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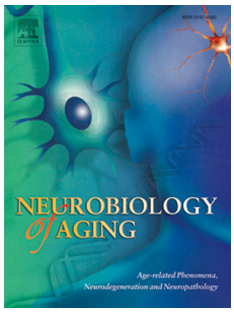

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A role for *ATXN1, ATXN2* and *HTT* intermediate repeats in frontotemporal dementia and Alzheimer's disease

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Keywords

Neurodegeneration, CAG repeats, intermediate alleles.

Abstract

We analyzed the frequency of intermediate alleles (IAs) in the *ATXN1, ATXN2* and *HTT* genes in several neurodegenerative diseases.

The study included 1,126 Alzheimer disease (AD), 440 frontotemporal dementia (FTD) and 610 Parkinson's disease (PD) patients. In all cohorts, we genotyped *ATXN1* and *ATXN2* CAG repeats. Additionally, in the FTD cohort we determined the number of *HTT* CAG-repeats.

The frequency of *HTT* IAs was higher in FTD patients (6.9%) vs controls (2.9%) and in the *C9orf72* expansion non carriers (7.2%) vs. controls (2.9%), although the difference was non-significant after correction for multiple testing. Compared to controls, progressive non-fluent aphasia (PNFA) groups showed a significantly higher frequency of *HTT IAs (13.6% vs 2.9% controls)*. For *the ATXN2* gene, we observed an IAs increased frequency in AD cases (AD 4.1% vs controls 1.8%) and in the behavioural FTD (bvFTD) group (4.8% vs 1.8%). For the *ATXN1* gene we found a significant increase of IAs in PNFA patients (18.6%) vs controls (6.7%).

In conclusion, our work suggests that the *HTT* and *ATXN1* IAS may contribute to PNFA pathogenesis and point to a link between *ATXN2* IAS and AD.

Keywords:

Neurodegeneration

CAG repeats

Intermediate alleles

Tauopathies

1. Introduction

Frontotemporal dementia (FTD) is a group of cognitive disorders caused by the degeneration in the frontal and temporal lobes, with clinical and pathological heterogeneous manifestations. Based on behavioral and language manifestations FTD is subdivided in behavioural FTD (bvFTD) and progressive non-fluent aphasia (PNFA) or fluent progressive aphasia (semantic dementia, SD). FTD is frequently familial, up to 43% of the cases according to some studies, with 10-27% showing an autosomal dominant inheritance (Rohrer, 2009). FTD is genetically heterogeneous, and FTD-causative mutations have been identified in several genes including C*9orf72, GRN, MAPT* and *TBK1* (Van Mossevelde et al., 2018). Some of the FTD-related mutations have also been identified in amyotrophic lateral sclerosis (ALS), suggesting a genetic overlap between the two disorders. In addition, other genetic factors would act as modifiers of the disease in FTD and motor neuron disease (MND) (van Blitterswijk et al., 2014). A pathogenic expansion in C*9orf72* is the most common genetic cause of FTD and ALS, accounting for 29% of familial FTD cases (Van Mossevelde et al., 2018). The clinical phenotype of the C*9orf72* expansion is very heterogeneous even within the same family, with the bvFTD subtype as the most common clinical presentation, although FTD-MND, MND and PNFA are also frequent (Simón-Sánchez et al., 2012). Moreover, C*9orf72* nucleotide expansion has also been found in patients with clinical diagnosis of Alzheimer's (AD), Parkinson´s (PD) and Huntington's (HD) disease, among others (Ahmed et al., 2016).

Spinocerebellar ataxia type 1 (SCA1), Spinocerebellar ataxia type 2 (SCA2) and HD are autosomal dominant progressive neurodegenerative diseases, caused by the presence of an expanded CAG-repeat (polyglutamine, polyQ) in the *ATXN1, ATXN2* and *HTT* genes, respectively. Some of the PolyQ expansions lie in an intermediate range between normal and pathological alleles. These intermediate alleles (IAs) are unstable and prone to increase their length to a pathological range in the offspring. The IAs CAG-repeats are in the range 27-35 for *HTT*, 27-33 in the *ATXN2*, and 33-38 in the *ATXN1*. In the last years, several studies have reported the potential effect of IAs in several neurodegenerative diseases. For instance, our group found that IAs in *HTT* might have a role in the pathogenesis of AD (Menéndez-González et al., 2019). In addition, IAs in *ATXN1* could act as a risk factor for ALS, mainly among among C*9orf72* expansion carriers (Lattante, 2018). The presence of IAs in the *ATXN2* gene has been associated with an increased risk of developing ALS (Conforti et al., 2012, Elden, 2010, Lee et al., 2011, Sproviero et al., 2017), but no significant association was found between ALS and IAs in *HTT* (Lee et al., 2011, Ramos et al., 2012). The frequency of IAs in *ATXN2* did not differ between FTD patients and healthy controls (Ross et al., 2011, van Blitterswijk et al., 2014), but these *ATXN2* alleles *c*ould act as modifiers of the FTD phenotype among carriers and non-carriers of the C*9orf72* expansion (Lattante et al., 2014, Rubino et al., 2019). The intermediate C*9orf72* expansion has been associated with a risk effect in familial and sporadic

FTD (Benussi et al., 2014, van der Zee et al., 2013). Together, these findings supported the idea that IAs might play an outstanding role in neurodegenerative disorders, but this hypothesis needs to be further explored.

The aim of this study was to determine the frequency of IAs in *ATXN1, ATXN2* and *HTT* in patients with AD, PD and FTD (both with or without *C9orf72* expansions).

2. Materials and methods.

2.1 Patients and controls.

2.1-Study Design

This was a multicentre study: patients were recruited from twelve centers of four countries. The anthropometric and clinical data was retrospectively collected from the medical records, and the DNA from all the participants was stored in the Hospital Biobanks. We analysed three cohorts of patients clinically diagnosed with AD, FTD and PD. In all them, we genotyped the CAG repeats in the *ATXN1* and *ATXN2* genes. We also determined the *HTT* CAG-genotype in the FTD cohort. A total of 150 of the Spanish FTD patients and all the AD and PD patients were previously *HTT ge*notyped and reported (Menéndez-González et al, 2019).

2.2-Patients and medical records

All the patients were Caucasian. Our FTD cohort consisted of 440 unrelated patients (293 from Spain, 101 from Italy, 26 from Belgium and 20 from Portugal) diagnosed with FTD (n=250), semantic dementia (n=32), progressive non-fluent aphasia (n=59), or FTD-MND (n=42), according to the behavioral and language variants criteria (Rascovsky et al., 2011; Gorno-Tempini et al., 2011***) (Supplementary Table 1***) . In 57 patients, FTD was classified as unspecified. A total of 175 patients were carriers of the C*9orf72* expansion. In all *C9orf72* non-carriers, we excluded the presence of the pathogenic variants in the *GRN* and *MAPT* genes.

Family history of dementia was present in 88.3% of the *C9orf72* expansion carriers and in 43.9% of the expansion non-c*arriers.*

We also analyzed 1,126 AD patients clinically diagnosed according to the NIH-AA criteria (McKhann et al., 2011) and 610 PD patients diagnosed according to the MDS criteria (Postuma et al., 2015).

All the patients were evaluated by neurologists from Hospital Universitario Central de Asturias (Spain); Hospital Santa Creu i Sant Pau (Spain); Centre for Neurodegenerative Disorders-University of Brescia (Brescia, Italy); Center for Neuroscience and Cell Biology, University of Coimbra (Coimbra, Portugal); Center for Molecular Neurology, VIB- University of Antwerp (Antwerp, Belgium), Regional Neurogenetic Centre, ASP CZ, Lamezia Terme (Catanzaro, Italy); Fondazione IRCCS Ca' Granda, Ospedale Policlinico (Milan, Italy).; RCCS Istituto Centro San Giovanni di Dio- Fatebenefratelli (Brescia, Italy), University of Florence Azienda Ospedaliero (Florence,Italy), Hospital Clínic (Barcelona, Spain); Hospital Gregorio Marañón (Madrid, Spain); IRCCS Istituto Fondazione IRCCS Istituto Neurologico Carlo Besta, (Brescia, Italy), and University Hospital Mutua de Terrassa, (Terrassa, Barcelona, Spain).

The control group was a cohort (n=509) of Spanish unrelated Caucasian individuals without symptoms of neurodegenerative disease. They were elderly subjects who agreed to participate and were recruited through the Health Community Service of the region of Asturias.

2.2 Genetic analysis

Genomic DNA was isolated from peripheral blood following standard procedures. The *HTT, ATXN1* and *ATXN2* CAG-repeat length were determined by polymerase chain reaction (PCR) with fluorescent-labeled primers, followed by capillary electrophoresis in an ABI 3130X automated DNA sequencer and the Gene Mapper version 4.0 software (Applied Biosystems). As a quality control of the genotyping method we sequenced several samples with different CAG-repeat alleles.

C9orf72 expansion

The *C9orf72* genetic status was determined by a triple repeat primed polymerase chain reaction (TP-PCR) as reported (DeJesus-Hernández et al., 2011, Gijselinck et al., 2012, Renton et al., 2011). The FTD patients were assessed for the presence of the *C9orf72* expansion. All the *C9orf72* positive subjects had more than 30 repeats.

2.3 Statistical analyses

The Chi-squared and Fisher's tests with Bonferroni's corrections for multiple testing were used to compare the frequency of *ATXN1, ATXN2* and *HTT* intermediate alleles between patients and controls. For the Bonferroni correction, a p value ≤ 0.05 was considered significant. In order to compare the distribution of the CAG-repeats between the different groups, we used the Kruskal-Wallis test to correct for samples that did not follow a normal distribution, with the Dunn's post-hoc test when necessary. The parametric Student's t-test was used to determine the correlation between IAs and the age of onset.

The statistical analyses were performed with SPSS (version 17) statistical packages.

2.4 Standard protocol approvals, registrations and patient consents

All the patients and controls gave their informed consent to participate in the study, approved by the Ethical Committees of the participating centers.

3. Results

In **Table 1** we show the main values in the patients and controls cohorts, as well as the clinical presentation in the FTD patients. In all the groups the most common *HTT* alleles had 17 and 18 CAG-repeats. In reference to the IAs, the longest was a 34 repeat and the most frequent was the 27 CAG-repeat (***supplementary Figure 1***). For *ATXN2* and *ATXN1* , the most prevalent alleles had 22 and 29-30 CAG repeats, respectively (***supplementary Figure 2 and Figure 3).*** The frequency of IAs in *HTT, ATXN1* and *ATXN2* in the controls was close to the reported in other European populations (Gardiner et al, 2019)

We did not find significant differences in the distribution of the normal *HTT, ATXN1* and *ATXN2* allele*s* between the different groups of patients and controls (Kruskal-Wallis test). For the IAs no difference in the *HTT, ATXN1* and *ATXN2* allele distribution was observed, likely due to the small number of patients carrying IAs (data not shown).

Table 1. Main demographic and clinical data in the studied cohorts.

Group	N	Male (%)	Age at examination (controls) / Age at onset (patients) mean±SD	Age range (min-max)
Controls	509	234 (46)	71.14±6.42	49-90
FTD	440	241 (54.8.)	61.42±9.90	29-85
bvFTD	250	149(59.6)	60.15±9.70	29-85
PNFA	59	24(40.7)	66.21±8.14	48-80
SD	32	16(50)	63.08±9.21	48-82
FTD-MND	42	28(66.7)	59.32±10.35	33-82
Unspecified	57	24(42.1)	62.21±11.04	37-83
FTD *C9orf72* non-carrier				
All C9-	265	143(54)	63.48±9.43	33-85
bvFTD	141	84(59)	61.83±8.89	37-85
PNFA	48	18(37)	68.05±7.23	52-80
SD	27	13(50)	63.40±9.07	48-82
FTD-MND	10	8(80)	62.90±13.61	33-82
Unspecified	39	17(43)	64.11±11.18	37-83

FTD *C9orf72* carrier				
All C9+	175	98(56)	57.86±9.71	29-79
bvFTD	109	62(56)	57.53±10.37	29-79
PNFA	11	6(54)	57.90±5.86	48-67
SD	5	3(60)	61.40±10.85	50-74
FTD-MND	32	20(62)	58.04±8.87	39-73
Unspecified	18	7(39%)	58.18±9.88	41-75
AD	1126	337(30)	74.32±9.67	20-96
PD	610	315(52)	59.85±13.6	25-87

FTD- frontotemporal dementia; bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia witht no specified phenotype; SD- standard deviation

Table 2 summarizes the frequency of intermediate *HTT* alleles in the different groups. In the FTD cohort 6.8% of patients were IA carriers, compared to 2.9% among the controls. An increased frequency of IAs was also observed in the non-carriers of C*9orf72* expansion (7.2% vs. 2.9% in controls). Among the clinical subgroups bvFTD and PNFA showed a difference in the frequency of *HTT* IAs (bvFTD 6.4% vs 2.9%; PNFA 13.6% vs 2.9%). However, only the association between PNFA and *HTT* IAs remained statistically significant after correction for multiple testing (p=0.032).

All the PNFA patients with *HTT* IAs were negative for the *C9orf72* expansion, while in the bvFTD group we found a total of 16 IAs carriers and 8 (50%) were *C9orf72* non-carriers (***Supplementary Table 2***)

Table 2. Frequencies of *HTT* intermediate alleles.

Group	Carriers of *HTT* IAs	p-value Chi-squared	p-value Fisher	Bonferroni
Controls	15 (2.9%)			
FTD	30(6.8%)	p=0.008		p=0.377
FTD C*9orf72* carriers	11 (6.3%)	p=0.08		p=1
FTD C*9orf72* non carriers	19 (7.2%)	p=0.011		p=0.591
bvFTD	16 (6.4%)	p=0.04		p=1
PNFA	8 (13.6%)		p=0.001	p=0.032
SD	1 (3.1%)		p=1	p=1
FTD-MND	3 (7.1%)		p=0.151	p=1
FTD unspecified	2 (3.5%)		p=1	p=1

post hoc Bonferroni correction was applied for the global number of tests
FTD- frontotemporal dementia; bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia witht no specified phenotype

In reference to the *ATXN2* gene, we observed an increased frequency of intermediate alleles (≥27 repeats) in the AD group compared to the controls (4.1% vs 1.8%)**.** Among the clinical subgroups, bvFTD showed a higher frequency of *ATXN2 IAs* (bvFTD 4.8% vs 2.9%). After correction for multiple testing no significant difference was observed, likely due to an insufficient number of individuals in the two clinical groups (***Table 3, supplementary table 3)***. Because alleles in the 29-33 range have been associated with the risk of developing ALS we determined the frequency of ≥ 29 CAG repeats in AD, FTD and PD. No significant association was observed but there was an increased frequency of IAs ≥29 repeats in the AD and FTD groups compared to controls (AD: 0.80% vs 0.42%,FTD: 0.90% vs 0.42%) (data not shown) .

Table 3. Frequencies of *ATXN2* intermediate alleles in the study cohorts.

Group	Carriers of *ATXN2* IAs	p-value Chi-squared	p-value Fisher	Bonferroni
Controls	9 (1.8%)			
FTD	17(3.9%)	p=0.08		p=1
FTD C*9orf72* carriers	6(3.4%)		p=0.230	p=1
FTD *C9orf72* non carriers	11 (4.2%)	p=0.08		p=1
bvFTD	12 (4.8%)	p=0.03		p=1
PNFA	2(3.4%)		p= 0.615	p=1
SD	0			
FTD-MND	0			
FTD unspecified	3 (5.3%)		p=0.111	p=1
AD	46 (4.1%)	p=0.024		p=0.86
PD	13(2.1%)	p=0.823		p=1

Post hoc Bonferroni correction was applied for the global number of tests.
FTD- frontotemporal dementia; bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease; FTD unspecified - Frontotemporal dementia witht no specified phenotype; AD-Alzheimer disease; PD-Parkinson disease.

In reference to the *ATXN1*, we considered 33 CAG repeats as the cut-off between normal and intermediate alleles. We found a significantly increased frequency in PNFA compared to controls (18.6% *vs* 6.7%; p=0.05) ***(Table 4 , Supplementary Table 4)***.

Table 4. Frequencies of *ATXN1* intermediate alleles.

Group	Carriers of *ATXN1* IAs	p-value Chi-squared	p-value Fisher	Bonferroni
Controls	34 (6.7%)			
FTD	35 (8%)	p=0.527		p=1
FTD *C9orf72* carriers	13(7.4%)	p=0.862		p=1
FTD *C9orf72* non carriers	22(8.3%)	p=0.498		p=1
bvFTD	14(5.6%)	p=0.680		p=1
PNFA	11(18.6%)		p=0.004	p=0.05
SD	2(6.3%)		p=1	p=1
FTD-MND	5(11.9%)		p=0.207	p=1
Unspecified	3(5.3%)		p=0.788	p=1
AD	81 (7.2%)	p=0.791		p=1
PD	58(9.5%)	p=0.108		p=1

post hoc Bonferroni correction was applied for the global number of tests
FTD- frontotemporal dementia; bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD-semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia witht no specified phenotype

Finally, we did not find differences in the mean onset-age between carriers and non-carriers of *HTT, ATXN2* and *ATXN1* intermediate alleles in the different studied cohorts (***Supplementary Table 5***).

4-Discussion

We had previously reported a significantly higher frequency of *HTT I*As among AD patients compared to healthy controls. Therefore, the *HTT* gene might play a role in the pathogenesis of AD (Menéndez-González et al, 2019). However, no significant difference between FTD patients and controls was observed, although we found a higher frequency of *HTT* IAs in FTD patients. The lack of significant association could be explained by the limited size of the FTD cohort.

In the present study, we increased the FTD sample size and examined the frequency of intermediate alleles at the *HTT, ATXN1, ATXN2* genes. We included 175 *C9orf72* expansion carriers and 265 non expansion carriers. In addition, we determined the frequencies of *ATXN2* and *ATXN1* IAs in AD and PD cohorts.

Concerning to *HTT,* we found an non-significantly increased frequency of IAs in the FTD group, particularly in the the *C9orf72* non-carriers. According to the clinical subgroups only PNFA showed a significant difference of *HTT* IAs compared to controls *(p=0.032)*. However, in the bvFTD group, we observed a non-significantly increased frequency of *ATXN2* IAs. Rubino et al. found a similar result in Italian population. For the *ATXN1,* we also observed a significantly increased frequency of IAs in the PNFA group (*p=0.05)*. In this clinical group, all the *HTT* IAs carriers and most of the *ATXN1* IAs carriers (7/8, 88%) were negative for the C*9orf72* expansion.

Previous studies evaluated the role of the CAG-repeat in several neurodegenerative and psychiatric disorders. A larger study based in the *European Huntington's Disease Registry* showed that elderly carriers of *HTT* IAs would have more chorea and faster cognitive decline than controls (Cubo et al., 2016). Also, a population based study found that carriers of *HTT* IAs could have a higher risk for apathy and suicidal ideation (Killoran et al., 2013), while an U-shaped relation was found between the number of repeats and the risk of suffering depression (Gardiner et al., 2017). Several studies also suggested a significant association between *ATXN2* IAs and ALS, and concluded that repeats in the 29-33 range were a strong risk factor for developing ALS and could also act as a phenotypic modifier (Chiò et al., 2015, Ramos et al., 2012). To our knowledge our study is the first describing an association between IAs in *HTT* and *ATXN1* genes and the PNFA.

In addition, we reported an increased frequency of the *ATXN2* IAs in the AD cohort, that was non-significant after correction for multiple testing but pointed to a pathogenic link between *ATXN2* and AD.

Huntington's disease and Spinocerebral Ataxia type 2 are neurodegenerative disorders linked to polyglutamine expansions and course with progressive motor symptoms, psychiatric disturbances, and cognitive decline. The polyglutamine domains of the proteins act as critical regulators of key cellular processes such as transcriptional regulation, mitochondrial energy production and autophagy (Ashkenazi et al., 2017, Hannan, 2018, Lee et al., 2011). These

pathways have been associated with aging and several age-related disorders, including AD (Caldeira et al., 2013, Gardner, Boles, 2011). Interestingly, SCA2 patients showed brain amyloid-beta alternative transcript splicing patterns that resembled those observed in AD (Li et al., 2016).

A recent study reported the association of the *ATXN1* CAG-repeat and the different clinical features in AD, such as memory, attention and atrophy of the medial temporal lobes (Gardiner et al., 2019). In our AD cohort, an association of the *ATXN1* repeats with AD risk, age at onset or the ApoE genotype was not observed.

Although our patients did not have neuropathological confirmation it is well known that all C*9orf72* cases are TDP-43 proteinopathies. It is also known that most of the sporadic SDs are also TDP-43 proteinopathies, while other subtypes of FTLD can be either Tau or TDP-43 proteinopathies (Josephs, 2011). Taking this facts into account our results suggested that IAs in the *ATXN1, ATXN2* and *HTT* genes could be associated with Tau proteinopathies. Interestingly, it has been proposed that HD is also a tauopathy (Gratuze et al., 2016): first, the mutant *HTT* protein alters tau splicing, phosphorylation, oligomerization and subcellular localization (Blum et al., 2015, Fernández-Nogales et al., 2016); second, patients with HD (in particular those with a young-onset) presented inclusions of aggregated tau within various structures of the brain (Fernández-Nogales et al., 2014, Vuono et al., 2015); third, the MAPT H2 haplotype influences the cognitive function in HD patients (Vuono et al., 2015***).*** In ***Figure 1,*** we illustrate the putative pathways by which mutant *HTT* (m*HTT*) might induce tauopathy.

Our results pointed to a link between IAs and tauopathies, but a more general role in neurodegeneration cannot be excluded. In fact, *ATXN1* IAs have been associated with the risk of developing ALS, mainly among *C9orf72* expansion carriers (Lattante et al, 2018). It might be of upmost importance to know whether IAs in *HTT*, *ATXN2* and *ATXN1* contribute to neurodegeneration. To address this issue, neuropathological and biochemical studies are needed to check whether polyQ deposits are present in the brain of IAs.

Finally, the genetic architecture of FTD and AD is complex and many genetic variants can modulate disease pathogenesis in different ways. These variants, including the number of CAG repeats, might have a synergistic effect in the disease onset and progression and also associate with the clinical phenotype. Our results also support the hypothesis that there are common pathways for a cluster of neurodegenerative diseases linked by tau dysfunction. Our study has several limitations, mainly the fact that the diagnosis of cases was not supported by neuropathological markers to confirm the diagnosis. Also, the retrospective and multicentre design might affect the genetic association results, and the sample size for some of the clinical subtypes of FTD was small. Therefore, our conclusions about these clinical groups should be taken with caution.

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Figure´s footnotes and title

Supplementary Figure 1

Footnote- (A) Distribution of *HTT* CAG repeats in patients and controls. (B) Distribution of *HTT* intermediate alleles.

Supplementary Figure 2

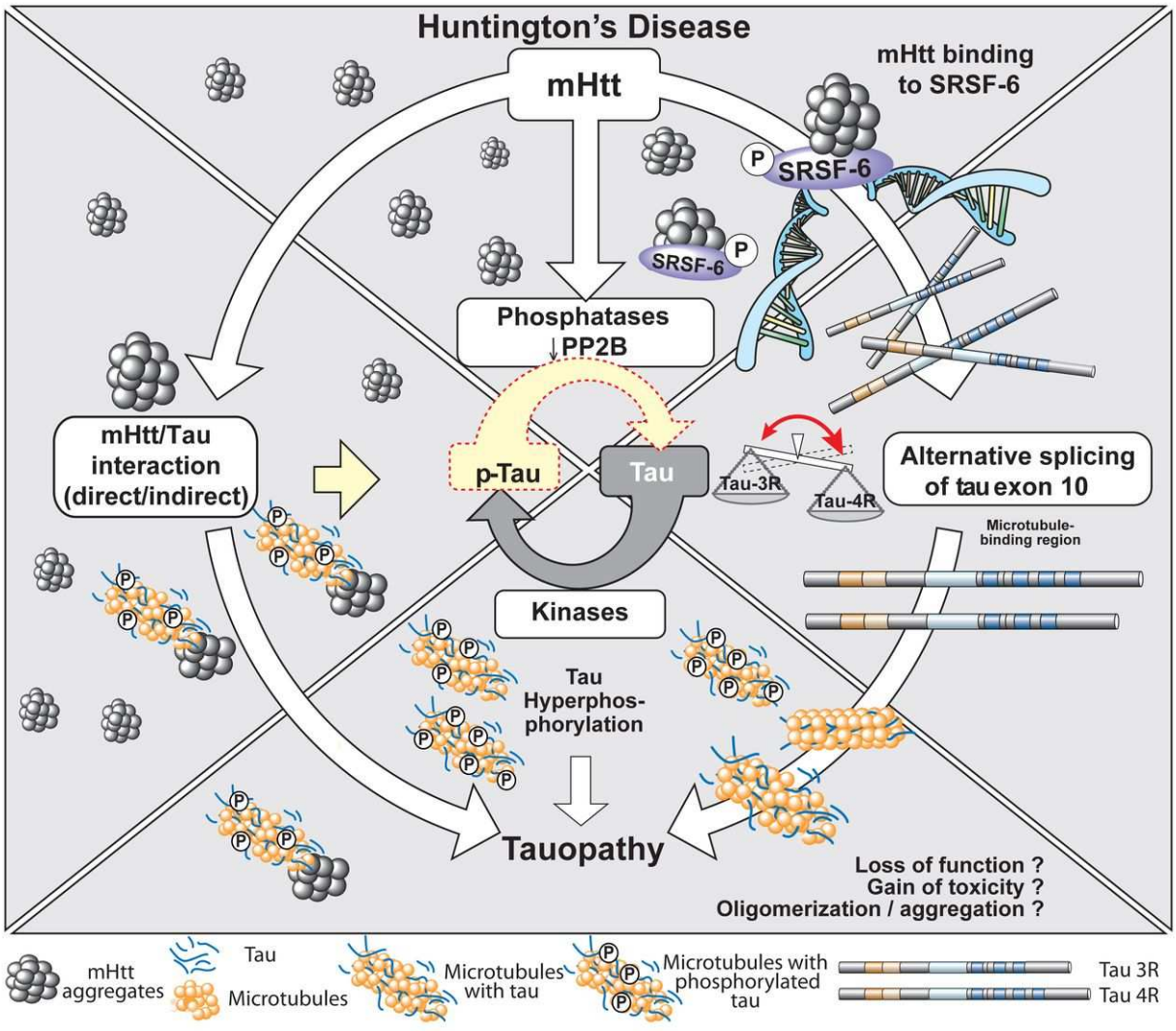
Footnote : A) Distribution of *ATXN2* CAG repeats in patients and controls .(B) Distribution of *ATXN2* intermediate alleles.

Supplementary Figure 3

Footnote : (A) Distribution of *ATXN1* CAG repeats in patients and controls .(B) Distribution of *ATXN1* intermediate alleles.

Figure 1

Footnote Schematic representation of the putative pathways by which m*HTT* induces tauopathy. Schematic recapitulation of the putative mechanisms underlying tau pathology in Huntington's disease according to data collected in human, mice and in *in vitro* settings. m*Htt* can interfere with a number of different cellular functions and therefore impact the role of various proteins. Its interaction with the tau splicing factor SRSF6 may cause an imbalance between tau isoforms (4R ≥ 3R). In the presence of m*HTT*, a significant decreased level of PP2B (calcineurin) is detected within cells, promoting tau hyperphosphorylation (p-tau). Direct (to be confirmed) or indirect (through a common binding partner such as microtubules) interaction of mHtt with tau could also result in tau phosphorylation. These various mechanisms are likely to act concomitantly to induce tau pathology. Reproduced with permission from Gratuze et al., 2016.


Huntington's Disease
mHtt
mHtt binding to SRSF-6
SRSF-6
SRSF-6
Phosphatases ↓PP2B
mHtt/Tau interaction (direct/indirect)
p-Tau
Tau
Tau-3R
Tau-4R
Alternative splicing of tau exon 10
Microtubule-binding region
Kinases
Tau Hyperphos-phorylation
Tauopathy
Loss of function ?
Gain of toxicity ?
Oligomerization / aggregation ?
mHtt aggregates
Tau
Microtubules
Microtubules with tau
Microtubules with phosphorylated tau
Tau 3R
Tau 4R

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