Pure *ATXN10* repeat expansion causes Parkinson's disease

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BACKGROUND and SUMMARY

Pentanucleotide repeat expansions of ATTCT in intron 9 of the *ATXN10* gene typically cause a distinct clinical phenotype of progressive spinocerebellar ataxia with or without seizures and present neuropathologically with Purkinje cell loss resulting in symmetrical cerebellar atrophy.

We report the first case with an *ATXN10* repeat expansion in a patient clinically presenting with typical L-Dopa responsive parkinsonism. In addition, we identified an unaffected sibling with one of the longest repeat expansion with reduced or delayed penetrance in the *ATXN10* gene published to date. We sequenced the entire repeat using novel single molecule sequencing paired with SMRT/Cas9 capture approach which provides a unique genetic tool to better understand phenotype-genotype correlations advancing clinical genetic diagnostics of repeat expansion disorders.

METHODS

We clinically characterized several affected and unaffected family members of a large 4-generation Mexican kindred with 28 affected family members with *ATXN10* expansions using standardized clinical assessment tools. Furthermore, to fully understand the genetic architecture of the *ATXN10* repeat expansion, we used a novel technology combining single molecule real time (SMRT) sequencing and CRISPR/Cas9-based capture method, and sequenced the entire span of ~5.1kb-6.5kb repeat expansions as one continuous fragment.

CLINICAL PRESENTATION of PROBAND

The proband first showed clinical signs at age 37, when his family noticed a "blank stare". At 38, he developed tremor of his chin, left hand ,and generalized stiffness. At 39, his family noticed increased irritability, moodiness and generalized weakness. At age 45, on neurological exam, he exhibited moderate left hand resting tremor, moderate bradykinesia and muscle rigidity, shuffling gait, mildly soft voice, and moderate hypomimia. Posture was mildly stooped and he showed absent postural response. He responded well to dopaminergic therapy (carbidopa/levodopa and ropinirole). No cerebellar symptoms were detected. After 5 years, he developed motor complications with wearing off phenomenon, gait freezing, and peak-dose dyskinesia. He underwent bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) at age 56 with marked relief of wearing off, gait freezing, and dyskinesias.

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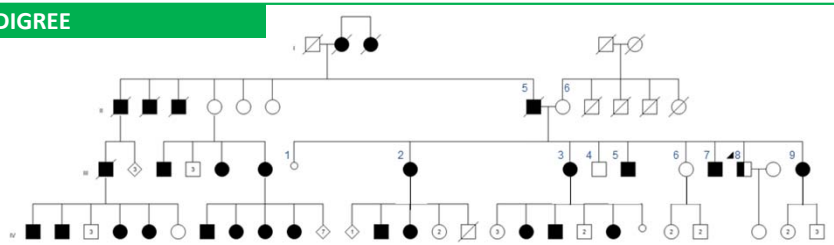
RESULTS

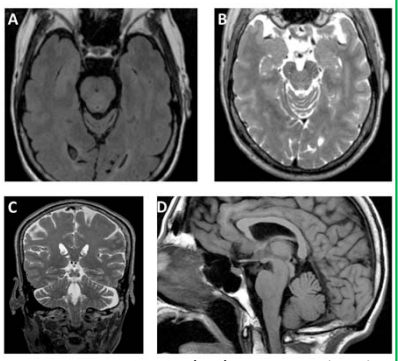
Four of the affected family members examined showed clinical features of progressive ataxia and seizures with cognitive and psychological changes including dementia. However, one affected individual presented with early-onset L-Dopa responsive parkinsonism and no signs of ataxia, and one sibling was clinically unaffected indicating reduced penetrance or delayed onset for this allele. Interestingly, no repeat interruptions were detected in the patient presenting with Parkinson's disease and his sister with reduced or delayed penetrance. However, in the siblings with typical ataxia, we found *ATXN10* repeat interruptions which have not been associated with seizures previously.

FAMILY PEDIGREE



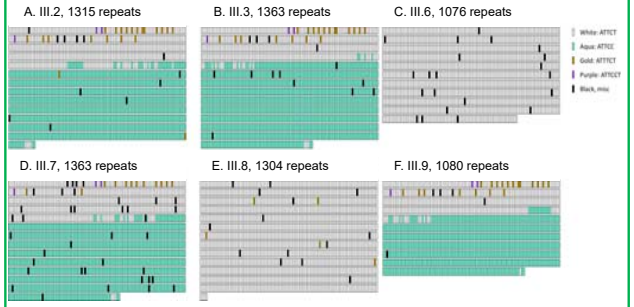
Four generation pedigree of Mexican family with autosomal-dominant ataxia and Parkinson's disease. Circles indicate female gender, squares indicate male gender, black symbols indicate affected individuals. The half black symbol with an arrowhead indicates the proband.

BRAIN MRI



Magnet resonance imaging (III.8). MRI was conducted as presurgical evaluation before DBS. A: axial FLAIR and B: axial T2 superior vermin cistern showing mild atrophy of the folia; C: coronal T2 illustrating expansion of extra-axial CSF containing spaces, D: Sagittal T1 shows mild superior cerebellar volume loss.

ATXN10 REPEAT SEQUENCING



ATXN10 repeat expansion sequence schematics based on PacBio sequencing. Repeat expansions are represented in the 5' (upper left) to 3' (lower right) direction. The schematics and expansion size given are based on the shortest most error-free read length for each individual and family members in the pedigree as follows: (A) III-2: 1315 repeats, (B) III-4: 1363 repeats, (C) III-7: 1076 repeats, (D) III-7: 1363 repeats, (E) III-8: 1304 repeats and (F) III-9: 1080 repeats. Each rectangle represents a sequence motif as follows: white, ATTCT; aqua, ATTCC; gold, ATTTCT; purple, ATTCCT. Black rectangles denote miscellaneous motifs that may represent errors in sequence reads.

CLINICAL SIGNS of AFFECTED INDIVIDUALS

	III.2	III.3	III.6	III.7	III.8 (Prob)	III.9
Gender	F	F	F	M	M	F
Age at onset (yrs)	35	48	Unaff.	48	38	37
Onset seizures (yrs)	60	57	-	53	-	-
Current age (years)	71	68	61	65	57	53
Duration of disease (years)	36	20	-	17	19	16
Seizures	+	+	-	+	-	-
Gait ataxia	+	+	-	+	-	+
Intention tremor	+	+	-	-	+	-
Dysarthria	+	+	-	+	-	+
Dysmetria	+	+	-	+	-	+
Dysdiadochokinesia	+	+	-	-	+	+
Nystagmus	+	+	-	+	-	+
Ocular dyskinesia	+	+	-	+	-	-
Hypotonia	-	-	-	-	-	-
Hyperreflexia	-	-	-	+	-	-
Babinski's sign	-	-	-	-	-	-
Leg spasticity	-	-	-	-	-	-
Aggressiveness	+	+	-	-	-	+
Depression	+	+	-	+	+	+
MoCA	9/30	2/30	29/30	U	U	25/30
SARA	23.5/40	24.5/40	0/40	U	6/40	16/40
B-SIT (% tile)	NP	NP	27%	U	29%	20%
B-SIT (category)	NP	NP	nl	U	nl	nl

Legend: M= male, F= female, + = symptom present, - = symptom not present, U = unknown, NP= not possible: patient was not able to perform test, MoCA = Montreal cognitive assessment, SARA = scale for assessment and rating of ataxia, B-SIT = Brief Smell Identification Test™

CONCLUSIONS

This is the first reported case with clinically typical L-dopa responsive parkinsonism and an *ATXN10* repeat expansion. We propose that the absence of repeat interruptions is responsible for the clinical presentation of Parkinson's disease. It will be important to understand the underlying genetic and molecular differences that lead to the changes in the neurodegenerative process in this family with different clinical and presumably neuropathological phenotypes.