color and Word test median score for the HD patients was significantly higher than that of the HDL2 patients. In addition, HDL2 patients performed worse than HD patients on the Luria test, although this test has not been useful in differentiating different dementias.[24] This suggests that the cognitive dysfunction in HDL2 may be similar to that of HD, although it introduces the possibility that HDL2 dementia may be different from HD in terms of severity and progression. Dedicated research to the neuropsychology of HDL2 is needed, as the present study did not control for relevant neuropsychological cofounders.[25]

The behavior and independence components of the UHDRS did not differentiate HDL2 from HD. The independence results, for both diseases, worsened with disease duration as was seen in the UHDRS cognitive and motor scores. The psychiatric measures showed no correlation with duration for either disease, a finding that has been previously described in HD[20] and likely reflects the unpredictable and nonlinear nature of the psychiatric syndromes in these disorders.

Due to the lack of systematic descriptions from the literature and reports of motor features that have been described to differentiate HDL2 from HD, the motor phenotype was of particular interest to the authors. Eye movements, initially reported as relatively preserved in HDL2, were abnormal in all HDL2 cases. Abnormal eye movements were detected in patients in the early stages of HDL2, and appeared worse with longer disease duration, mirroring the findings in HD.

Chorea was not significantly different between the HDL2 and HD groups and was present in all but one HDL2 case. In both diseases, the chorea score was the only clinical sign that did not increase with disease duration. This has been described previously in HD.[22]

Previous accounts of HDL2 have highlighted a higher rate of parkinsonism.[12] This was not shown in this study, as bradykinesia and rigidity were similar in the two diseases. Previous descriptions of HDL2 patients with a more parkinsonian phenotype may be attributable to evaluations performed later in the course of the disease when parkinsonism is more prominent.[1,11]

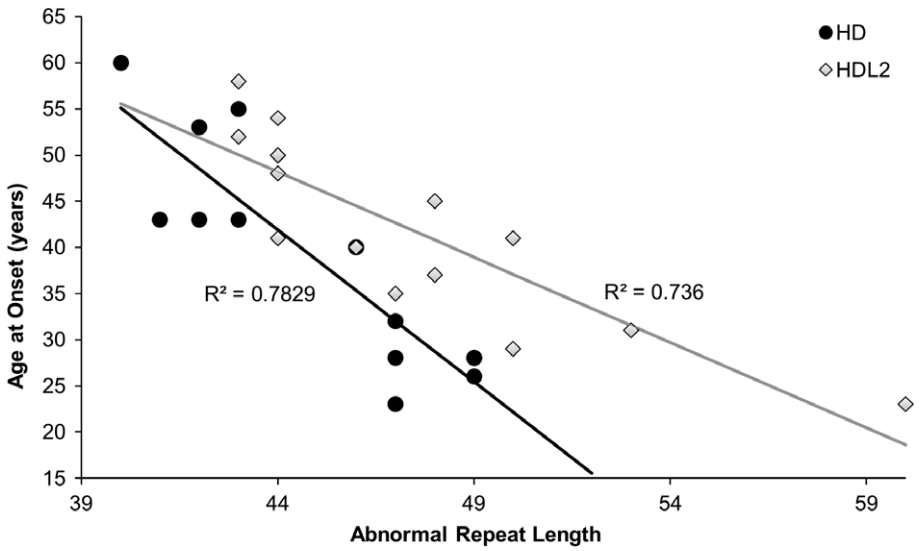


FIG. 2. Age of disease onset vs. abnormal repeat length.
Scatterplot showing inverse relationship between age of onset and abnormal triplet repeat length for both HDL2 and HD.
Abbreviations: HD, Huntington's disease; HDL2, Huntington's disease like 2.

Myoclonus has been previously described in HDL2.[12] All cases of myoclonus from this current study were in the HD group. The distribution of patients with myoclonus being only in the HD group and none in the HDL2 group is possibly due to the small sample size. This may result in a larger margin of error, and therefore this finding may not be a true reflection of the myoclonus in HD and HDL2. The existence of generalized epilepsy in two of our adult-onset patients is of interest as epilepsy associated with HD has only been described in the juvenile onset form of the disease.[26] Both patients with epilepsy from this study were brothers, and both had 47 CAG repeat expansions in the HD locus. The disease manifested relatively in their twenties in both cases. However, phenotypically the HD did not differ from the other HD study subject with predominant chorea, and their MRI scans showed typical HD changes with no focal cause for seizures.

While most movement abnormalities were similar in the HD and HDL2 groups, the dysarthria and dystonia scores were worse in the HDL2 patients. Dystonia is recognized as the TMS item with the poorest interrater reliability due to the subjectivity and difficulty with interpretation.[21] Our interrater agreement for dystonia showed substantial agreement (0.67), which is much higher than recently reported (0.34).[21]

Compared to HD patients, the age of disease onset in the HDL2 group was later for a given abnormal triplet repeat length. This has been was previously reported in a retrospective analysis of 41 HDL2 cases.[2] However, HDL2 patients in this study presented for diagnosis on average three years sooner once the disease had manifested when compared to the HD patients. This finding suggests that once the disease manifests in HDL2, there may be more prominent features resulting in these patients seeking medical care sooner after onset. The Luria test, dysarthria, and dystonia are more severe in HDL2 compared to HD as the UHDRS findings have shown in this study which may account for the HDL2 cases seeking aid earlier.

Given the similarity of HD and HDL2 phenotypically, identifying other features that HDL2 and HD share may help elucidate pathogenic pathways implicated in both diseases. Common features of triplet repeat disorders include a strong negative correlation between age of onset and the number of triplet repeats. The two groups had very similar inverse correlations (HDL2 [$R^2 = 0.74$], HD [$R^2 = 0.78$]), which has been previously noted in a systematic review of HDL2 cases.[12] Another feature that many CAG repeat disorders share is that they manifest clinically at a threshold of 35 to 40 triplet repeats.[27] This has been shown to be the threshold that polyglutamine proteins begin to aggregate in vitro studies.[28] Although there is some debate to the degree that polyglutamine proteins play in the pathogenesis of HDL2,[29] the identical number of 40 triplet repeats shared between HDL2 and HD at which the diseases manifest[8] may suggest some molecular overlap.

Current evidence suggests that the HD expansion mutation results in disease primarily through the expression of a protein with an excessively long stretch of polyglutamine residues, with contributions from toxic properties of the mutant RNA and loss of normal protein function.[30] In HDL2, in which pathogenic pathways are less established, evidence suggests that loss of *JPH3* expression and toxic properties of the mutant *JPH3* RNA contribute to neurodegeneration, with a role for cryptic antisense expression of a transcript encoding a protein with an expanded stretch of polyglutamine residues.[29,31,32] The similarities between the two diseases genetically, clinically, pathologically, and radiologically,

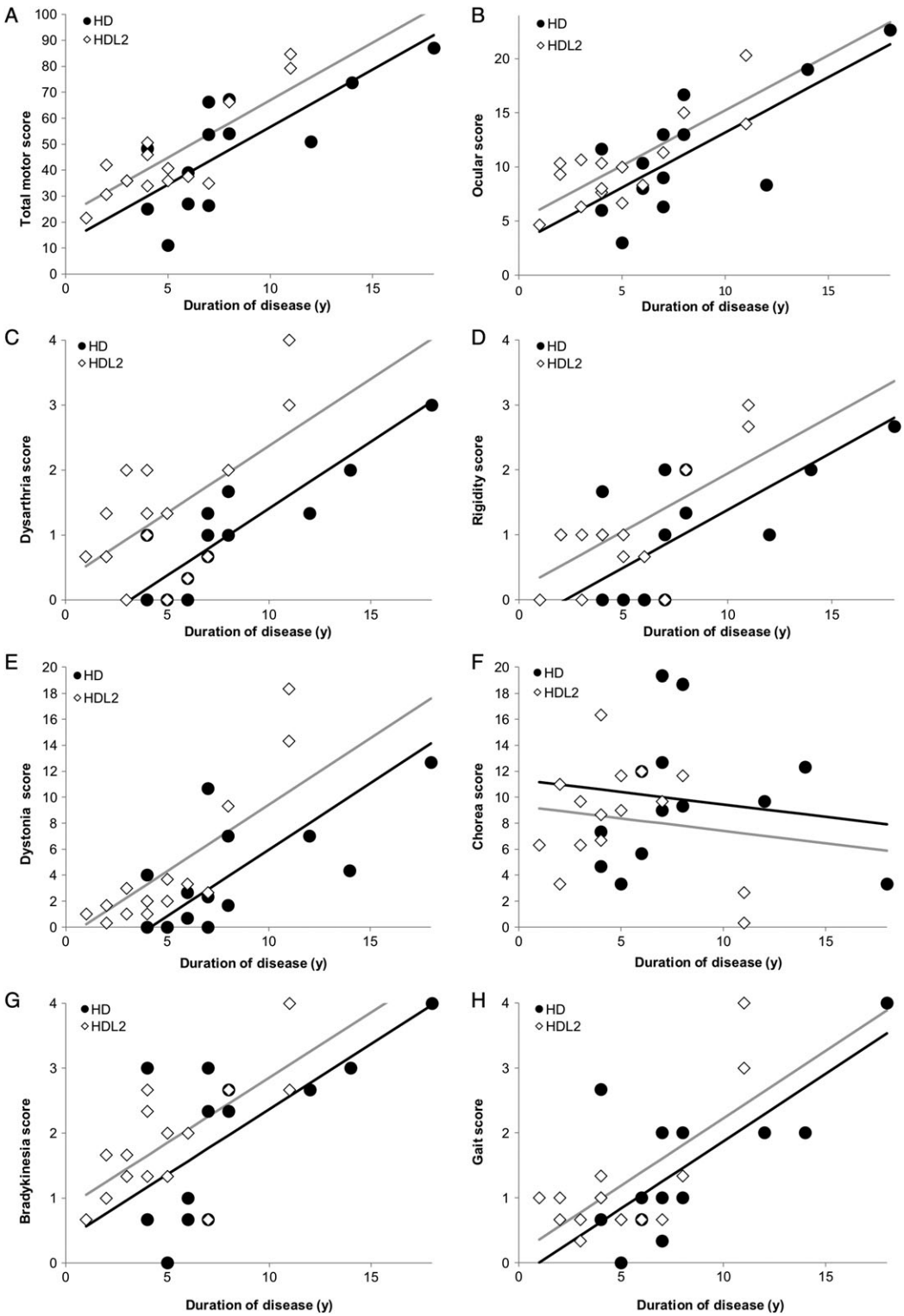


FIG. 3. Scatterplots for Unified Huntington's Disease Rating Scale Total Motor Score and sub-scores vs. duration of disease. Scatterplots demonstrating the TMS and some sub-scores from the UHDRS. (A) Total Motor Score (B) Ocular Score (C) Dysarthria Score (D) Rigidity Score (E) Dystonia (F) Chorea (G) Bradykinesia (H) Gait.
Abbreviations: HD, Huntington's Disease; HDL2, Huntington's Disease like 2; UHDRS TMS, Unified Huntington's Disease Rating Scale Total Motor Score; y, year.

TABLE 2 *Comparisons of the Unified Huntington's Disease Rating Scale between Huntington's disease like 2 and Huntington's disease groups*

UHDRS	HDL2			HD			*P* value between groups
A. UHDRS-TMS	**N**	**Mean**	**STD**	**N**	**Mean**	**STD**	
Total motor score	15	45.1	18.0	13	48.4	22.1	0.06
	N	**Median**	**IQR**	**N**	**Median**	**IQR**	
Combined ocular score	15	10.0	7.7-11.3	13	10.3	8.0-13.0	0.12
Dysarthria	15	1.3	0.7-2.0	13	1.0	0.3-1.3	**0.003**
Tongue protrusion	15	1.0	0.0-2.7	13	1.3	1.0 -2.0	0.13
Combined rigidity	15	1.0	0.7-1.0	13	1.0	0.0-2.0	0.06
Luria	15	4.0	2.3-4.0	13	2.3	1.0-3.7	**0.002**
Combined dystonia	15	2.0	1.0-3.7	13	2.7	0.7-7.0	**0.015**
Combined chorea	15	9.0	6.3-11.7	13	9.3	5.7-12.3	0.31
Bradykinesia	15	2.3	0.7-3.0	13	2.3	0.7-0.3	0.16
Retropulsion	15	1.7	1.0-2.0	13	2.0	2.0-2.0	0.71
Gait	15	1.0	0.7-1.3	13	1.0	0.7-2.0	0.26
Tandem gait	15	1.0	0.3-3.3	13	2.3	1.0-3.0	0.70
B. Functional scores	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	
Functional capacity assessment	15	5.0	3.0-9.0	13	5.0	2.0-7.0	0.23
Functional checklist	15	15.0	7.0-21.0	13	14.0	9.0-18.0	0.11
Independence score	15	70	60- 90	13	70	60-90	0.05
C. Behavioral assessment	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	
Behavior score	15	20.0	9.0-23.0	13	19.0	13.0-33.0	0.34
D. Cognitive assessment	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	
MoCA	7	13	11-16	10	16.5	13-20	0.15
SDMT written	5	14	10-20	10	15	11-21	0.82
SDMT oral	5	20	11-24	10	17.5	10-21	0.57
% Speed/accuracy	4	88.5	80.5-89.5	10	87.5	76-92	0.68
Stroop word	7	44	39-81	10	52	30-61	0.60
Stroop color	7	19	16-50	10	26	23-35	0.60
Stroop interference	7	7	2-12	10	18.5	15-21	**0.04**

(A) UHDRS Total Motor Scores - Noting some of the scores are combined. (B) Functional Scores (C) Total Behavioural Score (D) Cognitive Assessments. Note: Two-tailed significance at $P < 0.05$ for *P*-value between groups with statistically significant findings noted in bold font.
Abbreviations: HD, Huntington's Disease; HDL2, Huntington's disease like 2; IQR, interquartile range; MoCA, Montréal Cognitive Assessment; N, number; SDMT, Symbol Digit Modality Test; STD, Standard deviation; UHDRS TMS, Unified Huntington's Disease Rating Scale Total Motor Score.

are striking and suggest common mechanisms of pathogenesis. However, it is likely that divergent aspects of their pathogenesis result in subtle phenotypic differences like dysarthria and dystonia, or more striking symptoms at onset, leading to an earlier diagnosis. We have shown in this study that differences between HDL2 and HD cannot be differentiated by examining individual patients.

The key limitation of this study is the small sample size, reflecting the low prevalence of HDL2 even in a population in which the disease is more common, and the difficulty in ascertaining cases in areas with poor healthcare services.[3] Nonetheless, our analysis is the first systematic comparison of HD and HDL2. While subtle differences between the diseases cannot be excluded, our results strongly support that the clinical phenotype of the two diseases is indistinguishable in the clinical setting.

A possible limitation could be the inclusion of mixed ancestry patients into the analysis as a way of introducing other genetic modifying variables into the study. However, HDL2 has been exclusively reported in black and mixed ancestry patients around the world.[2,6,12] In Johannesburg, a significant proportion of the cases with HDL2 have mixed ancestry.[2] Therefore, the mixed ancestry group represents an important subsection of the HDL2 phenotype. Excluding this group would not be a true reflection of the HDL2 phenotype and furthermore, this would have reduced the number of cases available to study.

Another potential limitation of the study was the inclusion of HIV+ participants; however, there were important reasons for their inclusion. First, the HIV+ cases are representative of this population as South Africa has the highest prevalence of HIV in the world with seven million people infected.[33] Second, the HD phenotype has not been described as different in HIV from previous studies, although HD may manifest earlier in the presence of HIV.[34] HIV-associated neurocognitive disorders are common in HIV; therefore, the three HIV+ cases from this study were excluded from the cognitive analysis.[35] Comparatively, HIV associated movement disorders are rare, affecting 2 to 3% of cases with chorea and parkinsonism related to HIV often have secondary causes like toxoplasmosis or cerebral infarcts,[36] which were not present in these cases as evidenced by the MRI findings of the HIV+ cases.

Conclusions

Our results indicate that, like HD, HDL2 is heterogenous in its clinical phenotype and is characterized by dementia, chorea and oculomotor abnormalities as the manifesting symptoms, with progression to a rigid and bradykinetic state with worsening dystonia. However, compared to HD, HDL2 patients presented three years earlier for diagnosis from the time of the disease manifesting, had poorer scores on dysarthria and dystonia testing, and had worse results on the Luria and Stroop interference tests. These differences may suggest a more severe course in HDL2 compared to HD. However, this did not help in distinguishing

the two diseases when blinded examiners assessed the patients. Therefore, we suggest testing for HDL2 if the HD mutation is negative in a subject with African ancestry.

Previous studies have shown the UHDRS to be a sensitive tool to measure motor changes in HD. We have now demonstrated that HDL2 and HD share the same clinical features and that their motor phenotypes are indistinguishable. Thus, with the current evidence, developing a separate rating scale for HDL2 appears unnecessary. Therefore, we suggest that the UHDRS, once further validated, may be a useful method of monitoring HDL2 longitudinally and for determining treatment outcomes as it has been for HD.

Finally, the findings of this study support common pathogenic pathways between HD and HDL2 that remain unknown. Detecting these pathogenic mechanisms could assist in identifying therapeutic targets for both diseases.

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Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

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A.F.C.: 1A, 1B, 1C, 2B, 2C, 3B

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N.A.A.: 1C, 3B

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Disclosures

Ethical Compliance Statement: The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that The Human Research Ethics Committee of The University of the Witwatersrand approved this study (M140872) and subject consent was obtained for this work.

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Supporting Information

Supporting information may be found in the online version of this article.

Supporting Data. Assessment of the inter-rater reliability for Unified Huntington's Disease Rating Scale comparing the motor scores of the Huntington's disease like 2 and Huntington's disease groups.