nature reviews neurology

https://doi.org/10.1038/s41582-023-00906-y

Review article

Check for updates

Huntington disease-like 2: insight into neurodegeneration from an African disease

Amanda Krause[1] ✉, David G. Anderson[1,2], Aline Ferreira-Correia[3], Jessica Dawson[1,4], Fiona Baine-Savanhu[1], Pan P. Li[5] & Russell L. Margolis[5,6]

Abstract

Huntington disease (HD)-like 2 (HDL2) is a rare genetic disease caused by an expanded trinucleotide repeat in the *JPH3* gene (encoding junctophilin 3) that shows remarkable clinical similarity to HD. To date, HDL2 has been reported only in patients with definite or probable African ancestry. A single haplotype background is shared by patients with HDL2 from different populations, supporting a common African origin for the expansion mutation. Nevertheless, outside South Africa, reports of patients with HDL2 in Africa are scarce, probably owing to limited clinical services across the continent. Systematic comparisons of HDL2 and HD have revealed closely overlapping motor, cognitive and psychiatric features and similar patterns of cerebral and striatal atrophy. The pathogenesis of HDL2 remains unclear but it is proposed to occur through several mechanisms, including loss of protein function and RNA and/or protein toxicity. This Review summarizes our current knowledge of this African-specific HD phenocopy and highlights key areas of overlap between HDL2 and HD. Given the aforementioned similarities in clinical phenotype and pathology, an improved understanding of HDL2 could provide novel insights into HD and other neurodegenerative and/or trinucleotide repeat expansion disorders.

Sections

[1]Division of Human Genetics, National Health Laboratory Service and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [2]University of Glasgow, Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, UK. [3]Department of Psychology, School of Human and Community Development, Faculty of Humanities, University of the Witwatersrand, Johannesburg, South Africa. [4]Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada. [5]Division of Neurobiology, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [6]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. ✉e-mail: amanda.krause@wits.ac.za

Key points

- Huntington disease (HD)-like 2 (HDL2) is a rare autosomal dominant genetic disease caused by a CTG/CAG trinucleotide repeat expansion in a variably spliced exon of the *JPH3* gene (encoding junctophilin 3) located on chromosome 16q24.2.
- All documented patients with HDL2 have African ancestry and a shared haplotype across the *JPH3* locus, suggesting a common ancient African origin, possibly in West Africa.
- Fewer than 100 cases of HDL2 have been reported worldwide, emphasizing the need for concerted efforts to systematically ascertain patients for longitudinal studies.
- HDL2 is the HD phenocopy that has the strongest clinical resemblance to HD across the disease course, with overlapping movement, psychiatric, cognitive and radiological features, progressing to non-verbal and akinetic dementia and premature death.
- Loss of function of the junctophilin 3 protein, RNA toxicity of the sense strand and expanded CAG, and polyglutamine toxicity from the antisense strand have all been implicated in HDL2 pathogenesis.
- Studies comparing HDL2 to HD provide unique opportunities to improve our understanding of the role of junctophilin 3 in the brain and of repeat expansion pathogenesis, allowing the development of novel biomarkers and therapeutic options.

Introduction

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder characterized by the triad of movement abnormalities, cognitive decline and psychiatric symptoms[1]. George Huntington described the disease that bears his name 151 years ago[2], and 2023 marks the 30-year anniversary of the first report of the causative mutation[3] and 22 years since HD-like 2 (HDL2) — a disorder caused by an expanded trinucleotide repeat in the *JPH3* gene (encoding junctophilin 3) — was first described[4]. Of the HD phenocopies described, HDL2 is the disorder that is clinically most akin to HD, with many similar genetic, radiological and neuropathological features. HD and HDL2 show no appreciable differences with regard to disease progression or clinical presentation; however, in contrast to HD, which has a wide geographical distribution, HDL2 occurs exclusively in individuals with African ancestry[5–7].

HD research has progressed considerably with the establishment of large patient cohorts[8,9], allowing deep clinical phenotyping[10], biomarker development[11], improved understanding of early disease manifestations[8], detailed molecular genetic characterization and clinical trials of potential disease-modifying therapies[12]. Most of these advances were made in Europe and North America and largely reflect studies in populations with European ancestry. These populations have a much higher reported HD prevalence than African populations[13], in which HD still remains relatively poorly characterized.

Research into HDL2 has been challenging as resources in Africa are limited, patient identification is slow and specialty clinics with expertise in diagnosis and longitudinal care are scarce. This Review examines how our knowledge of HDL2 has evolved since its discovery and how this progress has provided insights into HD and neurodegenerative disease in Africa and elsewhere, particularly the African diaspora. We highlight the challenges that are specific to research into neurodegenerative disease in Africa and areas in which future investigations of HDL2 are likely to improve our understanding of both this condition and related diseases, including HD. We conclude by noting that HDL2 illustrates the urgent need for further studies of neurodegenerative diseases on the African continent.

HD and its phenocopies

HD is caused by a trinucleotide repeat expansion (>35 repeats) in the *HTT* gene (encoding huntingtin), which is located on chromosome 4p16.3. This mutation is identified in over 95% of patients presenting with a typical HD phenotype and typically shows an autosomal dominant mode of inheritance[14]. The proportion of patients with an HD phenotype who test negative for the *HTT* mutation varies between cohorts but is usually small; some mutation-negative cases are attributable to technical issues such as sample switches, clerical or testing errors, or primer binding site mutations[15]. However, approximately 3% of individuals with an HD phenotype have a different disorder that resembles HD for part or all of its disease course; these disorders are known as HD phenocopies[16,17].

Mutations in several genes have been shown to underlie HD phenocopies. Most of these diseases show autosomal dominant inheritance, and *C9orf72* repeat expansion disorders, spinocerebellar ataxia type 17 (SCA17) and HDL2 are the most commonly reported, although other conditions, such as dentatorubral–pallidoluysian atrophy, HDL1, benign hereditary chorea, SCA1, SCA2, SCA3, neuroferritinopathy and Fahr disease, are also included owing to phenotypic overlap. Rare autosomal recessive diseases, such as Friedreich ataxia, ataxia telangiectasia, ataxia with oculomotor apraxia types 1 and 2, choreoacanthocytosis, aceruloplasminaemia, Wilson disease and Niemann–Pick type C, and X-linked recessive diseases, such as McLeod neuroacanthocytosis syndrome and Lubag syndrome, should also be considered in the differential diagnosis of a patient with an HD-like phenotype[18]. HD phenocopies can also result from non-genetic causes.

The hexanucleotide repeat expansion in the *C9orf72* gene on chromosome 9p21.2 seems to be the most common HD phenocopy in European populations, accounting for 1.95% of patients with an HD phenocopy in a UK cohort[19]. Although a small proportion of individuals with the expansion develop an HD-like phenotype, most present with features more consistent with frontotemporal lobar degeneration and/or amyotrophic lateral sclerosis. SCA17, previously referred to as HDL4, is caused by an abnormal CAG/CAA repeat expansion in the *TBP* gene (encoding TATA-box-binding protein). In one study of HD-like cases, expansions in this gene were identified in five patients, accounting for 1.75% of the cohort[16]. The SCA17 phenotype is characterized by ataxia, dementia and hyperkinetic movements, including chorea and dystonia, as well as psychiatric symptoms, pyramidal signs and rigidity[14]. In patients with SCA17 who do not have prominent cerebellar ataxia, the phenotype can overlap with HD.

HDL1 is an extremely rare disease caused by an octapeptide repeat insertion in the *PRNP* gene, which encodes the major prion protein[20]. HDL3 is something of a misnomer, as it has childhood onset and only a partial resemblance to HD[21]. This condition has only been reported in a single family and its genetic basis remains unknown. By contrast, HDL2, the focus of this Review, is remarkably similar to HD, and individual cases cannot be distinguished from HD without specific genetic testing.

Epidemiology of HDL2

HD has a worldwide distribution, with the highest frequencies (10.6–13.7 per 100,000 individuals) occurring in European populations[13,22]. HD is considerably less common in India, Asia and South America[22], and the data from Africa are largely anecdotal, with few systematic studies of prevalence[23]. The prevalence of HD in Africa has most recently been estimated to be 0.25 per 100,000 individuals[13] on the basis of studies from Cameroon[24] and South Africa[25]. Although HD is undoubtedly less common in African than in European populations, under-ascertainment is likely owing to historically poor health access, diagnostic inequities and cultural beliefs around the nature of the disease[25,26].

HDL2 was first described by Margolis et al. in 2001 in an extended African-American family[4]. Multiple families with HDL2 were subsequently identified in the USA, all with definite or probable African ancestry[27,28]. Across North American studies of HD-like cases, once HD is excluded, the overall frequency of HDL2 ranges from 0% to 15%[28]. The potential for under-ascertainment owing to racial bias in access to neurological and genetic care is notable and of ongoing concern[29]. HDL2 has now been shown to account for up to 4% of cases with an HD phenotype in South America[30], and the disease has been anecdotally reported in Central America and the Caribbean[25,30]. In individuals not directly from Africa, the presence of the HDL2 mutation is likely to reflect African genetic contributions introduced into the Americas through the slave trade in the sixteenth and seventeenth centuries[6,28,30–32].

One individual with HDL2 and apparent European ancestry was reported in Brazil[33]. However, detailed haplotype analysis revealed that the repeat expansion was found on a haplotype that has been identified only in individuals with African ancestry — a not entirely unexpected finding, given that an estimated 19.6% of the Brazilian population has African ancestry[33–36]. In some parts of Europe, the prevalence of HDL2 has increased in recent years owing to the influx of African migrants[37–40].

To date, the largest number of HDL2 cases has been reported in South Africa, where approximately one-third of patients with African ancestry with a confirmed HD genetic diagnosis test positive for the *JPH3* repeat expansion[37]. Many of these cases are from the area surrounding Johannesburg in the northern part of the country, where approximately 55 families with HDL2 have been diagnosed genetically by the molecular diagnostic laboratory in the Division of Human Genetics at the National Health Laboratory Service. Most are singleton cases with little family information available (A.K., unpublished work). No patients have been identified to date with dentatorubral–pallidoluysian atrophy, SCA17, *C9orf72* repeat expansion disorders or other HD phenocopies; however, the cohort sizes have been small and the genetic studies limited[41].

A small number of HDL2 cases has been reported from the rest of Africa. We are aware of one published case from Botswana[42], a family with three cases from Mali and one case from Namibia (all tested in South Africa; A. K., unpublished work (Namibia); A. Bocoum, unpublished work (Mali)). As most of the African slave trade routes originated in Central and West Africa rather than in Southern Africa[43], individuals who introduced HDL2 into the Americas were likely to have been from these regions, strongly suggesting that HDL2 is present but currently undiagnosed or unreported in these areas. A study of 45 patients with an HD phenotype drawn from six African countries (representing Central, West and East Africa) detected an *HTT* expansion in 24 (53%) of the participants[44]. We hypothesize that HDL2 might account for a substantial proportion of those who tested negative.

HDL2 is now reported as the most common HD phenocopy in individuals with African ancestry, but still accounts for less than 5% of individuals with an HD phenotype[28,30,37,39]. Strikingly, all known HDL2 cases have definite or probable African ancestry. Worldwide, the total number of patients with HDL2 reported in the literature remains small (under 100) — data for all known patients are shown in Table 1, organized by reported country of origin. In addition, the table displays the percentage that each country contributes to the overall number of published cases of HDL2. Figure 1 shows the worldwide published cases by geographical origin of the patients, which is assumed to be the country in which the patient currently resides if no further information was provided when the case was reported.

Large, multigenerational HDL2 pedigrees have been challenging to ascertain because patients are often unaware of the medical and symptomatic history of previous generations. This issue is compounded by several factors, including but not limited to reduced access to health care owing to poverty and misinformation and the influence of diverse cultural perceptions of health and illness on health-seeking behaviours in many African communities[45,46].

Table 1 | Published cases of Huntington disease-like 2

Country of origin	Number of cases	Contribution to total global cases (%)
South Africa[6,7,50,74,96,130]	40	44.0
USA[4,69–71,76,77,86]	24	26.4
Brazil[31,33,87,131,132]	12	13.2
Venezuela[32]	4	4.4
Mexico[71]	3	3.3
West Indies[38,39,69]	3	3.3
UK[16,78]	2	2.2
Botswana[42]	1	1.1
Democratic Republic of the Congo[39]	1	1.1
Morocco[75]	1	1.1
Total	91	100

Genetics of HDL2

Table 2 compares the key genetic and pathogenetic features of HD and HDL2. HDL2 is an autosomal dominant trinucleotide repeat disorder[4,27]; the CTG repeat expansion occurs in the variably spliced exon 2A of the *JPH3* gene on chromosome 16q24.2. A CAG repeat occurs in an antisense transcript, termed *JPH3-AS*[27,47]. Figure 2 shows the gene structure and the alternatively spliced transcripts. The repeat size ranges are similar to those reported in HD: normal alleles contain 5–28 repeats, and full penetrance seems to occur in individuals with 40 repeats or more[27]. Whether mutable normal alleles or incompletely penetrant ranges of repeat length exist in HDL2, as in HD, is currently unknown. Three individuals with *JPH3* repeat lengths of 33, 34 and 35 were reported to have clinical features only nominally consistent with HDL2[28]).

Data for childhood-onset or juvenile-onset HDL2 or for very large repeat expansions in *JPH3* are scarce. One individual was reported to have a repeat length of 48 and disease onset at 12 years of age; this is approximately 30 years earlier than would be predicted and far younger than in other family members, perhaps indicating an error in the reporting of this case[28]. The longest repeat length detected to date is 63 triplets in an individual from South Africa who was diagnosed

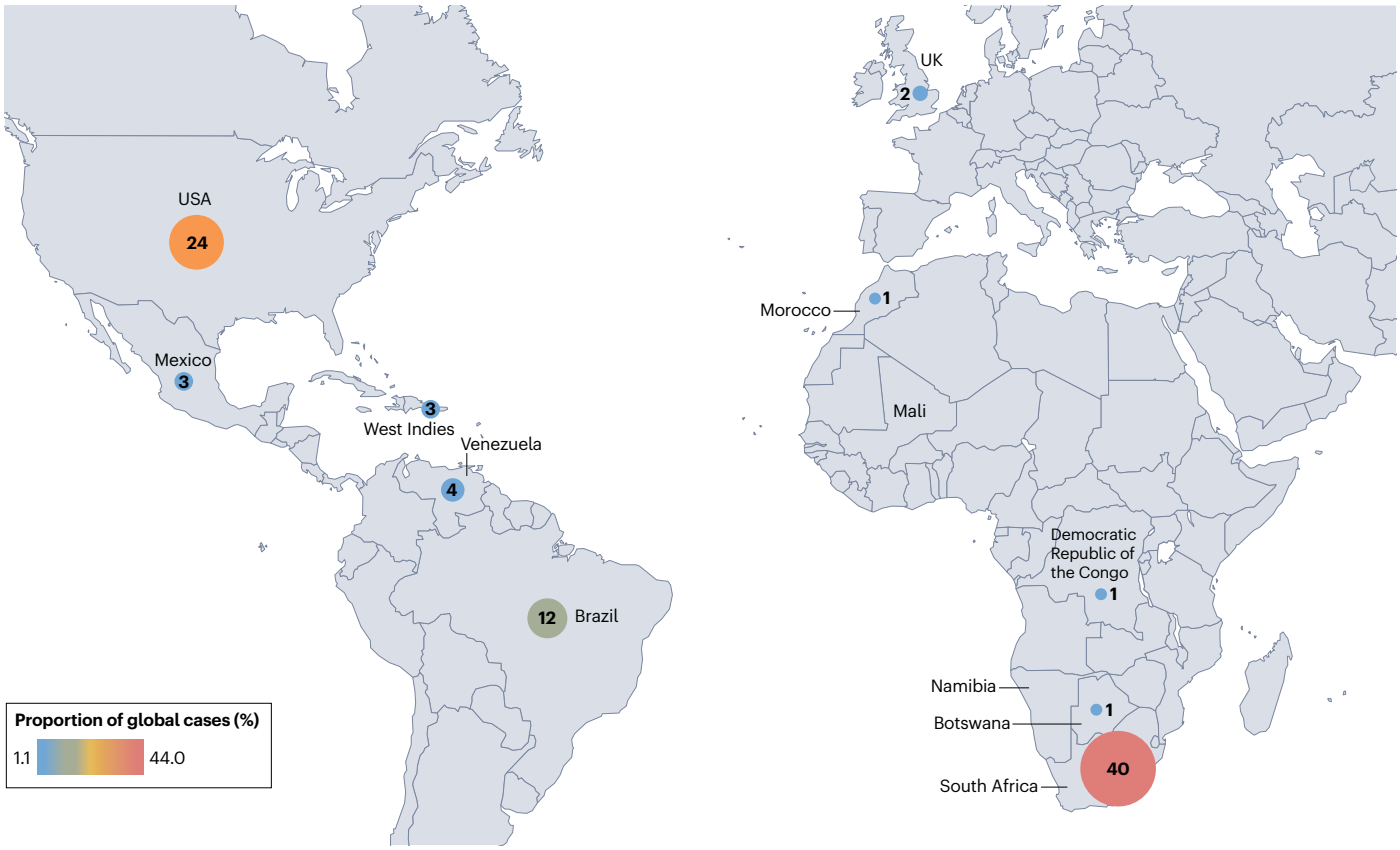

Fig. 1 | Global distribution of HDL2. All cases of Huntington disease-like 2 (HDL2) published since 2001 are represented on the world map; the majority were reported in South Africa and the USA. The diameter of each circle corresponds to the number of cases reported in that country, and the colour reflects the proportion of global cases attributed to the respective country. In addition to the published cases shown on the map, we are aware of other African cases — a family with three cases from Mali (A. Bocoum, unpublished work) and one case from Namibia (A. K., unpublished work).

with HDL2 at the age of 18 years (J. Carr, unpublished work). Early-onset HDL2 could present atypically, which, combined with poor awareness of HDL2, could mean that juvenile HDL2 has been overlooked. Alternatively, longer alleles might not occur or could be lethal embryonically or at a young age.

In South Africa, juvenile HD has been reported to occur more frequently in individuals of mixed ancestry than in white individuals[48,49]. Moreover, among South African patients with HDL2, those of mixed ancestry appear to have longer repeats than those of African ancestry[50] (A.K., unpublished work). If verified, these observations could suggest that genetic background can influence germline repeat expansion, which in turn has implications for understanding the mechanisms leading to anticipation.

A feature of the epidemiology of neurodegenerative repeat expansion diseases is that longer normal allele lengths in a population (ethnic group, country or other large geographical region) correlate with higher disease prevalence[51]. The premise is that tip-over of large repeats into the disease-associated range occurs at a low rate, 'replacing' alleles lost owing to reduced reproductive fitness in individuals with large expansions[52,53]. In Africa, the *HTT* locus shows a narrower repeat length distribution than in Europe, with fewer large (but in the normal range) or intermediate alleles[23,26], consistent with a lower prevalence of HD in African than in European populations. A similar pattern is observed for myotonic dystrophy, which is extremely rare in Africa[54,55]. Conversely, no difference in repeat distribution has been observed between African and other populations at the *FMR1* locus, consistent with observations that fragile X syndrome occurs as frequently in Africa as elsewhere in the world[56–58].

At the *JPH3* locus, initial studies from South Africa provided little evidence for a right-skewed repeat length distribution of normal alleles as an explanation for the African specificity of HDL2 (ref. 6). However, preliminary analysis of data from the 1000 Genomes Project cohort showed that the largest mean CTG repeat lengths occurred in two of the three African populations examined (from The Gambia and Kenya), whereas the smallest mean CTG repeat lengths were identified in South Asian populations[59] (from Japan and China). The African populations also had broader non-disease allele distributions than European and Asian populations, with the widest distribution in The Gambia, followed by Kenya and South Africa (J.D. & P. Valdmanis, unpublished work)[59]. On the basis of these data, it is tempting to speculate that the highest predisposition for HDL2 should be in West African populations, consistent with the presumed West African origin of most North and South American cases.

To date, whole-genome studies have only produced a few anecdotal reports of pathogenic repeat expansions at the *JPH3* locus. None was identified by the 1000 Genomes Project, the Human Pangenome

Reference Consortium or the Human Genome Structural Variant Consortium, and only one full expansion was reported by TOPMed[60] (J.D. & P. Valdmanis, unpublished work).

The *JPH3* repeat expansion seems to occur on a single haplotype. In 33 South African and North American cases, a three-SNP (rs2544635, rs3849254 and rs918368) core haplotype was associated with the expansion mutation[6]. Similar findings were obtained in a study incorporating two additional SNPs (rs8051218 and rs3860288) in a sample of 32 South African individuals with HDL2 (ref. 59). These findings imply a single origin for the repeat expansion. Of note, although this disease-associated haplotype was also detected on non-disease alleles from populations that formed part of the 1000 Genomes Project, its frequency was lower and it was identified only in individuals of African ancestry (from South Africa, The Gambia and Kenya). By contrast, multiple haplotypes have been associated with the *HTT* expansion, with the European A1 and A2 haplotypes showing the most marked rightward shift of the normal allele distribution and the highest predisposition to HD[51,61].

We propose that the HDL2-associated mutation, or at least the genetic predisposition to the repeat expansion, originated in sub-Saharan Africa. The widespread distribution of the same haplotype in individuals with HDL2 who originate from across Africa suggests a common ancestor predating not only the slave trade of the sixteenth and seventeenth centuries, which would have introduced the mutation to the Americas, but also the Bantu population expansion 2,000–3,000 years ago, which introduced the mutation to southern Africa[6].

The mechanism by which the disease-associated haplotype predisposes individuals to the *JPH3* repeat expansion remains unknown. Although several long alleles in the normal range (27–33 CTG repeats) have been observed on the common disease-associated haplotype in African populations, repeats of similar length have also been observed on other haplotypes[59]. This observation suggests that tip-over expansion from the normal repeat range to the pathogenic range occurs in HDL2 as hypothesized for HD (see above). The limited data make it difficult to provide clear answers on the precise geographical and mechanistic origins of the HDL2-associated mutation.

Table 2 | Key features of HD and HDL2

Feature	HD	HDL2
Population distribution	Worldwide	African ancestry
Associated gene	*HTT* on chromosome 4p16.3	*JPH3* on chromosome 16q24.2
Expansion mutation	CAG/(CTG?)	CTG/CAG
Normal repeat	10–26 repeats	5–28 repeats
Expanded repeat	36–180+ repeats	40–60 repeats
Anticipation	Linked to paternal transmission	Uncertain
Disease-associated haplotype	Multiple	Single
Somatic expansion	Yes	Minimal?
Loss of function	Axonal transport	Calcium signalling
Polyglutamine toxicity	Sense strand	Antisense strand
RNA toxicity	Possible	Sense strand

HD, Huntington disease; HDL2, HD-like 2.

In HD, synonymous sequence variation in the *HTT* repeat tract influences the age of onset and somatic instability. These variants alter the canonical sequence ((CAG)*n*-CAACAG-CCGCCA-(CCG)*n*) through either duplication of the CAG interruption, which is associated with a delayed age of onset, or loss of the CAG and CCG interruption, which is associated with an earlier age of onset[62–64]. Loss of the CCG interruption ((CAG)*n*-CAACAG-(CCG)*n*) has been identified as a modifier in African patients with HD and is associated with an earlier age of diagnosis through a mechanism that does not seem to be driven by somatic expansion[65]. These studies were predominantly conducted on DNA derived from peripheral blood samples; therefore, the possibility of increased somatic instability specifically in the HD-affected brain cannot be excluded. An assessment of 32 patients with HDL2 showed that the CTG/CAG sequence across the trinucleotide repeat tract was uninterrupted, with variation being observed only in the repeat length, indicating the absence of *cis*-acting factors influencing the age of onset of this condition[59].

Preliminary data suggest that somatic expansion occurs less frequently in HDL2 than in HD and that the somatic expansion is not significantly associated with age of onset in HDL2 (ref. 59). Thus, apart from the inverse correlation of repeat length with age (each additional repeat increase beyond threshold is associated with a 1.2–2.9-year earlier age of onset)[28,59], no other phenotypic modifiers have been established for HDL2. Whether *trans*-acting phenotypic modifiers of HDL2 exist, similar to the variations in DNA mismatch repair genes that alter age of onset in HD[66–68], remains unknown. Both diseases could potentially be modified by genetic and non-genetic factors that are specific to the African population.

The roles of parent-of-origin effects or anticipation in HDL2 remain uncertain. In one American pedigree, a father diagnosed at 39 years of age had an expanded repeat length of 52 triplets, whereas his son was diagnosed at the age of 22 years and had a repeat length of 59 triplets[69]. No other large changes in repeat length have been detected in either maternal or paternal transmission or among members of a sibship. Additionally, no documented de novo events or tip-over from the normal repeat length into the expanded repeat range have been documented.

Clinical features of HDL2

The initial clinical descriptions of HDL2 were based largely on examination of the index family and limited record review of other cases[4,27,37,70–72]. However, subsequent systematic comparisons between HDL2 and HD have provided a more detailed understanding of the HDL2 phenotype. HDL2 has emerged as the HD phenocopy that most strongly resembles HD throughout its course, with closely overlapping motor, cognitive and psychiatric features[4,7,37,73,74]. A limitation in defining the phenotypic range of HDL2 is that almost all reported cases have been ascertained because they have presented with a clinical phenotype resembling HD; therefore, it is not surprising that the limited available literature focuses on cross-sectional comparisons of the HDL2 and HD phenotypes[4,37,75]. Although the HDL2 phenotype within families is similar and the phenotype across different repeat lengths observed remains within the range of the HD phenotype, it is possible that non-HD presentations of HDL2 remain to be identified.

Motor features

The similarity of the HDL2 and HD motor phenotypes has been recognized since the first reports of HDL2 in 2001 (refs. 4,27). The affected members of the index HDL2 family presented in the fourth decade of life with prominent chorea, poor coordination, rigidity, dysarthria,

bradykinesia and dystonia[4]. Largely on the basis of this single pedigree, in which the expanded repeats in *JPH3* later emerged as among the longest ever detected for HDL2, early descriptions suggested substantial parkinsonism and preserved oculomotor function, potentially distinguishing HDL2 from HD[4,76–78]. A systematic review later documented parkinsonism in one-third of individuals with HDL2 and oculomotor dysfunction in less than half[37]. However, the review noted the need for a more comprehensive assessment of HDL2 in view of the typically unsystematic, incomplete nature of available case reports. Furthermore, these case studies failed to report which clinical features were absent, highlighting the need to conduct more thorough assessments.

To address limitations in the available literature, a systematic clinical comparison of unrelated, matched HD ($n = 13$) and HDL2 ($n = 15$) cases was undertaken in South Africa, enabled by the relatively high prevalence of HDL2 in that country[7]. A complete neurological examination was performed, including use of the Unified HD Rating Scale (UHDRS)[64], and recorded on video. Clinicians with expertise in HD, blinded to the genetic diagnosis, were unable to reliably differentiate HDL2 from HD on the basis of the video recordings. To date, this small study remains the only systematic clinical comparison of HD and HDL2 (refs. 7,79).

Motor features that were previously thought to differentiate HDL2 from HD, including rigidity and bradykinesia, were not found to be significantly more common in HDL2 after controlling for duration of disease[7]. In particular, eye movement abnormalities were noted as an early and frequent manifestation in HDL2 and were clinically indistinguishable from the characteristic oculomotor signs of HD[80]. After controlling for disease duration, dysarthria and dystonia sub-scores were higher in HDL2 than in HD, and overall UHDRS motor scores tended to be higher in HDL2, suggesting subtle quantitative and qualitative differences in the diseases that were not discernible in individual patients[7].

The longitudinal course of HDL2 has not been systematically studied, but case reports suggest that most motor features worsen over the disease course, with the notable exception of chorea[7] — similar to well-established findings in HD[81]. Observations of individuals with HDL2 indicate progressive weight loss, bradykinesia, rigidity, dysphagia and dystonia with worsening balance and gait[4,31,33,69]. The motor signs and symptoms progress and contribute to a fatal outcome within 15–20 years[4,71,77].

The average age of onset for the motor symptoms in HDL2 is 41 years[6,37,44], comparable to observations in HD[1]. However, direct comparisons of patients in South Africa suggest that, once motor symptoms are manifest, patients with HDL2 present to health-care services, presumably for confirmation of diagnosis or management of symptoms, up to 5 years earlier than patients with HD, although the clinical features are similar[7,82]. This observation is consistent with findings of more severe dystonia and dysarthria in HDL2 than in HD after controlling for disease duration[7,45]. Although case ascertainment biases cannot be excluded, this difference might suggest that the clinical presentation of HDL2 is more severe or that the disease progresses more rapidly after onset compared with HD.

Psychiatric presentation

Psychiatric symptoms are an early and core aspect of the clinical presentation of HDL2 (refs. 77,83–86) and might be the presenting disease feature more commonly in HDL2 than in HD[83]. The limited literature indicates that the psychiatric manifestations of HDL2, like those of HD, often involve personality changes[50,69,70,87], depression[71,76,77,86], irritability[40,42], agitation and aggressive behaviour[36,40,42,50,77,88]. Social withdrawal, apathy and sleep disorders are less frequently reported[69,70,83], and hallucinations[36], impulsivity[76,86], anxiety and mutism[86] have been observed only rarely.

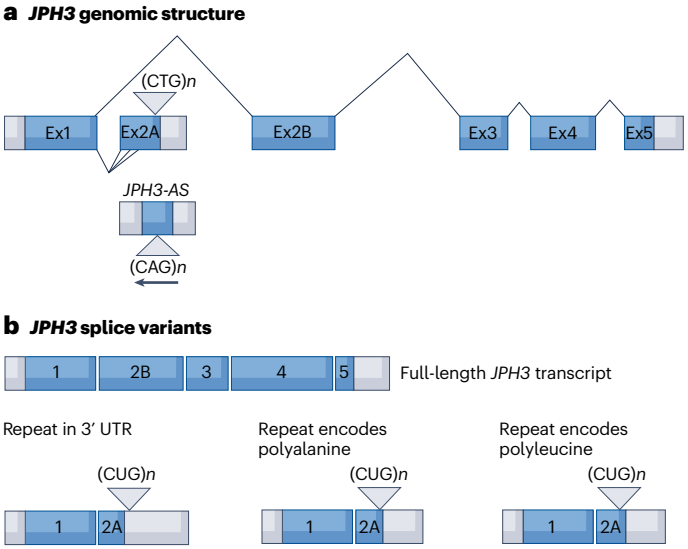

Fig. 2 | The *JPH3* locus. a, Genomic structure of the *JPH3* (encoding junctophilin 3) locus. The gene has six known exons, and the trinucleotide repeat, in the CTG orientation, occurs in exon 2A (Ex2A), which is alternatively spliced. Blue shading indicates protein-coding regions of exons. On the antisense strand, a single-exon gene termed *JPH3-AS* encodes a transcript with the repeat in the CAG orientation. **b**, *JPH3* splice variants. The full-length transcript does not include Ex2A and, therefore, the CUG repeat is absent. Three alternatively spliced *JPH3* transcripts have been detected, containing exon 1 spliced to different sites of Ex2A. In these three variants, the repeat is either in the 3′ untranslated region (UTR) or is in frame to encode polyleucine or polyalanine. The relative expression levels of these transcripts and the effects of the repeat expansion on each transcript have yet to be established. Adapted with permission from ref. 47, American Association of Neuropathologists.

On the basis of UHDRS scores, the systematic comparison of HD and HDL2 in South African patients did not find significant differences in mood and behavioural disturbances between the two conditions[7]. However, as in previous case reports, a presentation based on psychiatric symptoms other than movement abnormalities was more common in HDL2 than in HD, raising the possibility that the early onset of non-motor symptoms contributes to the earlier age at diagnosis for people with HDL2. The prominent psychiatric symptoms could also lead to misdiagnosis of the early symptoms and, thus, to under-ascertainment of HDL2 (ref. 83).

Cognitive presentation

Cognitive decline, and its eventual progression to dementia, is recognized as a core feature of HDL2 (refs. 14,89). The few available descriptions of HDL2-associated cognitive deficits indicate a pattern similar to HD, with abnormalities identified in expressive and comprehensive language, time orientation[40,69,86] and executive function (planning, abstract thinking, self-regulation and inhibition control)[40]. Deficits in episodic, declarative, visual and logical memory[75,86], working memory[86], and attention[69,75,86] have been reported less consistently.

A detailed neuropsychological assessment of seven individuals with HDL2 (two women and five men, age range 32–57 years) at different

stages of disease progression (UHDRS total functional capacity range 3–13 and motor score range 30–52) revealed marked deficits in psychomotor speed dexterity and visuoconstructive ability, which presented very early in the disease[90]. Deficits in attention, auditory–verbal and visual memory, and executive function seemed to present later in the disease and were not consistent in all patients. Working memory was mostly preserved in these individuals[89]. Three of the study participants were compared with seven demographically matched patients with HD who had similar repeat numbers and disease duration but were not matched by the severity of clinical presentation. Significant group differences were identified in tasks assessing working memory and auditory–verbal learning, but these differences may have been attributable to methodological limitations (such as variability in clinical presentation) and might not represent authentic neuropsychological differences between HDL2 and HD[90].

The neuropsychological description of HDL2 could be obscured by differences between patients in demographic factors that affect cognition (for example, years of education or multilingualism) and by variables that affect psychometric testing of non-Western populations[91] (for example, low validity, levels of test-wiseness or proficiency in language of assessment). These effects might be compounded by cultural nuances that limit the value of outcome measures such as disease duration and functional capacity, which do not always reflect the severity of the motor and cognitive symptoms of HDL2. The progression of cognitive symptoms in relation to other clinical and genetic variables in HDL2 remains to be fully and systematically explored.

Neuroimaging features of HDL2

Up until 2016 — the cut-off date for a systematic review published in 2017 (ref. 37) — findings on only 20 brain MRI scans from patients with HDL2 had been published, all of which were qualitative descriptions of standard scans as part of clinical case study reports. Prominent atrophy of the caudate nucleus, putaminal nucleus and cortex was noted, indistinguishable from findings in HD. Longitudinal MRI changes had been examined in only one individual with HDL2 (ref. 31). Two MRI scans performed 5 years apart demonstrated progressive atrophy, similar to that found in HD. On the basis of these findings, HDL2 was considered to be indistinguishable from HD on qualitative MRI scans[4,37].

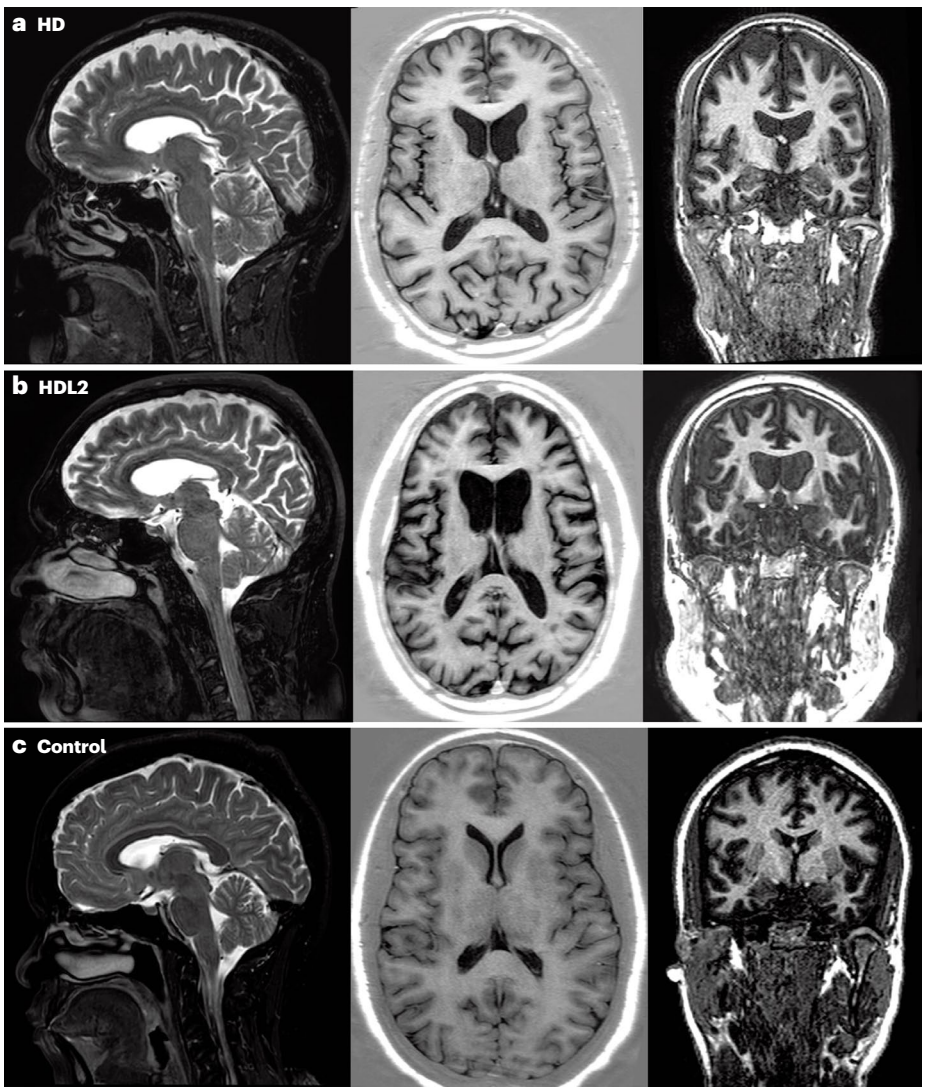

Fig. 3 | Structural MRI findings in HD and HDL2. Comparison of 1.5 T brain MRI scans from a 35-year-old individual with Huntington disease (HD; part **a**), a 32-year-old individual with HD-like 2 (HDL2; part **b**) and a 32-year-old healthy control individual (part **c**). The first column shows sagittal T2-weighted fast spin-echo MRI scans, highlighting cerebral atrophy in the frontal and parietal lobes of the two affected patients. The second column shows axial T1 magnetization-prepared rapid gradient-echo MRI scans that demonstrate similar loss of caudate nuclei and putaminal volume in the two patients compared with the control. The third column shows coronal T1 inversion recovery MRI scans, demonstrating atrophy of the basal ganglia, associated with ventriculomegaly, in the two patients.

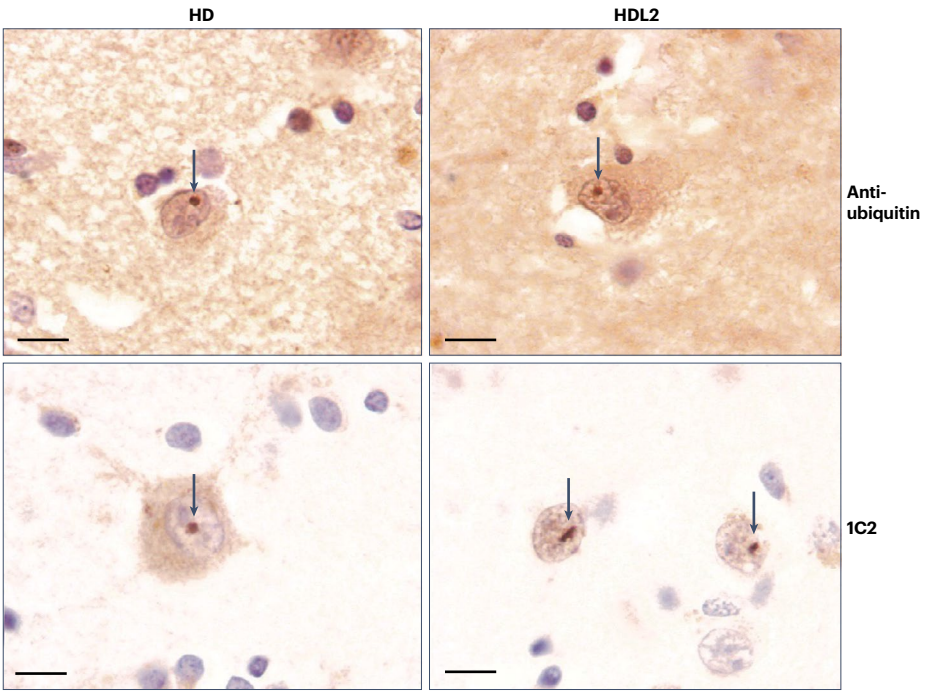

Fig. 4 | Neuronal aggregates in HD and HDL2. The images show motor cortex tissue from patients with Huntington disease (HD) or HD-like 2 (HDL2) immunostained with 1C2 (which detects expanded polyglutamine tracts and TATA-box-binding protein) and anti-ubiquitin antibodies. The staining reveals single spherical or cigar-shaped nuclear aggregates (arrows) within neurons. Scale bar, 10 µm. Adapted with permission from ref. 73, OUP.

As part of a South African cohort study, brain MRI findings from 9 patients with HDL2, 11 patients with HD and an age-matched control group were compared using a blinded cross-sectional quantitative design[74]. Cortical and subcortical structures were assessed using semi-automated brain volumetry. Figure 3 shows brain MRI scans from one patient from each group. The patterns of atrophy in HDL2 and HD were generally similar; however, thalamic volume loss was greater in HDL2 than in HD after controlling for repeat length, disease duration and age of disease onset. Furthermore, a trend was observed towards overall greater volume loss in HDL2 than in HD, particularly in the basal ganglia. These MRI findings support the reports of marked clinical similarity between HD and HDL2 but with earlier diagnosis and marginally greater motor symptoms in patients with HDL2 (ref. 74).

Two individuals with HDL2 have been assessed using nuclear imaging techniques. In an individual who was diagnosed with HDL2 in Italy, ^{18}F-fluorodeoxyglucose-PET showed severe bilateral hypometabolism of the basal ganglia and preserved cortical, thalamic and brainstem metabolism[40]. A similar pattern has been observed in HD using ^{18}F-fluorodeoxyglucose-PET[92]. The second report was from an individual with 52 CTG/CAG repeats, disease duration of 6 years, and parkinsonism and chorea. Dopamine transporter single-photon emission CT showed reduced uptake in striatal presynaptic dopamine receptors[78]. A similar pattern of reduced striatal radiotracer uptake on dopamine transporter single-photon emission CT has been reported in patients with HD with more advanced disease[93]. The role of nuclear imaging in HDL2 remains unresolved.

HDL2 pathology

The gross and microscopic brain pathologies of HD and HDL2 are remarkably similar, although systematic neuropathology has been reported in only seven people with HDL2 (refs. 4,69,73). Like HD pathology, HDL2 pathology is characterized by prominent cerebral and striatal atrophy and a reduced volume of well-myelinated white matter but no notable cerebellar or brainstem atrophy. Other observations include loss of striatal projection neurons, astrocytic gliosis of the putamen and caudate with a dorsal to ventral gradient, and less involvement of the nucleus accumbens than of other regions of the basal ganglia. Electron microscopy revealed sporadic cortical neurons undergoing dark cell degeneration, and many neurons showed autophagic vacuoles and nuclear membrane invagination[4,69,73].

As in HD, immunostaining of brain tissue with 1C2 (relatively specific for expanded polyglutamine (polyQ) tracts but also detects TATA-box binding protein), anti-ubiquitin, anti-torsin A, and anti-TBP antibodies demonstrated the presence of 1–2 µm spherical or ovoid intracellular aggregates in HDL2 (refs. 73,94). Unlike in HD, and as expected, the aggregates were not stained by anti-huntingtin antibodies. In HD, the aggregates are localized to both the nucleus (perinucleolar) and the neuropil, whereas in HDL2, they have been detected only near the nucleolus (Fig. 4). The frequency and ultrastructural appearance of the aggregates were similar in HD and HDL2 (Fig. 5). Although the extent of gliosis in the pons and medulla was the same in HD and HDL2, aggregates were present in these regions in HD but not in HDL2. Similarly to HD, the distribution of aggregates in HDL2 only partially corresponded to regions of neurodegeneration. More detailed systematic neuropathological comparisons, particularly at the cellular level, might reveal subtle distinctions between HD and HDL2.

Shortly after HDL2 was described, acanthocytes were reported in four individuals diagnosed with this condition[70,71]. These findings suggested that HDL2 should be classified as a neuroacanthocytosis syndrome[95], setting it apart from HD. However, a case–control study comparing blood smears from patients with HDL2, patients with HD and healthy control individuals[96] found no acanthocytes in any of these groups, and none has been reported in any subsequent patient

diagnosed with HDL2 (ref. 37). These findings led to removal of the neuroacanthocytosis classification from HDL2 (ref. 97).

HDL2 pathogenesis

The pathogenesis of HDL2 is best viewed in comparison with HD. In HD, the predominant working hypothesis is that the CAG repeat expansion in exon 1 of the *HTT* gene leads to expression of a protein with an expanded polyQ tract, and that this tract, perhaps as a result of conformational changes, exerts a neurotoxic effect[98]. A wide range of potential pathogenic pathways underlying this toxic gain of function have been proposed. Neuronal somatic expansion driven by mismatch repair mechanisms[99] seems to increase repeat length within vulnerable neurons — a potentially pivotal component of the pathogenic process.

Alternative or modulating pathogenic mechanisms contribute to HD pathogenesis, including toxicity of the RNA transcript containing the long CUG repeat[100], repeat-associated non-AUG (RAN) translation of transcripts into alternative long poly(amino acid) tracts[101], alternative splicing leading to a truncated and more toxic protein fragment[102], transcription of an antisense transcript[103] and loss of function of the huntingtin protein[104]. These mechanisms, in varying degrees, are likely to contribute to the pathogenesis in all trinucleotide repeat disorders, including HDL2. Loss of function of the junctophilin 3 protein, toxicity of the sense strand transcript at the RNA level via the expanded CTG repeat and polyQ toxicity (from the antisense strand) have all been implicated in HDL2 (Fig. 6).

Loss of junctophilin 3 function

Junctophilin 3 is one of a conserved family of four proteins[105–107], each of which is characterized by an N-terminal tail that inserts into the endoplasmic reticulum (or the sarcoplasmic reticulum in muscle) and a C-terminus that binds to the internal surface of the plasma membrane. Junctophilin 1 is expressed predominantly in skeletal muscle and junctophilin 2 is expressed in skeletal and cardiac muscle, and both generate a physical bridge between the sarcoplasmic reticulum and the plasma membrane. Mutations in *JPH2* lead to various cardiac defects[108].

Junctophilin 3 and 4 are both expressed predominantly in the brain and form a similar junction between the plasma membrane and the endoplasmic reticulum. In neurons, this junction brings together endoplasmic reticulum ryanodine receptors and calcium and potassium channels (CaV1 and KCa3.1, respectively), which act as a complex to regulate the slow afterhyperpolarization current and, hence, neuronal function[106,109–111]. Cells in which both proteins were suppressed showed marked abnormalities in slow afterhyperpolarization[111]. In response to certain stressors, truncated and full-length forms of junctophilin 2 translocate to the nucleus and seem to function as transcription factors[112,113] but whether junctophilin 3 is similarly regulated remains to be determined.

Both *JPH3* mRNA and junctophilin 3 protein levels were found to be reduced in postmortem frontal cortex tissue from individuals with HDL2 but not from individuals with HD[47], suggesting a specific effect of the *JPH3* mutation on junctophilin 3 protein rather than a non-specific effect of neurodegeneration. Loss of *JPH3* expression induced a mild-to-moderate motor phenotype in mice, with loss of both alleles having more marked effects than loss of a single allele, although the presence of *JPH4* is likely to partially compensate for the loss of *JPH3* (refs. 47,114). Knockout of the single *junctophilin* gene in *Drosophila* led to modest neurodegeneration and a slight reduction in survival, perhaps mediated by an effect on Notch signalling[115]. Loss of

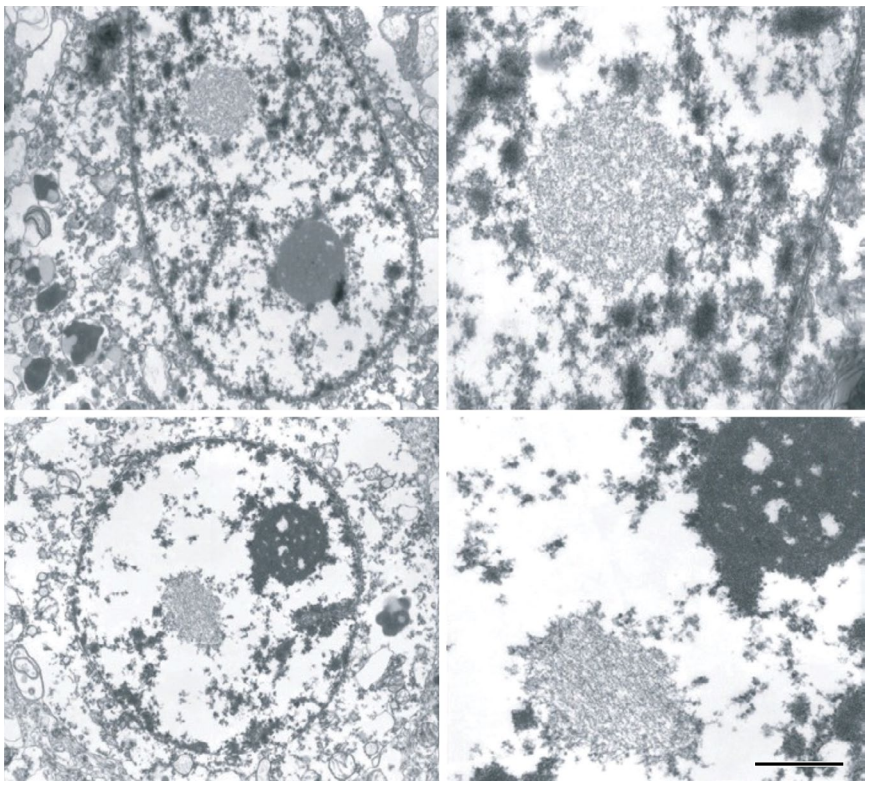

Fig. 5 | Electron micrographs of intranuclear aggregates in HD and HDL2 cortical neurons. The aggregates appear as loose fibrillar material 10–20 nm in diameter near the nucleolus, without contact with the nuclear envelope. Scale bar, 1 µm. HD, Huntington disease; HDL2, HD-like 2. Adapted with permission from ref. 73, OUP.

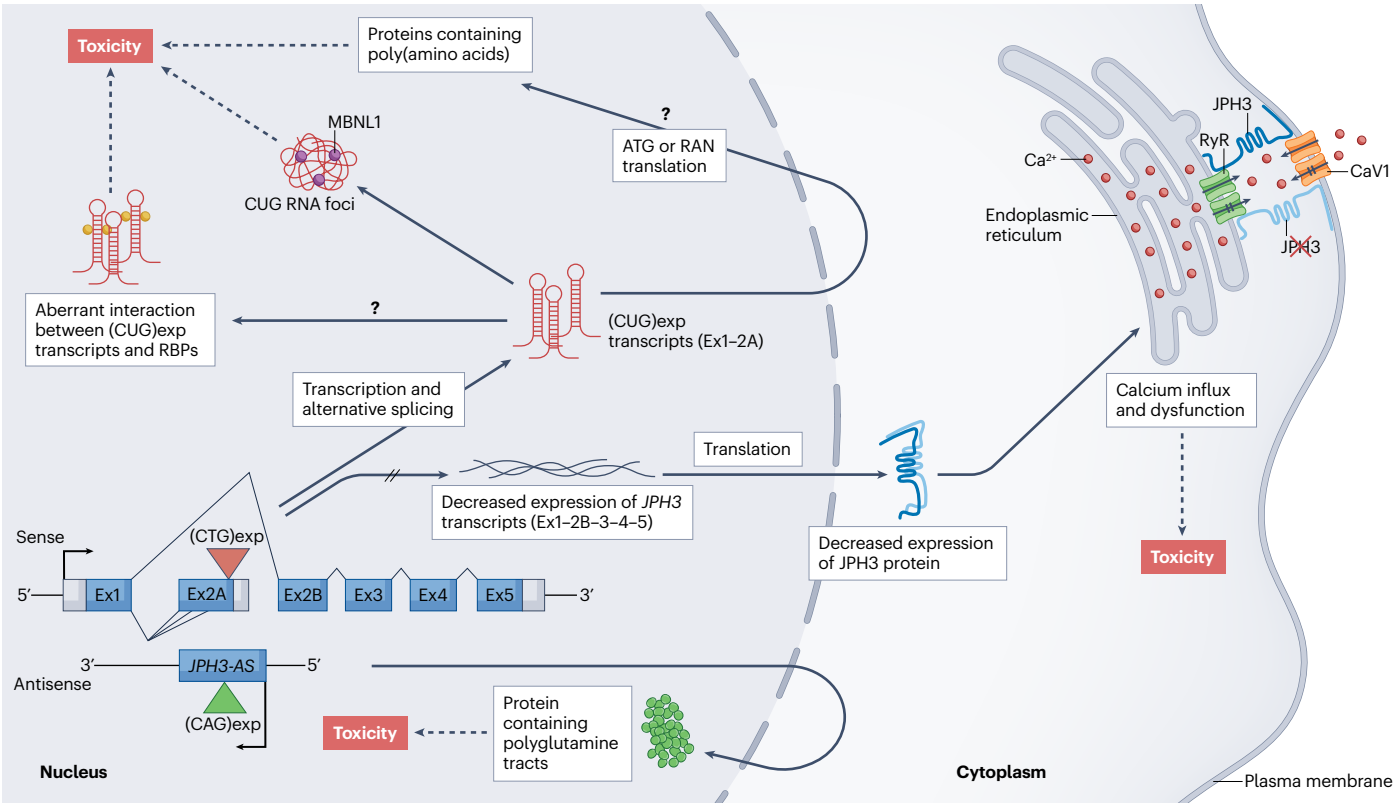

Fig. 6 | Proposed mechanisms of HDL2 pathogenesis. Huntington disease-like 2 (HDL2) is likely to be caused by several non-mutually exclusive pathogenic mechanisms involving multiple transcripts and protein products expressed from the *JPH3* (encoding junctophilin 3 (JPH3)) locus. On the sense strand, the mutant transcript (including the exon 1 (Ex1)–Ex2A splice variant) containing a CUG repeat expansion (exp) aggregates into RNA foci[82], aberrantly interacts with RNA-binding proteins (RBPs) such as the nuclear splicing factor MBNL1, and produces proteins containing poly(amino acids) through repeat-associated non-ATG-initiated (RAN) translation. On the antisense strand, the *JPH3* antisense (*JPH3-AS*) transcript containing a CAG repeat expansion[47] is translated into proteins containing long polyglutamine tracts[122], which might be responsible for the 1C2-positive nuclear inclusions that are observed in postmortem brain tissue from individuals with HDL2 (ref. 73) (Fig. 4) and the bacterial artificial chromosome-HDL2 mouse model[122]. The CTG repeat expansion in Ex2A leads to decreased expression of both the *JPH3* transcript and the JPH3 protein in the brain[47]. JPH3 stabilizes junctional membrane complexes and regulates neuronal calcium flux, and loss of this protein increases cellular vulnerability to the toxic effects of expanded CUG repeats, potentially via disruption of calcium flux or endoplasmic reticulum dysregulation[134]. CaV1, L-type calcium channel; RyR, ryanodine receptor.

junctophilin increased the toxicity of transgenes expressing expanded polyQ tracts in this model.

A number of patients with neurological and/or neurodevelopmental abnormalities have been identified with copy number variants that include *JPH3* (ref. 116). Although most of these copy number variants encompass many genes, at least three are relatively small microdeletions, limited largely to *JPH3* (ref. 117). In addition, there are reports of at least three individuals with *JPH3* point mutations and neurological and cognitive phenotypes[118]. Table 3 summarizes the data reported for patients with loss-of-function mutations associated with *JPH3*.

Together, the findings from patients with HDL2, animal models and individuals with probable loss of *JPH3* expression suggest that loss of junctophilin 3 function can lead to neurological and cognitive abnormalities but, on its own, does not recapitulate the full HDL2 phenotype, with neurodegeneration absent or at least much less prominent. Similar differences between the HD phenotype and mice with loss of *HTT* expression have been observed[119,120]. However, the *JPH3* expansion mutation does seem to decrease *JPH3* expression, leading to the conclusion, subject to further experimental exploration, that loss of junctophilin 3 function contributes to HDL2 but does not account for the full phenotype[47]. The extent to which the HD-associated expansion in *HTT* leads to loss of huntingtin expression or function and the impact of such loss on the HD phenotype remains unclear.

Toxicity of expanded CTG repeats

The *JPH3* CTG/CAG repeat expansion mutation is notable in that the repeat on the sense strand is CTG rather than CAG and, thus, does not encode a polyQ tract. Furthermore, it is situated in exon 2A of the *JPH3* gene — a variably spliced exon that is not included in the full-length *JPH3* transcript. However, at least four alternative splice variants of *JPH3* do contain exon 2A, along with exon 1 (refs. 27,47). The variants use different splice acceptor sites, resulting in different reading frames and transcripts of slightly different lengths. In one variant, the CAG repeat is in the 3′ untranslated region; in a second variant (potentially the most common), the repeat is in frame and encodes polyalanine (polyA); and in the other two variants, the repeat is in frame and encodes polyleucine. So far, neither expanded polyA nor expanded polyleucine tracts encoded by exon 2A have been detected in the brains of individuals

with HDL2 (ref. 47). This raises the possibility that, as in myotonic dystrophy type 1 (DM1) and type 2 (DM2)[121], RNA transcripts containing an expanded CUG repeat might directly contribute to pathogenesis.

In support of this hypothesis, in neurons from the striatum and frontal cortex of individuals with HDL2, nuclear RNA foci were detected by in situ hybridization with riboprobes designed to detect CUG repeats and *JPH3* exon 2A[82]. Other riboprobes also detected *JPH3* exon 2B and, less consistently, intron 1, indicating that the foci contain *JPH3* transcripts, potentially in both spliced and unspliced forms. Furthermore, as in DM1 and DM2, the RNA splicing factor MBNL1 co-localized with the foci and was depleted from other cellular regions. Preliminary investigations suggested a subtle shift in *APP* and *MAPT* RNA splicing, consistent with a loss of MBNL1 activity, in the cortex in HDL2 similar to that observed in DM1 (ref. 82). In both mouse and cell models, expression of *JPH3* exon 2A with a repeat expansion led to the formation of *JPH3* RNA foci co-localized with MBNL1 and to cell toxicity. Together, these findings suggest that *JPH3* transcripts with an expanded repeat could contribute to the HDL2 phenotype.

Polyglutamine toxicity

As described above, the neuropathology of HDL2 is characterized by neuronal aggregates[4], with no evidence of a contribution from proteins derived from *JPH3* or its alternative transcripts[47]. However, bioinformatic analyses detected three open reading frames (ORFs) on the *JPH3* antisense strand that include an in-frame CAG repeat, which could encode polyQ as well as downstream polyA signals[122]. An antisense transcript was indeed expressed in a transgenic mouse in which the transgene was a bacterial artificial chromosome (BAC) containing the entire human *JPH3* gene, including introns and flanking regions, with an expanded repeat (BAC-HDL2 mouse)[122]. The transcript included two start codons in the polyQ ORF and a polyA signal around 4 kb from the repeat; experimental evidence indicates that the 0.25 kb region immediately upstream of the ORF functions as a robust promoter. As predicted, junctophilin 3 antisense protein with an expanded polyQ tract could be detected in protein extracts from these mice and showed substantial enrichment in insoluble nuclear fractions. However, this antisense protein was not detected by immunoblotting in brain tissue from patients with HDL2 (ref. 47).

The discrepancy between the mouse model and the human brain might reflect low expression of the junctophilin antisense protein in the human brain or sequestration of this protein in human tissue. In addition, expression of the antisense protein could be elevated in BAC-HDL2 mice (R.L.M., unpublished data). In a modified BAC-HDL2 transgene mouse model, in which the junctophilin 3 antisense but not the sense protein is expressed, the phenotype was similar to lines that expressed both sense and antisense strands[122]. This observation provides additional evidence that the *JPH3* antisense transcript, which encodes an expanded polyQ tract, has a role in HDL2 pathogenesis. Furthermore, as would be predicted if HDL2, like HD, was at least partially a consequence of polyQ pathogenesis, the HD and HDL2 proteomes show partial convergence[5]. For example, sequestration of the transcription factor CBP by both HD and HDL2 aggregates seems to lead to loss of the neurotrophic factor BDNF[122,123].

Treatment of HDL2

Symptomatic treatment

So far, no reports have specifically centred on treating patients with HDL2, and no open-label or randomized controlled therapeutic trials have been conducted. Case reports have concentrated on reporting the disease phenotype and comparing it with HD[37]. Consequently, and perhaps not surprisingly, established symptomatic pharmacotherapies for HD have also been applied in the treatment of HDL2. Some reports have documented improvements in HDL2 hyperkinetic features following treatment with neuroleptic drugs such as haloperidol[77,124]. The parkinsonian features observed in HDL2 have not been linked to the use of dopamine antagonists used to treat the condition and are likely to be a feature of disease progression[7,50,76,77]. The psychiatric symptoms, in particular depression and anxiety, have shown responsiveness to selective serotonin reuptake inhibitors such as citalopram and sertraline[76,77,86].

The role of deep brain stimulation (DBS) in HD treatment remains uncertain, and the outcomes from ongoing trials are eagerly anticipated[125]. Currently, no patients with HDL2 have been reported to have received DBS. Given that DBS can exacerbate dysphasia and dysphagia in certain settings[126] and that severe speech and swallowing difficulties have been reported in HDL2, DBS should be considered with caution[7].

No disease-modifying therapies are currently available for HDL2, and symptomatic management remains the primary focus. Interdisciplinary care has a crucial role in HD management[127], and our experience also underscores its value in enhancing quality of life in individuals with HDL2.

Towards disease-modifying therapies

Despite substantial advances, our understanding of the pathogenesis of HDL2 is still limited. A clearer understanding of the role of both the loss of junctophilin 3 function and the accumulation of excessive RNA

Table 3 | Pathogenic loss-of-function variants or deletions of *JPH3*

Mutation	Type	Zygosity	Phenotype	Imaging and laboratory findings
c.1014C>G (p.Tyr338*)[118]	Nonsense	Heterozygous	Dyskinesia and cognitive impairment	Normal CSF neurotransmitters; normal MRI and EEG
c.1310del (p.Arg437Leufs*34)[118]	Frameshift	Homozygous	Developmental delay, moderate intellectual disability, behavioural problems and episodic dystonia	Normal CSF neurotransmitters; normal MRI and EEG
c.1740dup (p.Val581Argfs*137)[117]	Frameshift	Homozygous	Paroxysmal dystonia, tremor, dysmetria, paraesthesia, and abnormalities of gait, eye movement, strength and development	Normal CSF biomarkers; normal MRI and EEG
GRCh38/hg38 16q24.1-24.2 (chr16:86866284-87849379)x1 (ref. 133)	Deletion	Heterozygous	Developmental delay and abnormalities of the gastrointestinal tract	Enlarged cerebellum on brain MRI

CSF, cerebrospinal fluid.

Glossary

Acanthocytes
Red blood cells with spiculated protrusions from the cell membrane of varying size and distribution.

Anticipation
A phenomenon whereby disease onset occurs earlier and more severely with each successive generation.

Synonymous sequence variation
DNA sequence variation that does not change the amino acid sequence of the encoded protein.

and poly(amino acid) toxic products related to the trinucleotide repeat is needed to develop disease-modifying therapies[128]. Studies have shown the potential of using the UHDRS and MRI as outcome measures in HDL2 (refs. 7,28), paving the way for future therapeutic investigations when candidate disease-modifying interventions emerge, especially from studies of HD and related neurodegenerative disorders.

Conclusions

Of the described HD phenocopies, HDL2 most closely resembles HD across its disease course but has strikingly different epidemiology. HDL2 has its origins in Africa, as indicated by the African ancestry identified for all known patients to date. However, the genetic epidemiology across Africa, including disease prevalence and distribution relative to HD, remains largely unknown. The detection of HDL2 in North and South America, including the Caribbean, following the route of the slave trade of previous centuries, suggests that the disease must occur in West and Central Africa, the ancestral home of most of the enslaved people. However, virtually no cases have been described in this part of Africa, probably reflecting under-ascertainment owing to the minimal services across Africa for the clinical recognition, genetic testing and care of individuals with neurodegenerative disorders such as HD and HDL2.

Although much has been learned about HDL2, its longitudinal course and full phenotypic spectrum remain unclear. Systematic multinational studies and disease registries are not yet a reality, and only a handful of predictive tests has been performed. Considering the concentration of HDL2 in Africa, the paucity of HD research in Africa, and the unique genetic and environmental background of African populations, the most informative approach for both diseases would be to compare HD and HDL2 in Africans. The lessons of Enroll-HD[129] — a large longitudinal observational study for HD — suggest the need for a similar platform on the African continent, both for HD and HDL2, to collect standardized data from patients pre-symptomatically and longitudinally through their disease course, to share data, and to bring patients together. In addition, such standardized data could facilitate quantitative assessments of disease phenotype and epidemiology, biomarker development and, ultimately, clinical trials. This effort would also aid the development of a clinical infrastructure to provide appropriate care for patients with movement and neurodegenerative disorders in Africa. With the advances in therapeutic development in HD and other neurodegenerative disorders, some of which might benefit people with HDL2, the possibility that African patients will be overlooked is concerning.

The nearly indistinguishable clinical and neuropathological phenotypes of HD and HDL2 suggest that studies of HDL2 could provide insights into common pathways of pathogenesis. PolyQ toxicity is likely to contribute to both diseases, presumably through common mechanisms. Huntingtin and junctophilin 3 have diverse functions, yet the loss of function of each protein seems to contribute to a common pathogenesis. Furthermore, the lack of sequence and haplotype variability in HDL2, and potentially less somatic instability in HDL2 than in HD, suggest that comprehensive assessment of HDL2 will provide additional insight into the roles of these phenomena in HD and related disease. Given the rich genetic variation in Africa, studies of non-allelic disease modifiers of HD and HDL2 in this region could prove particularly illuminating. In summary, a deeper and more systematic investigation of HDL2, with a focus on Africa, is likely to increase our understanding of disease pathogenesis and facilitate the development of novel therapeutic approaches, which might also benefit people with HD and related disorders.

Published online: 19 December 2023

References

1. Walker, F. O. Huntington's disease. *Lancet* **369**, 218–228 (2007).
2. Franklin, G. L., Teive, H. A. G., Meira, A. T., Nepomuceno, A. M. T. & Tabrizi, S. J. "On chorea": 150 years of the beginning of hope. *Mov. Disord.* **37**, 2194–2196 (2022).
3. MacDonald, M. E. et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* **72**, 971–983 (1993).
4. Margolis, R. L. et al. A disorder similar to Huntington's disease is associated with a novel CAG repeat expansion. *Ann. Neurol.* **50**, 373–380 (2001).
5. Margolis, R. L. & Rudnicki, D. D. Pathogenic insights from Huntington's disease-like 2 and other Huntington's disease genocopies. *Curr. Opin. Neurol.* **29**, 743–748 (2016).
6. Krause, A. et al. Junctophilin 3 (JPH3) expansion mutations causing Huntington disease like 2 (HDL2) are common in South African patients with African ancestry and a Huntington disease phenotype. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **168**, 573–585 (2015).
7. Anderson, D. G. et al. Comparison of the Huntington's disease like 2 and Huntington's disease clinical phenotypes. *Mov. Disord. Clin. Pract.* **6**, 302–311 (2019).
8. Tabrizi, S. J. et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol.* **8**, 791–801 (2009).
9. Paulsen, J. S. et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. *J. Neurol. Neurosurg. Psychiatry* **79**, 874–880 (2008).
10. Ruderfer, D. M. & Dudley, J. T. Deep phenotyping predicts Huntington's genotype. *Nat. Biotechnol.* **34**, 823–824 (2016).
11. Weir, D. W., Sturrock, A. & Leavitt, B. R. Development of biomarkers for Huntington's disease. *Lancet Neurol.* **10**, 573–590 (2011).
12. Tabrizi, S. J. et al. Potential disease-modifying therapies for Huntington's disease: lessons learned and future opportunities. *Lancet Neurol.* **21**, 645–658 (2022).
13. Medina, A., Mahjoub, Y., Shaver, L. & Pringsheim, T. Prevalence and incidence of Huntington's disease: an updated systematic review and meta-analysis. *Mov. Disord.* **37**, 2327–2335 (2022).
14. Schneider, S. A. & Bird, T. Huntington's disease, Huntington's disease look-alikes, and benign hereditary chorea: what's new? *Mov. Disord. Clin. Pract.* **3**, 342–354 (2016).
15. Andrew, S. E. et al. Huntington disease without CAG expansion: phenocopies or errors in assignment? *Am. J. Hum. Genet.* **54**, 852–863 (1994).
16. Wild, E. J. et al. Huntington's disease phenocopies are clinically and genetically heterogeneous. *Mov. Disord.* **23**, 716–720 (2008).
17. Schneider, S. A., Walker, R. H. & Bhatia, K. P. The Huntington's disease-like syndromes: what to consider in patients with a negative Huntington's disease gene test. *Nat. Clin. Pract. Neurol.* **3**, 517–525 (2007).
18. Nguyen, Q. T. R. et al. Combining literature review with a ground truth approach for diagnosing Huntington's disease phenocopy. *Front. Neurol.* **13**, 817753 (2022).
19. Hensman Moss, D. J. et al. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. *Neurology* **82**, 292–299 (2014).
20. Moore, R. C. et al. Huntington disease phenocopy is a familial prion disease. *Am. J. Hum. Genet.* **69**, 1385–1388 (2001).
21. Kambouris, M., Bohlega, S., Al-Tahan, A. & Meyer, B. F. Localization of the gene for a novel autosomal recessive neurodegenerative Huntington-like disorder to 4p15.3. *Am. J. Hum. Genet.* **66**, 445–452 (2000).
22. Rawlins, M. D. et al. The prevalence of Huntington's disease. *Neuroepidemiology* **46**, 144–153 (2016).
23. Baine, F. K. et al. Huntington disease in the South African population occurs on diverse and ethnically distinct genetic haplotypes. *Eur. J. Hum. Genet.* **21**, 1120–1127 (2013).
24. Cubo, E. et al. The burden of movement disorders in Cameroon: a rural and urban-based inpatient/outpatient study. *Mov. Disord. Clin. Pract.* **4**, 568–573 (2017).
25. Baine, F. K., Krause, A. & Greenberg, L. J. The frequency of Huntington disease and Huntington disease-like 2 in the South African population. *Neuroepidemiology* **46**, 198–202 (2016).

26. Kay, C. et al. The molecular epidemiology of Huntington disease is related to intermediate allele frequency and haplotype in the general population. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **177**, 346–357 (2018).
27. Holmes, S. E. et al. A repeat expansion in the gene encoding junctophilin-3 is associated with Huntington disease-like 2. *Nat. Genet.* **29**, 377–378 (2001).
28. Margolis, R. L. et al. Huntington's disease-like 2 (HDL2) in North America and Japan. *Ann. Neurol.* **56**, 670–674 (2004).
29. Robbins, N. M. et al. Black patients matter in neurology: race, racism, and race-based neurodisparities. *Neurology* **99**, 106–114 (2022).
30. Walker, R. H. et al. Huntington's disease-like disorders in Latin America and the Caribbean. *Parkinsonism Relat. Disord.* **53**, 10–20 (2018).
31. Rodrigues, G. G. R. et al. Huntington's disease-like 2 in Brazil–report of 4 patients. *Mov. Disord.* **23**, 2244–2247 (2008).
32. Paradisi, I., Ikonomu, V. & Arias, S. Huntington disease-like 2 Venezuela: frequency ethnic origin. *J. Hum. Genet.* **58**, 3–6 (2013).
33. Santos, C. et al. Huntington disease-like 2: the first patient with apparent European ancestry. *Clin. Genet.* **73**, 480–485 (2008).
34. Parra, F. C. et al. Color and genomic ancestry in Brazilians. *Proc. Natl Acad. Sci. USA* **100**, 177–182 (2003).
35. de Souza, A. M., Resende, S. S., de Sousa, T. N. & de Brito, C. F. A. A systematic scoping review of the genetic ancestry of the Brazilian population. *Genet. Mol. Biol.* **42**, 495–508 (2019).
36. Rodrigues, G. G. R., Teive, H. A. G. & Tumas, V. Huntington's disease-like 2 and apparent ancestry. *Clin. Genet.* **75**, 207 (2009).
37. Anderson, D. G. et al. A systematic review of the Huntington disease-like 2 phenotype. *J. Huntingt. Dis.* **6**, 37–46 (2017).
38. Stevanin, G. et al. Huntington's disease-like phenotype due to trinucleotide repeat expansions in the TBP and JPH3 genes. *Brain* **126**, 1599–1603 (2003).
39. Mariani, L. et al. Expanding the spectrum of genes involved in Huntington disease using a combined clinical and genetic approach. *JAMA Neurol.* **73**, 1105–1114 (2016).
40. Ruscitti, F. et al. A case of Huntington disease-like 2 in a patient of African ancestry: the everlasting support of clinical examination in the molecular era. *Clin. Case Rep.* **10**, e6308 (2022).
41. Baine, F. K., Peerbhai, N. & Krause, A. A study of Huntington disease-like syndromes in black South African patients reveals a single SCA2 mutation and a unique distribution of normal alleles across five repeat loci. *J. Neurol. Sci.* **390**, 200–204 (2018).
42. Ocampo, C., Daimari, R. & Oyekunle, A. A. Huntington's disease-like 2 with an expansion mutation of the Junctophilin-3 gene; first reported case from Botswana. *J. Clin. Neurosci.* **47**, 126–127 (2018).
43. Micheletti, S. J. et al. Genetic consequences of the transatlantic slave trade in the Americas. *Am. J. Hum. Genet.* **107**, 265–277 (2020).
44. Muthinja, M. J. et al. An exploration of the genetics of the mutant Huntingtin (mHtt) gene in a cohort of patients with chorea from different tribes in 6 sub-Saharan African countries. Preprint at *medRxiv* https://doi.org/10.1101/2022.07.13.22272435 (2022).
45. Chukwuneke, F. N., Ezeonu, C. T., Onyire, B. N. & Ezeonu, P. O. Culture and biomedical care in Africa: the influence of culture on biomedical care in a traditional African society, Nigeria, West Africa. *Niger. J. Med.* **21**, 331–333 (2012).
46. Glover, S. M. Mark Nichter: global health: why cultural perceptions, social representations, and biopolitics matter. *Hum. Ecol.* **37**, 669–670 (2009).
47. Seixas, A. I. et al. Loss of junctophilin-3 contributes to Huntington disease-like 2 pathogenesis. *Ann. Neurol.* **71**, 245–257 (2012).
48. Hayden, M. R., MacGregor, J. M., Saffer, D. S. & Beighton, P. H. The high frequency of juvenile Huntington's chorea in South Africa. *J. Med. Genet.* **19**, 94–97 (1982).
49. Quarrell, O., O'Donovan, K. L., Bandmann, O. & Strong, M. the prevalence of juvenile Huntington's disease: a review of the literature and meta-analysis. *PLoS Curr.* **4**, e4f8606b742ef3 (2012).
50. Bardien, S. et al. A South African mixed ancestry family with Huntington disease-like 2: clinical and genetic features. *Mov. Disord.* **22**, 2083–2089 (2007).
51. Warby, S. C. et al. CAG expansion in the Huntington disease gene is associated with a specific and targetable predisposing haplogroup. *Am. J. Hum. Genet.* **84**, 351–366 (2009).
52. Pearson, C. E., Nichol Edamura, K. & Cleary, J. D. Repeat instability: mechanisms of dynamic mutations. *Nat. Rev. Genet.* **6**, 729–742 (2005).
53. McMurray, C. T. Mechanisms of trinucleotide repeat instability during human development. *Nat. Rev. Genet.* **11**, 786–799 (2010).
54. Goldman, A., Ramsay, M. & Jenkins, T. Absence of myotonic dystrophy in southern African Negroids is associated with a significantly lower number of CTG trinucleotide repeats. *J. Med. Genet.* **31**, 37–40 (1994).
55. Gennarelli, M. et al. CTG repeats distribution and Alu insertion polymorphism at myotonic dystrophy (DM) gene in Amhara and Oromo populations of Ethiopia. *Hum. Genet.* **105**, 165–167 (1999).
56. Chiurazzi, P. et al. Extended gene diversity at the FMR1 locus and neighbouring CA repeats in a sub-Saharan population. *Am. J. Med. Genet.* **64**, 216–219 (1996).
57. Ritchie, R. J., Chakrabarti, L., Knight, S. J., Harding, R. M. & Davies, K. E. Population genetics of the FRAXE and FRAXF GCC repeats, and a novel CGG repeat, in Xq28. *Am. J. Med. Genet.* **73**, 463–469 (1997).
58. Peprah, E. K., Allen, E. G., Williams, S. M., Woodard, L. M. & Sherman, S. L. Genetic diversity of the fragile X syndrome gene (FMR1) in a large sub-Saharan West African population. *Ann. Hum. Genet.* **74**, 316–325 (2010).
59. Levesley, J. Investigating allele sequence diversity at the Huntington disease loci HTT and JPH3 in African ancestry individuals. *The University of the Witwatersrand: Electronic Theses and Dissertations* https://wiredspace.wits.ac.za/items/25004bb1-ea69-4035-bec5-1134d077c768. (2021).
60. Ibañez, K. et al. Population frequency of repeat expansions indicates increased disease prevalence estimates across different populations. Preprint at: *medRxiv* https://doi.org/10.1101/2023.07.03.23292162 (2023).
61. Squitieri, F. et al. DNA haplotype analysis of Huntington disease reveals clues to the origins and mechanisms of CAG expansion and reasons for geographic variations of prevalence. *Hum. Mol. Genet.* **3**, 2103–2114 (1994).
62. Ciosi, M. et al. A genetic association study of glutamine-encoding DNA sequence structures, somatic CAG expansion, and DNA repair gene variants, with Huntington disease clinical outcomes. *EBioMedicine* **48**, 568–580 (2019).
63. Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. CAG repeat not polyglutamine length determines timing of Huntington's disease onset. *Cell* **178**, 887–900.e14 (2019).
64. Wright, G. E. B. et al. Length of uninterrupted CAG, independent of polyglutamine size, results in increased somatic instability, hastening onset of Huntington disease. *Am. J. Hum. Genet.* **104**, 1116–1126 (2019).
65. Dawson, J. et al. A probable cis-acting genetic modifier of Huntington disease frequent in individuals with African ancestry. *HGG Adv.* **3**, 100130 (2022).
66. Maiuri, T. et al. DNA damage repair in Huntington's disease and other neurodegenerative diseases. *Neurotherapeutics* **16**, 948–956 (2019).
67. Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. Identification of genetic factors that modify clinical onset of Huntington's disease. *Cell* **162**, 516–526 (2015).
68. Lee, J. et al. Genetic modifiers of Huntington disease differentially influence motor and cognitive domains. *Am. J. Hum. Genet.* **109**, 885–899 (2022).
69. Greenstein, P. E., Vonsattel, J. G., Margolis, R. L. & Joseph, J. T. Huntington's disease like-2 neuropathology. *Mov. Disord.* **22**, 1416–1423 (2007).
70. Walker, R. H. et al. Autosomal dominant chorea-acanthocytosis with polyglutamine-containing neuronal inclusions. *Neurology* **58**, 1031–1037 (2002).
71. Walker, R. H. et al. Huntington's disease-like 2 can present as chorea-acanthocytosis. *Neurology* **61**, 1002–1004 (2003).
72. Krause, A., Temlett, J. & Van der Meyden, K. CAG/CTG repeat expansions at the HDL2 locus are a common cause of Huntington disease in Black South Africans (Abstr.). *Am. J. Hum. Genet.* **71**, 528 (2002).
73. Rudnicki, D. D., Pletnikova, O., Vonsattel, J. G., Ross, C. A. & Margolis, R. L. A comparison of Huntington disease and Huntington disease-like 2 neuropathology. *J. Neuropathol. Exp. Neurol.* **67**, 366–374 (2008).
74. Anderson, D. G. et al. Emerging differences between Huntington's disease-like 2 and Huntington's disease: a comparison using MRI brain volumetry. *Neuroimage Clin.* **21**, 101666 (2019).
75. Stevanin, G. et al. CAG/CTG repeat expansions at the Huntington's disease-like 2 locus are rare in Huntington's disease patients. *Neurology* **58**, 965–967 (2002).
76. Schneider, S. A., Marshall, K. E., Xiao, J. & LeDoux, M. S. JPH3 repeat expansions cause a progressive akinetic-rigid syndrome with severe dementia and putaminal rim in a five-generation African-American family. *Neurogenetics* **13**, 133–140 (2012).
77. Walker, R. H., Jankovic, J., O'Hearn, E. & Margolis, R. L. Phenotypic features of Huntington's disease-like 2. *Mov. Disord.* **18**, 1527–1530 (2003).
78. Mulroy, E. et al. Huntington disease like 2 (HDL-2) with parkinsonism and abnormal DAT-SPECT — a novel observation. *Parkinsonism Relat. Disord.* **71**, 46–48 (2020).
79. [No authors listed] Unified Huntington's disease rating scale: reliability and consistency. Huntington Study Group.*Mov. Disord.* **11**, 136–142 (1996).
80. Lasker, A. G. & Zee, D. S. Ocular motor abnormalities in Huntington's disease. *Vis. Res.* **37**, 3639–3645 (1997).
81. Rosenblatt, A. et al. Age, CAG repeat length, and clinical progression in Huntington's disease. *Mov. Disord.* **27**, 272–276 (2012).
82. Rudnicki, D. D. et al. Huntington's disease-like 2 is associated with CUG repeat-containing RNA foci. *Ann. Neurol.* **61**, 272–282 (2007).
83. Ferreira-Correia, A., Krause, A. & Anderson, D. G. The neuropsychiatry of Huntington disease-like 2: a comparison with Huntington's disease. *J. Huntingt. Dis.* **9**, 325–334 (2020).
84. Margolis, R. L. & Holmes, S. E. Huntington's disease-like 2: a clinical, pathological, and molecular comparison to Huntington's disease. *Clin. Neurosci. Res.* **3**, 187–196 (2003).
85. Duff, K. et al. Psychiatric symptoms in Huntington's disease before diagnosis: the predict-HD study. *Biol. Psychiatry* **62**, 1341–1346 (2007).
86. Fischer, C. A., Licht, E. A. & Mendez, M. F. The neuropsychiatric manifestations of Huntington's disease-like 2. *J. Neuropsychiatry Clin. Neurosci.* **24**, 489–492 (2012).
87. Castilhos, R. M. et al. Huntington disease and Huntington disease-like in a case series from Brazil. *Clin. Genet.* **86**, 373–377 (2014).
88. Paradisi, I., Ikonomu, V. & Arias, S. Huntington disease-like 2 (HDL2) in Venezuela: frequency and ethnic origin. *J. Hum. Genet.* **58**, 3–6 (2013).
89. Ferreira-Correia, A., Anderson, D. G., Cockcroft, K. & Krause, A. The neuropsychological deficits and dissociations in Huntington disease-like 2: a series of case-control studies. *Neuropsychologia* **136**, 107238 (2020).
90. Ferreira-Correia, A., Anderson, D. G., Cockcroft, K. & Krause, A. A comparison between the neurocognitive profile of Huntington disease-like 2 and Huntington disease: exploring the presence of double dissociations. *Appl. Neuropsychol. Adult* **29**, 223–233 (2022).

91. Ferreira-Correia, A. & Cockcroft, K. Controlling for inequality in neuropsychological assessment: using Crawford and Howell's (1998) single-case methodology with norms from demographically homogeneous groups of South Africans. *S. Afr. J. Psychol.***53**, https://doi.org/10.1177/00812463221151100 (2023).
92. Roussakis, A. & Piccini, P. PET imaging in Huntington's disease. *J. Huntingt. Dis.* **4**, 287–296 (2015).
93. Gamez, J. et al. Does reduced [^{123}I]-FP-CIT binding in Huntington's disease suggest pre-synaptic dopaminergic involvement? *Clin. Neurol. Neurosurg.* **112**, 870–875 (2010).
94. Trottier, Y. et al. Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. *Nature* **378**, 403–406 (1995).
95. Danek, A. & Walker, R. H. Neuroacanthocytosis. *Curr. Opin. Neurol.* **18**, 386–392 (2005).
96. Anderson, D. G. et al. Absence of acanthocytosis in Huntington's disease-like 2: a prospective comparison with Huntington's disease. *Tremor Other Hyperkinet Mov.* **7**, 512 (2017).
97. Walker, R. H. & Danek, A. "Neuroacanthocytosis" — overdue for a taxonomic update. *Tremor Other Hyperkinet Mov.* **11**, 1 (2021).
98. Tabrizi, S. J., Flower, M. D., Ross, C. A. & Wild, E. J. Huntington disease: new insights into molecular pathogenesis and therapeutic opportunities. *Nat. Rev. Neurol.* **16**, 529–546 (2020).
99. Iyer, R. R. & Pluciennik, A. DNA mismatch repair and its role in Huntington's disease. *J. Huntingt. Dis.* **10**, 75–94 (2021).
100. Marti, E. RNA toxicity induced by expanded CAG repeats in Huntington's disease. *Brain Pathol.* **26**, 779–786 (2016).
101. Banez-Coronel, M. et al. RAN translation in Huntington disease. *Neuron* **88**, 667–677 (2015).
102. Sathasivam, K. et al. Aberrant splicing of HTT generates the pathogenic exon 1 protein in Huntington disease. *Proc. Natl Acad. Sci. USA* **110**, 2366–2370 (2013).
103. Chung, D. W., Rudnicki, D. D., Yu, L. & Margolis, R. L. A natural antisense transcript at the Huntington's disease repeat locus regulates HTT expression. *Hum. Mol. Genet.* **20**, 3467–3477 (2011).
104. Saudou, F. & Humbert, S. The biology of huntingtin. *Neuron* **89**, 910–926 (2016).
105. Lehnart, S. E. & Wehrens, X. H. T. The role of junctophilin proteins in cellular function. *Physiol. Rev.* **102**, 1211–1261 (2022).
106. Piggott, C. A. et al. *Caenorhabditis elegans* junctophilin has tissue-specific functions and regulates neurotransmission with extended-synaptotagmin. *Genetics* **218**, iyab063 (2021).
107. Takeshima, H., Komazaki, S., Nishi, M., Iino, M. & Kangawa, K. Junctophilins: a novel family of junctional membrane complex proteins. *Mol. Cell* **6**, 11–22 (2000).
108. Landstrom, A. P., Beavers, D. L. & Wehrens, X. H. T. The junctophilin family of proteins: from bench to bedside. *Trends Mol. Med.* **20**, 353–362 (2014).
109. Kakizawa, S., Moriguchi, S., Ikeda, A., Iino, M. & Takeshima, H. Functional crosstalk between cell-surface and intracellular channels mediated by junctophilins essential for neuronal functions. *Cerebellum* **7**, 385–391 (2008).
110. Takeshima, H., Hoshijima, M. & Song, L. Ca^{2+} microdomains organized by junctophilins. *Cell Calcium* **58**, 349–356 (2015).
111. Sahu, G. et al. Junctophilin proteins tether a Cav1-RyR2-KCa3.1 tripartite complex to regulate neuronal excitability. *Cell. Rep.* **28**, 2427–2442.e6 (2019).
112. Guo, A. et al. E-C coupling structural protein junctophilin-2 encodes a stress-adaptive transcription regulator. *Science* **362**, eaan3303 (2018).
113. Lahiri, S. K. et al. Nuclear localization of a novel calpain-2 mediated junctophilin-2 C-terminal cleavage peptide promotes cardiomyocyte remodeling. *Basic Res. Cardiol.* **115**, 49 (2020).
114. Nishi, M. et al. Motor discoordination in mutant mice lacking junctophilin type 3. *Biochem. Biophys. Res. Commun.* **292**, 318–324 (2002).
115. Calpena, E. et al. The *Drosophila* junctophilin gene is functionally equivalent to its four mammalian counterparts and is a modifier of a Huntingtin poly-Q expansion and the Notch pathway. *Dis. Model. Mech.* **11**, dmm029082 (2018).
116. Firth, H. V. et al. DECIPHER: database of chromosomal imbalance and phenotype in humans using ensembl resources. *Am. J. Hum. Genet.* **84**, 524–533 (2009).
117. Bourinaris, T. et al. Allelic and phenotypic heterogeneity in Junctophillin-3 related neurodevelopmental and movement disorders. *Eur. J. Hum. Genet.* **29**, 1027–1031 (2021).
118. Steel, D. et al. Both heterozygous and homozygous loss-of-function JPH3 variants are associated with a paroxysmal movement disorder. *Mov. Disord.* **38**, 155–157 (2023).
119. Auerbach, W. et al. The HD mutation causes progressive lethal neurological disease in mice expressing reduced levels of huntingtin. *Hum. Mol. Genet.* **10**, 2515–2523 (2001).
120. Murthy, V. et al. Hypomorphic mutation of the mouse Huntington's disease gene orthologue. *PLoS Genet.* **15**, e1007765 (2019).
121. Timchenko, L. Development of therapeutic approaches for myotonic dystrophies type 1 and type 2. *Int. J. Mol. Sci.* **23**, 10491 (2022).
122. Wilburn, B. et al. An antisense CAG repeat transcript at JPH3 locus mediates expanded polyglutamine protein toxicity in Huntington's disease-like 2 mice. *Neuron* **70**, 427–440 (2011).
123. Nucifora, F. C. J. et al. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. *Science* **291**, 2423–2428 (2001).
124. Rodrigues, G. R. et al. Clinical and genetic analysis of 29 Brazilian patients with Huntington's disease-like phenotype. *Arq. Neuropsiquiatr.* **69**, 419–423 (2011).
125. Bonomo, R. et al. Deep brain stimulation in Huntington's disease: a literature review. *Neurol. Sci.* **42**, 4447–4457 (2021).
126. Yu, H., Takahashi, K., Bloom, L., Quaynor, S. D. & Xie, T. Effect of deep brain stimulation on swallowing function: a systematic review. *Front. Neurol.* **11**, 547 (2020).
127. Testa, C. M. & Jankovic, J. Huntington disease: a quarter century of progress since the gene discovery. *J. Neurol. Sci.* **396**, 52–68 (2019).
128. Jiang, J., Tang, M., Huang, Z. & Chen, L. Junctophilins emerge as novel therapeutic targets. *J. Cell. Physiol.* **234**, 16933–16943 (2019).
129. Sathe, S. et al. Enroll-HD: an integrated clinical research platform and worldwide observational study for Huntington's disease. *Front. Neurol.* **12**, 667420 (2021).
130. Magazi, D. S. et al. Huntington's disease: genetic heterogeneity in black African patients. *S. Afr. Med. J.* **98**, 200–203 (2008).
131. Vasconcellos, L. F. R. et al. Huntington's Disease like 2 presenting with isolated Parkinsonism. *J. Neurol. Sci.* **373**, 105–106 (2017).
132. Teive, H. A. G. et al. Huntington's disease-like 2: the first case report in Latin America in a patient without African ethnic origin. *Mov. Disord.* **22**, S27 (2007).
133. Seeley, A. H. et al. Macrocerebellum, epilepsy, intellectual disability, and gut malrotation in a child with a 16q24.1-q24.2 contiguous gene deletion. *Am. J. Med. Genet. A* **164A**, 2062–2068 (2014).
134. Perni, S. & Beam, K. Neuronal junctophilins recruit specific Ca_V and RyR isoforms to ER-PM junctions and functionally alter $Ca_V2.1$ and $Ca_V2.2$. *eLife* **10**, e64249 (2021).

Author contributions

A.K., D.G.A., A.F.-C. and R.L.M. researched data for the article and made substantial contributions to discussions of the content, and each wrote a section. J.D. and F.B.-S. contributed to the Genetics section. J.D. generated some of the unpublished data mentioned in the article. P.P.L. contributed to the Pathogenesis section and references. All authors edited and reviewed the document before submission.

Competing interests

The authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Neurology* thanks R. Walker, S. Schneider and E. Wild for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

© Springer Nature Limited 2023