Science Advances
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Supplementary Materials for

Short tandem repeat expansions in sporadic amyotrophic lateral sclerosis and frontotemporal dementia

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Sci. Adv. **9**, eade2044 (2023)
DOI: 10.1126/sciadv.ade2044

This PDF file includes:

Supplementary Figs.

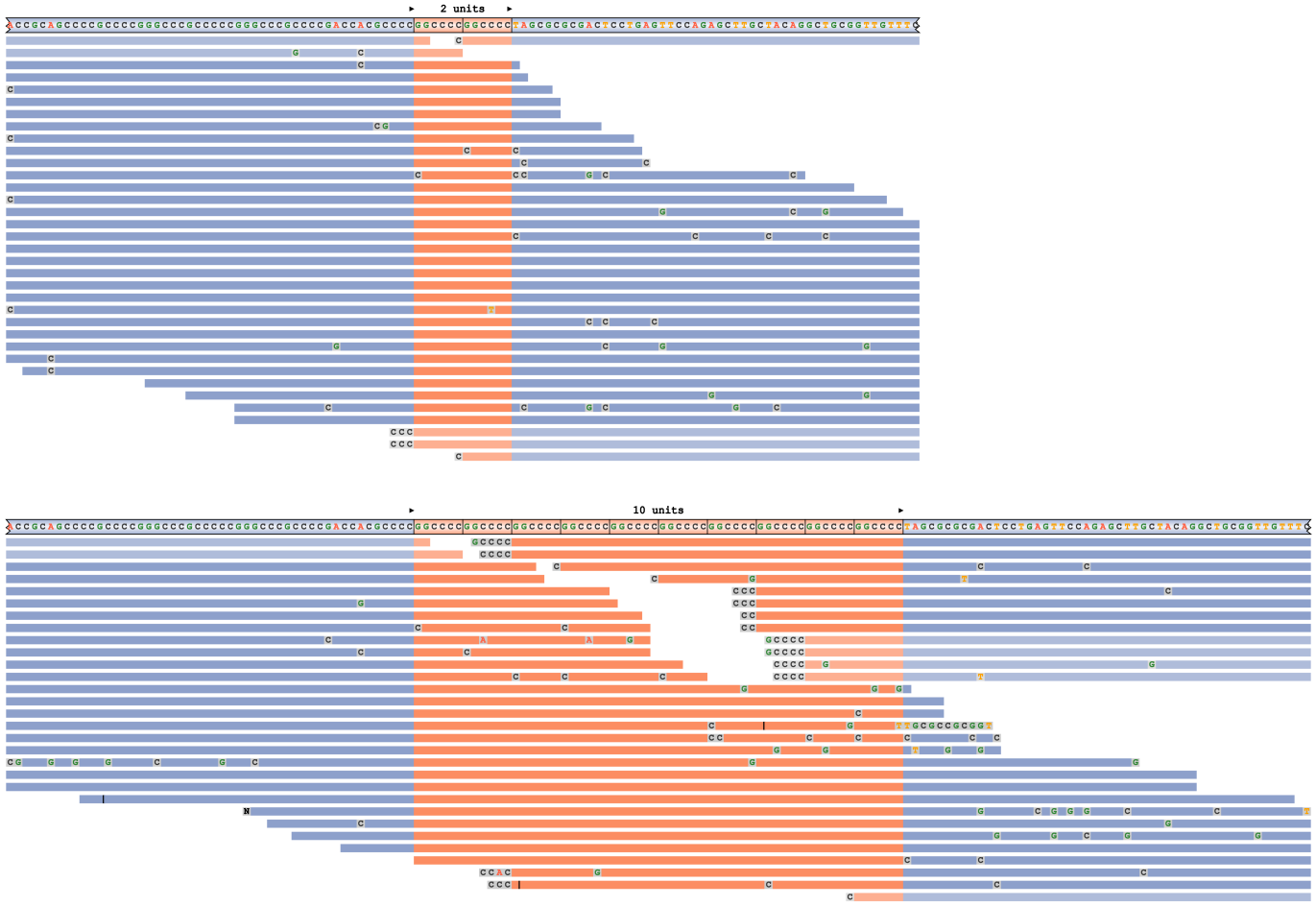

Fig. S1: Representative REViewer image of read alignments from ExpansionHunter for *C9orf72*.

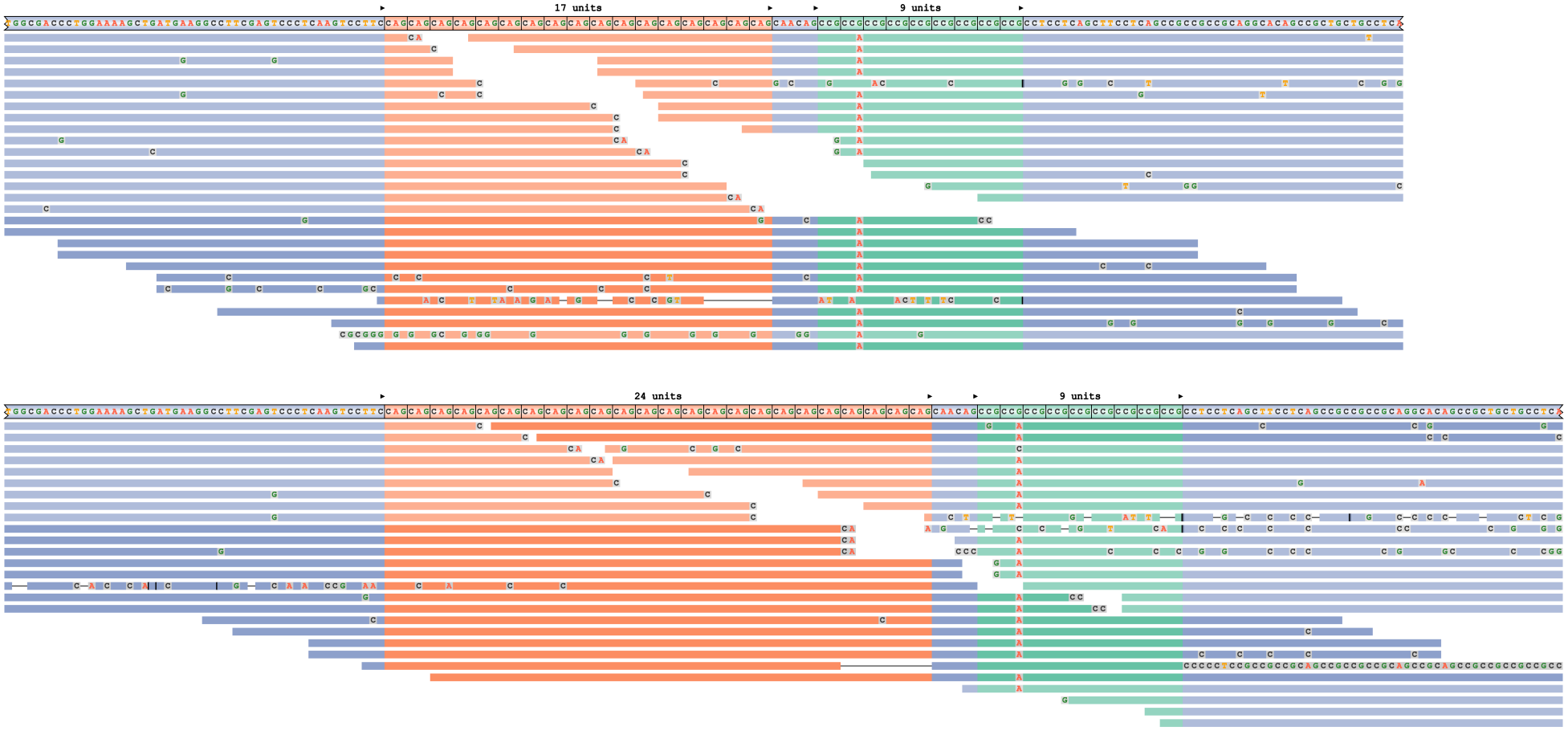

Fig. S2: Representative REViewer image of read alignments from ExpansionHunter for *HTT*.

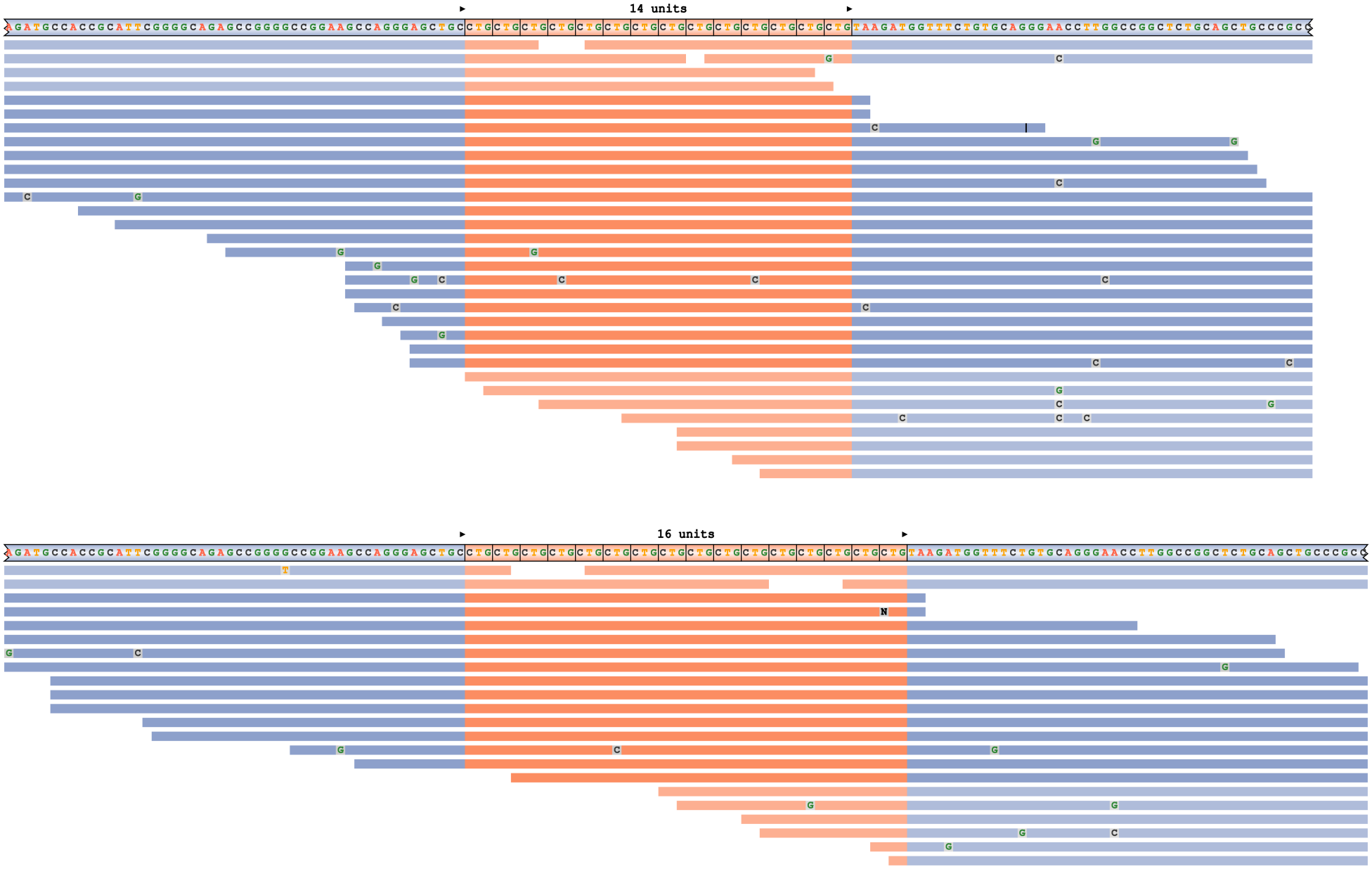

Fig. S3: Representative REViewer image of read alignments from ExpansionHunter for *JPH3*.

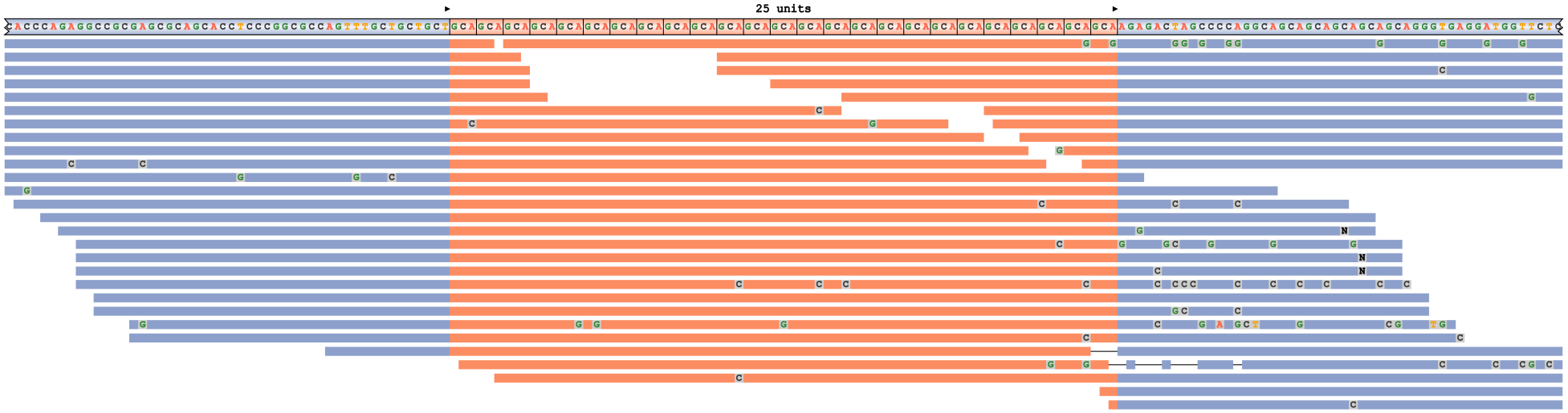

Fig. S4: Representative REViewer image of read alignments from ExpansionHunter for *AR*.

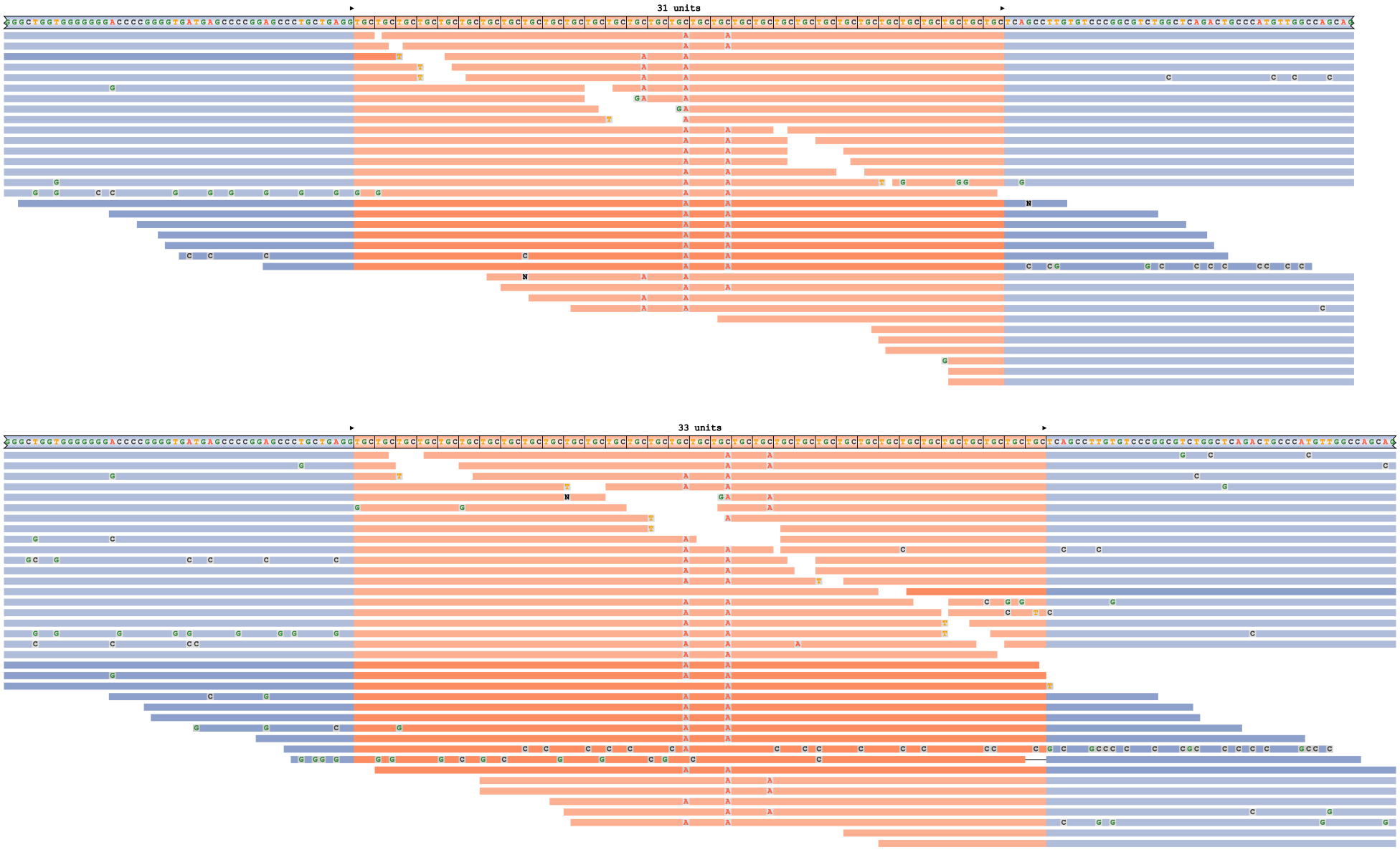

Fig. S5: Representative REViewer image of read alignments from ExpansionHunter for *ATXN1*.

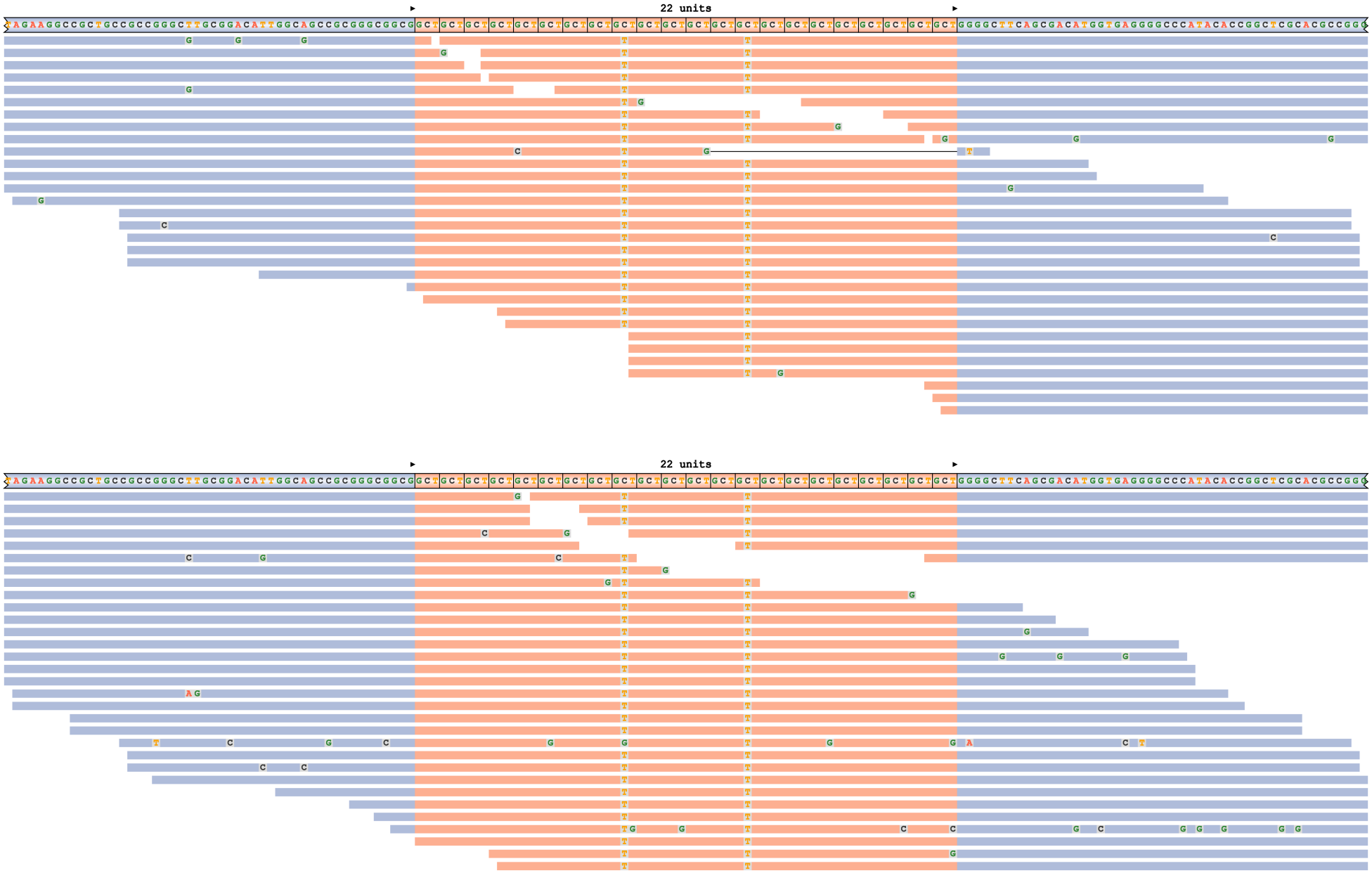

Fig. S6: Representative REViewer image of read alignments from ExpansionHunter for *ATXN2*.

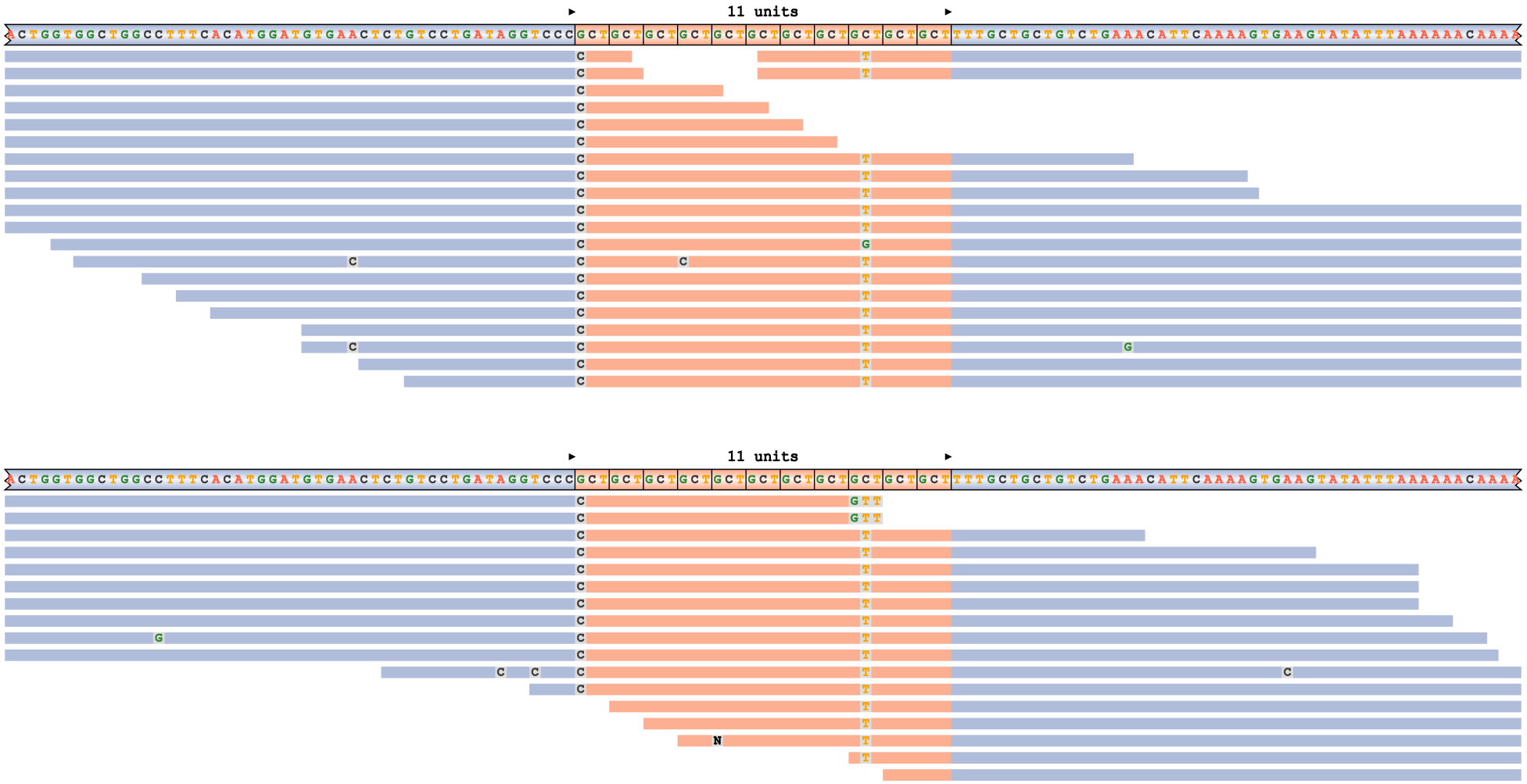

Fig. S7: Representative REViewer image of read alignments from ExpansionHunter for *ATXN3*.

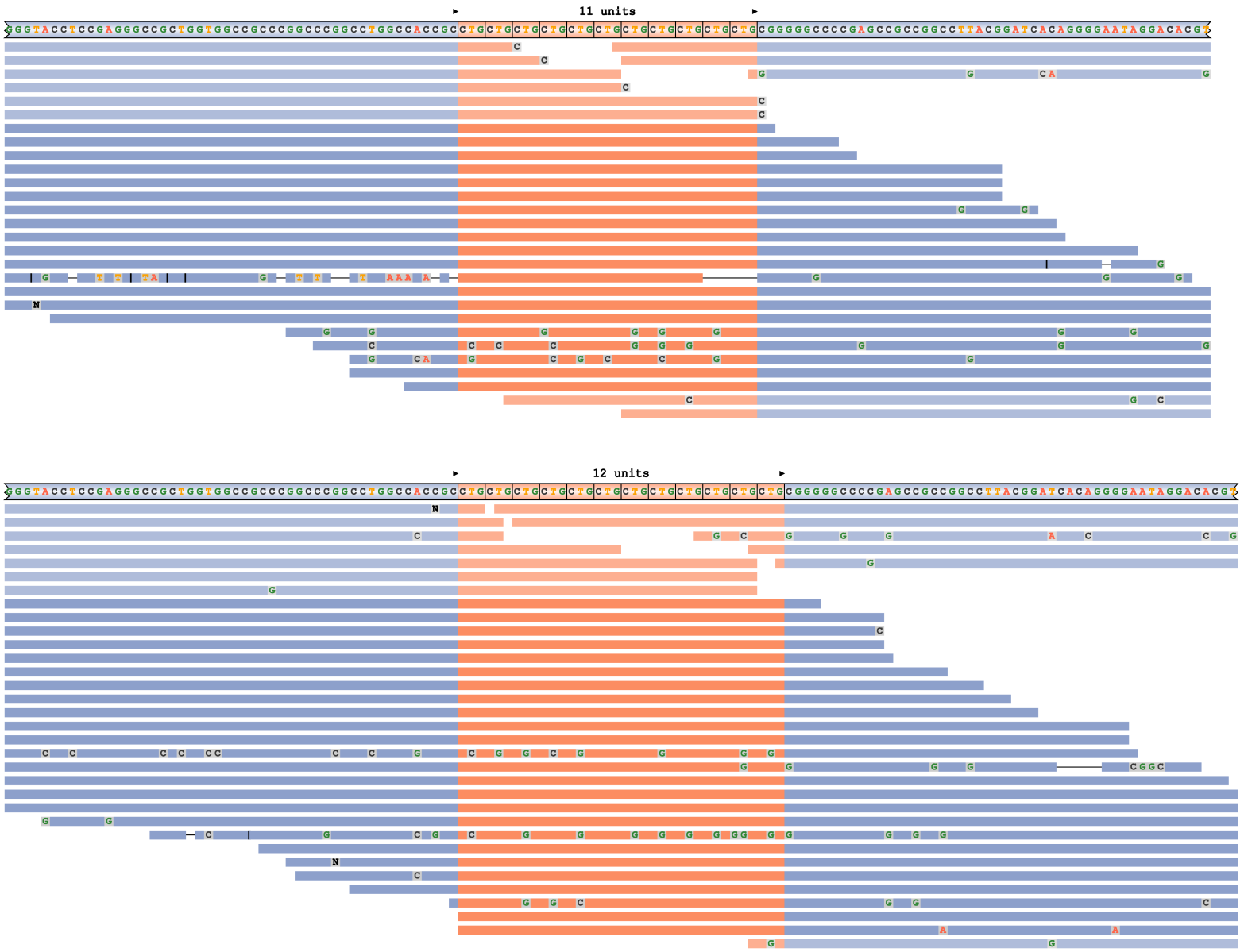

Fig. S8: Representative REViewer image of read alignments from ExpansionHunter for *CACNA1A*.

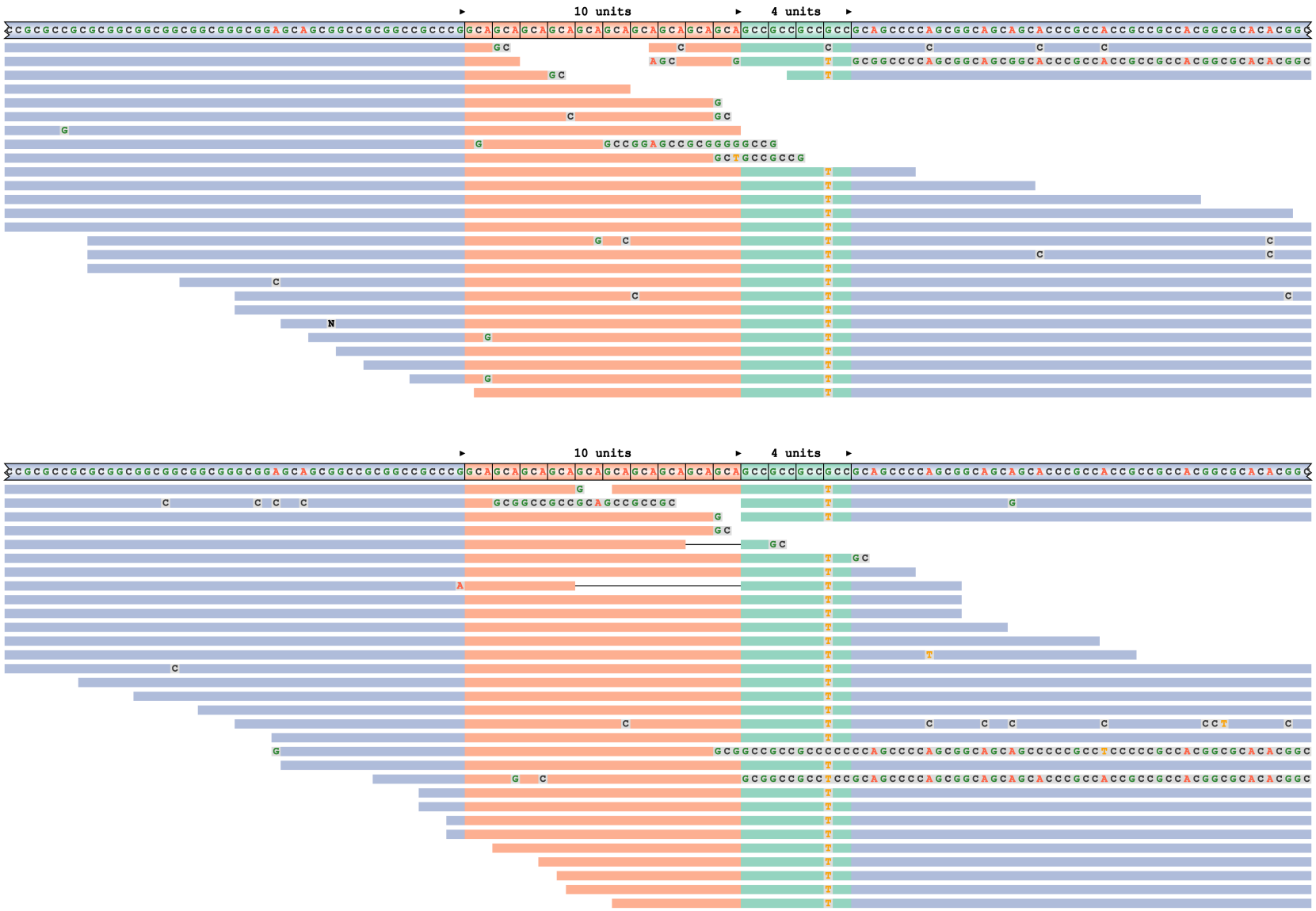

Fig. S9: Representative REViewer image of read alignments from ExpansionHunter for *ATXN7*.

Fig. S10: Representative REViewer image of read alignments from ExpansionHunter for *ATXN8*.

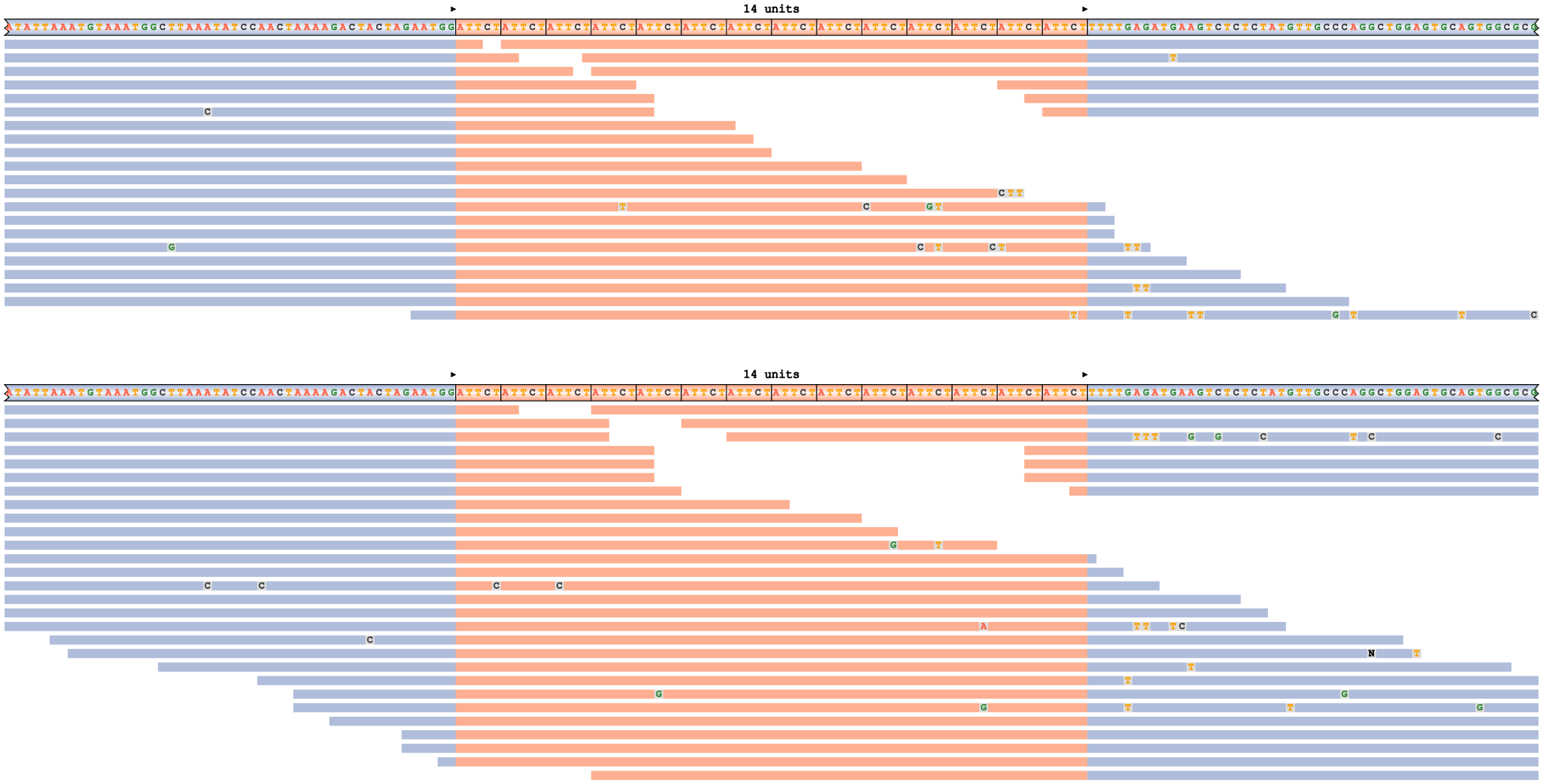

Fig. S11: Representative REViewer image of read alignments from ExpansionHunter for *ATXN10*.

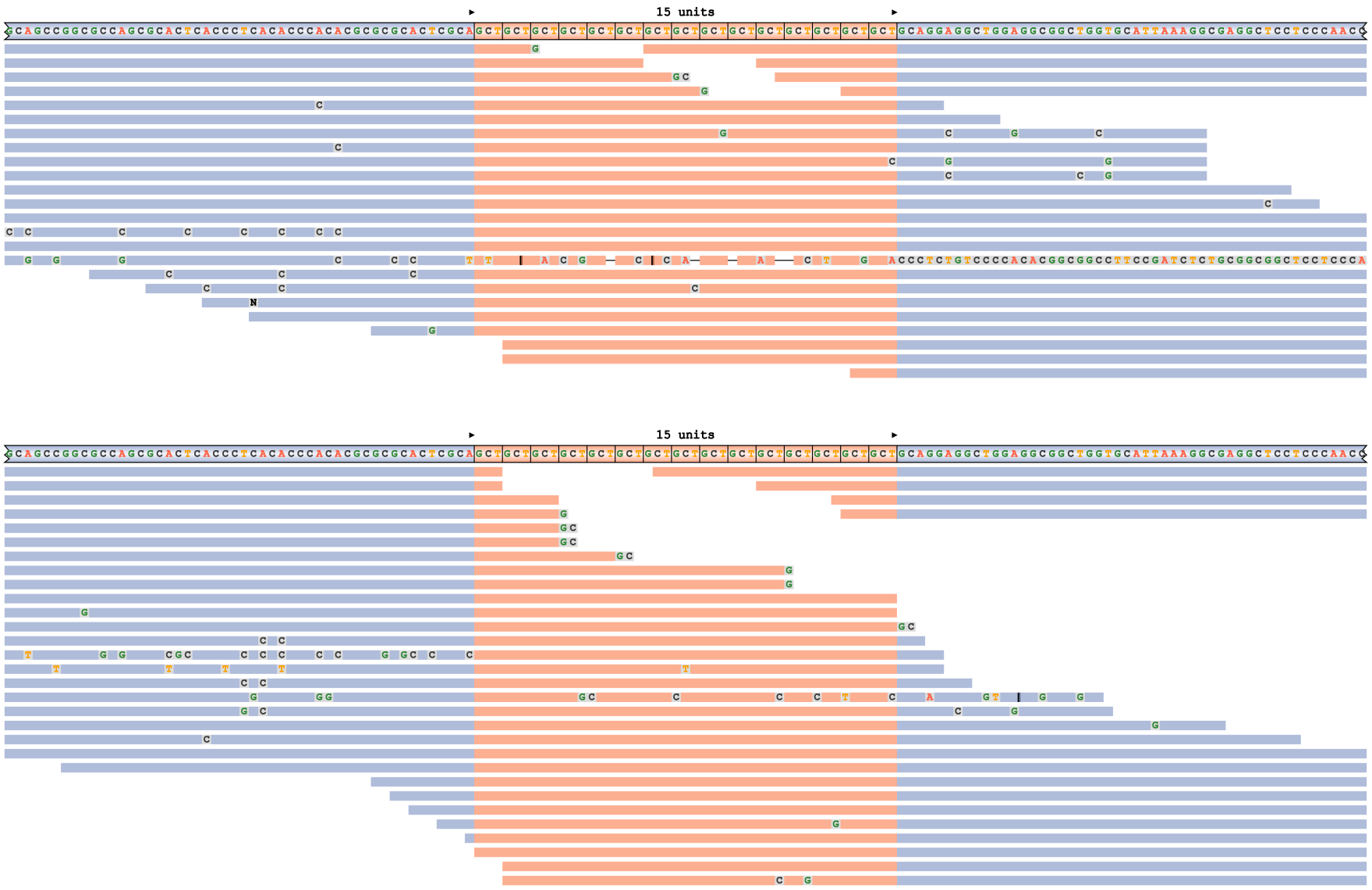

Fig. S12: Representative REViewer image of read alignments from ExpansionHunter for *PPP2R2B*.

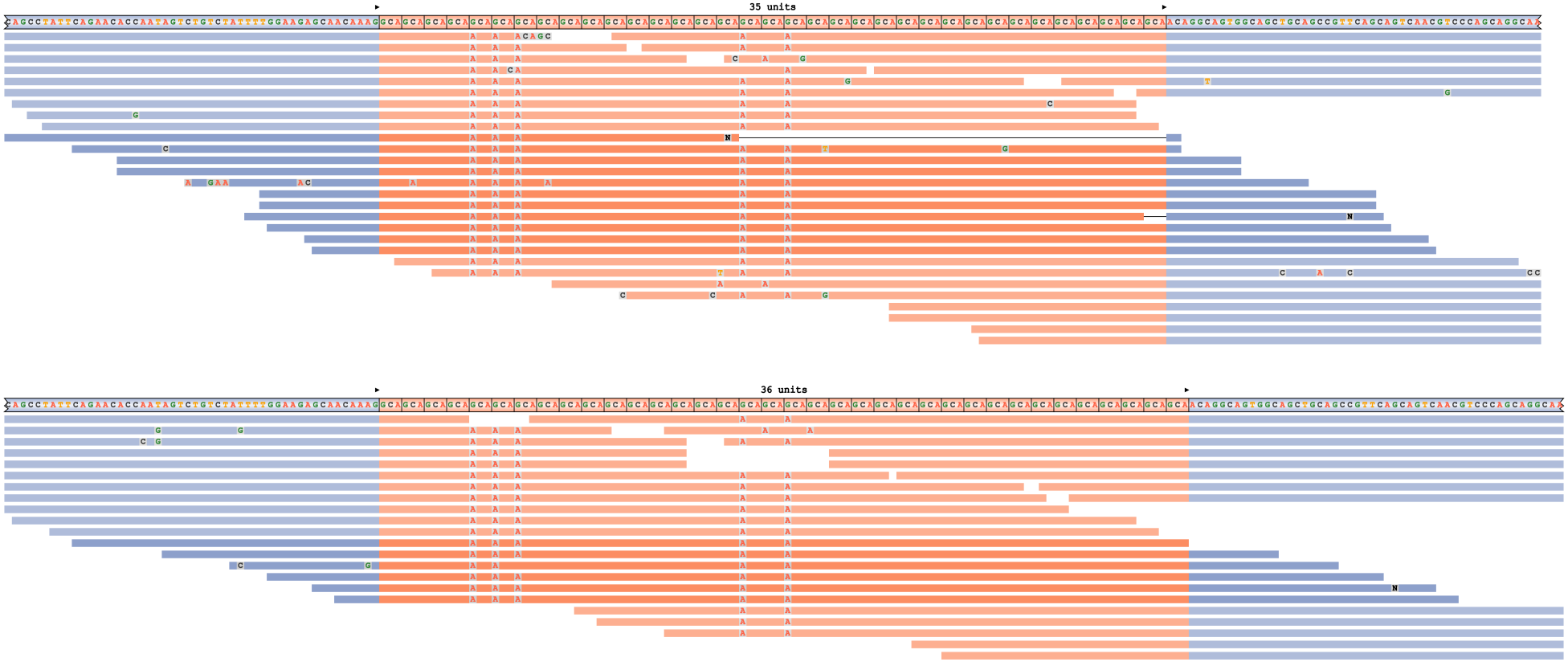

Fig. S13: Representative REViewer image of read alignments from ExpansionHunter for *TBP*.

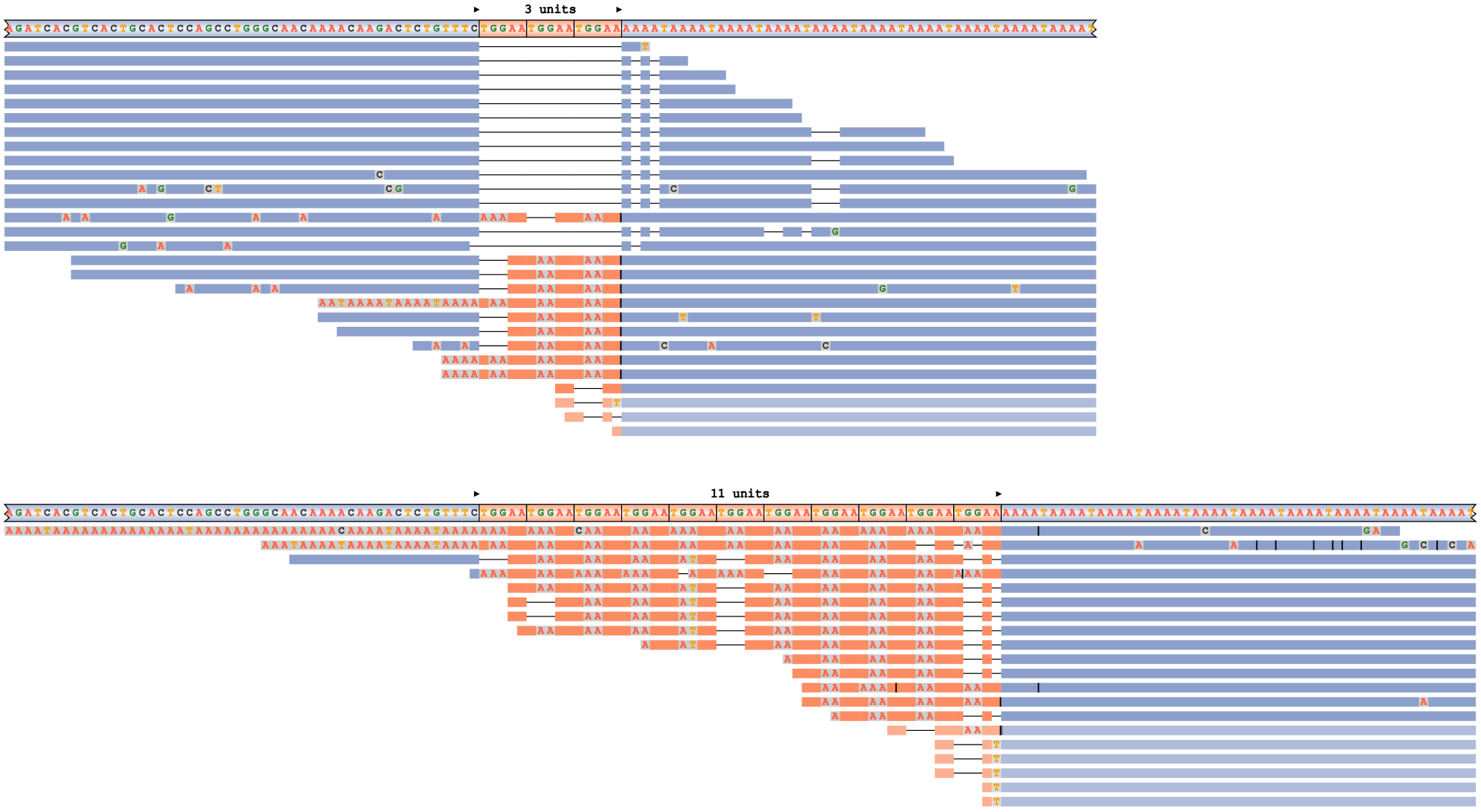

Fig. S14: Representative REViewer image of read alignments from ExpansionHunter for *BEAN*.

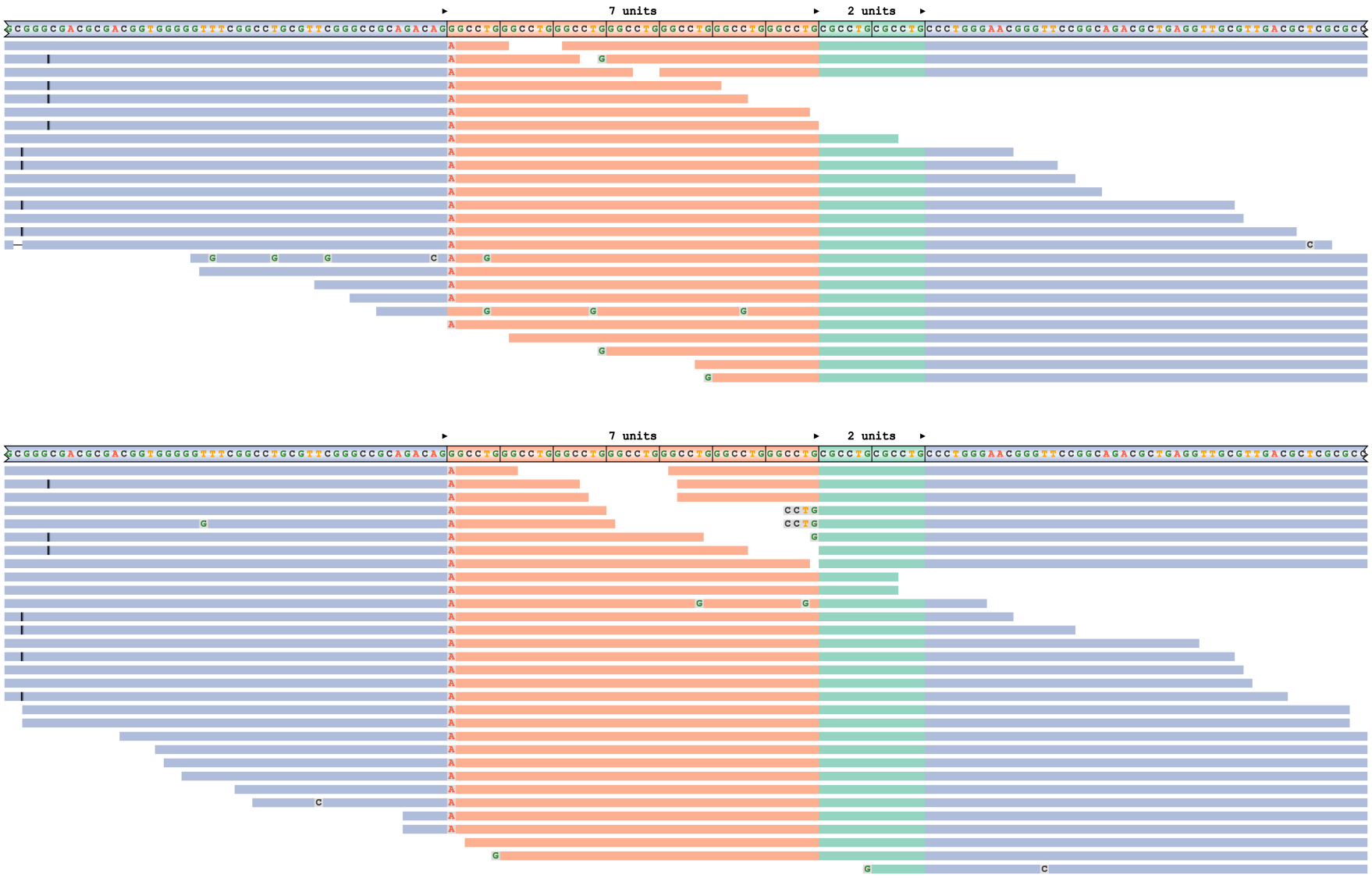

Fig. S15: Representative REViewer image of read alignments from ExpansionHunter for *NOP56*.

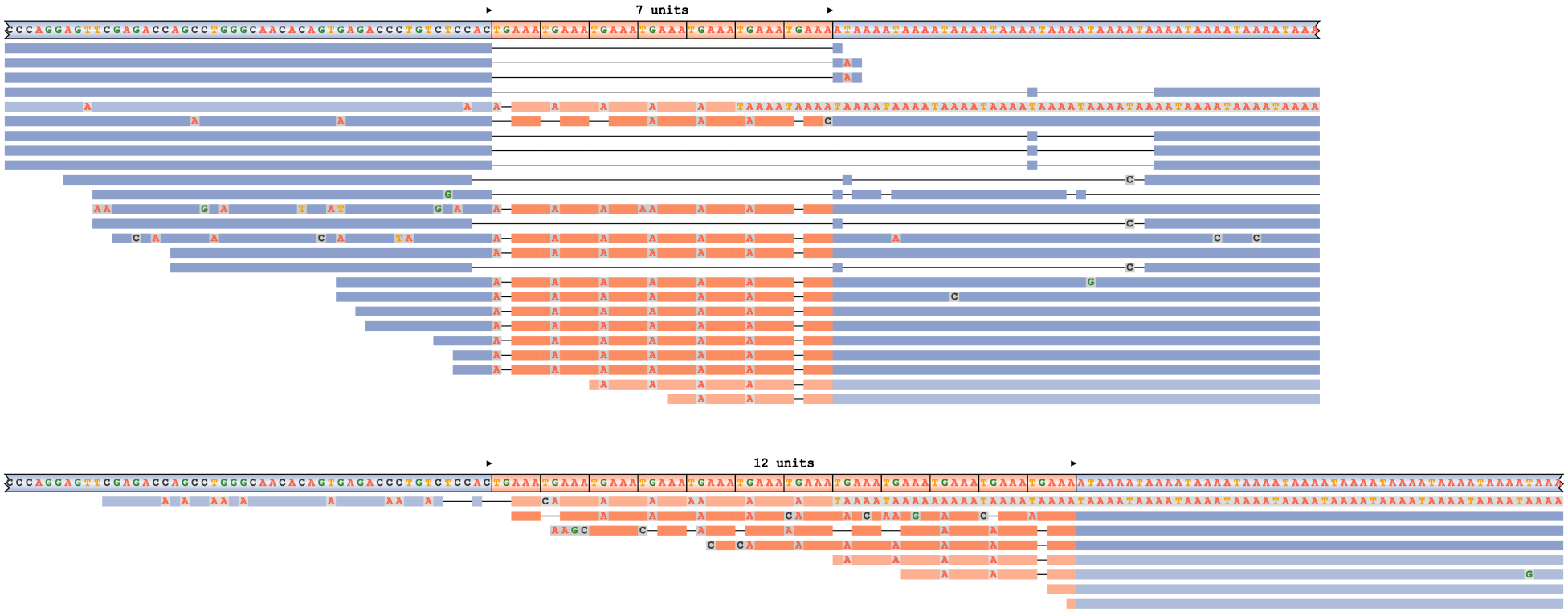

Fig. S16: Representative REViewer image of read alignments from ExpansionHunter for *DAB1*.

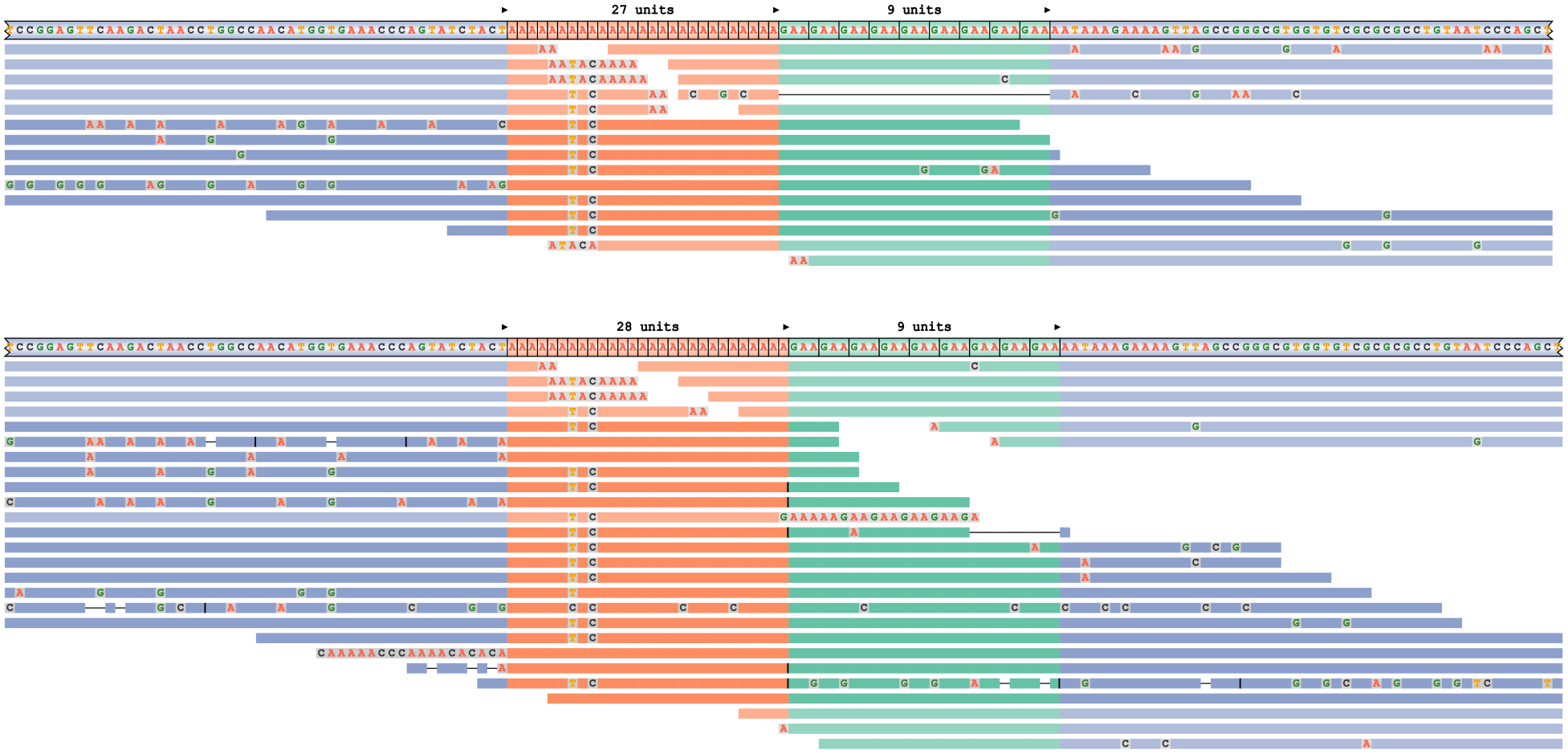

Fig. S17: Representative REViewer image of read alignments from ExpansionHunter for *FXN*.

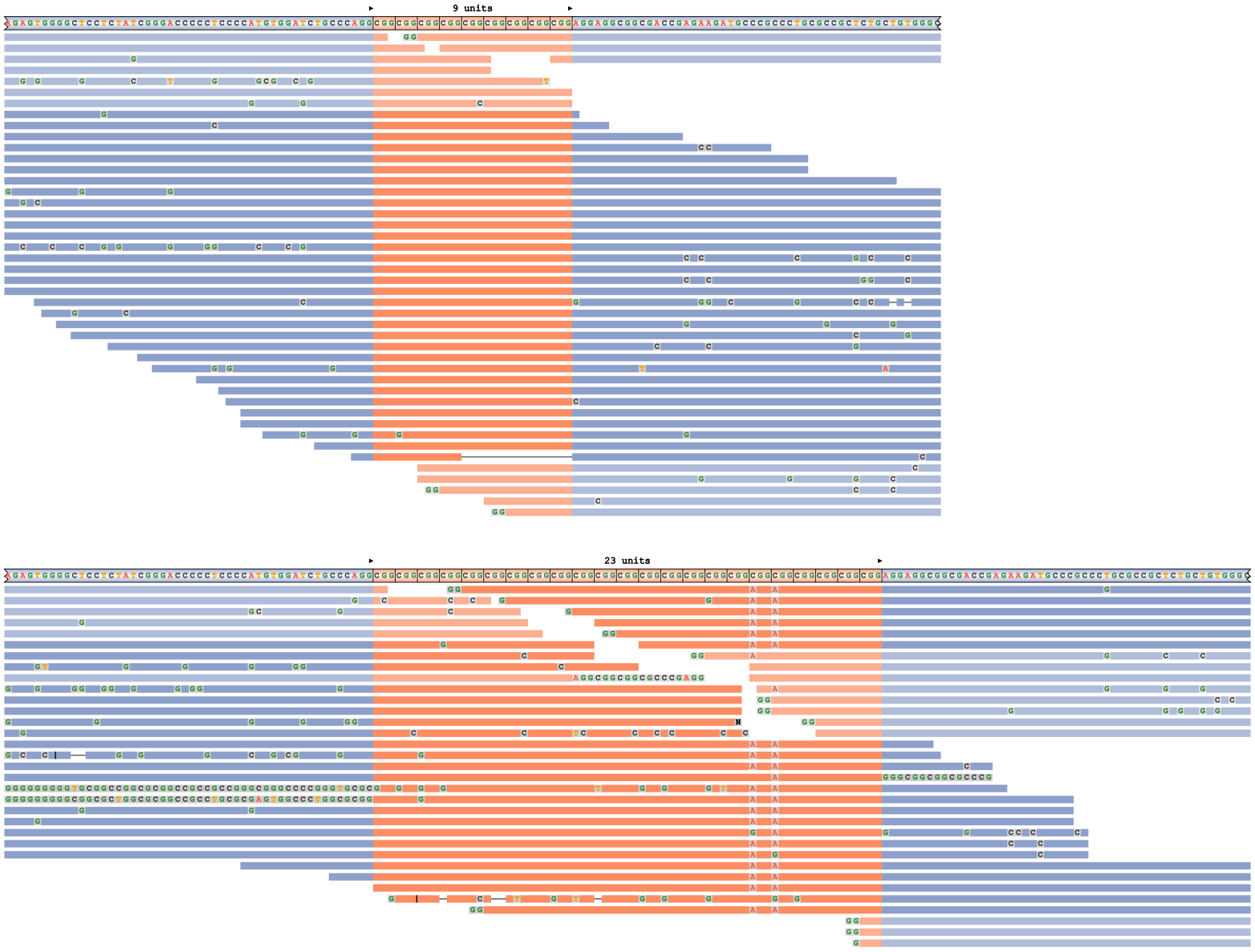

Fig. S18: Representative REViewer image of read alignments from ExpansionHunter for *NOTCH2NLC*.

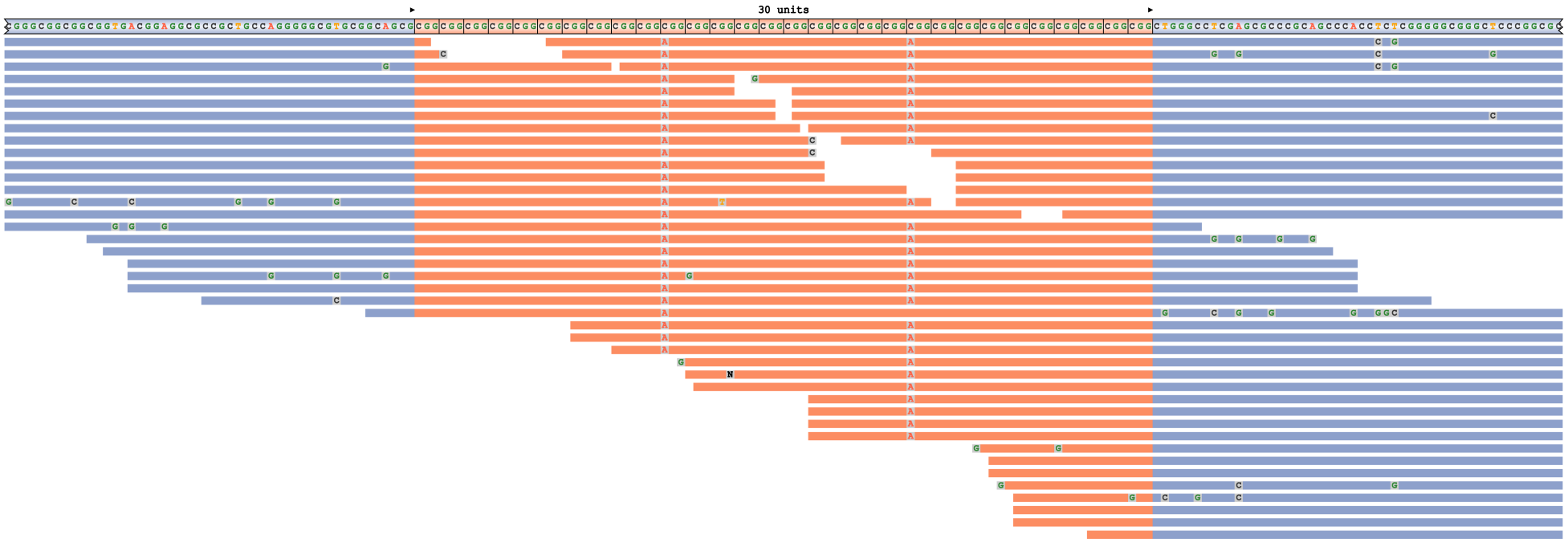

Fig. S19: Representative REViewer image of read alignments from ExpansionHunter for *FMR1*.

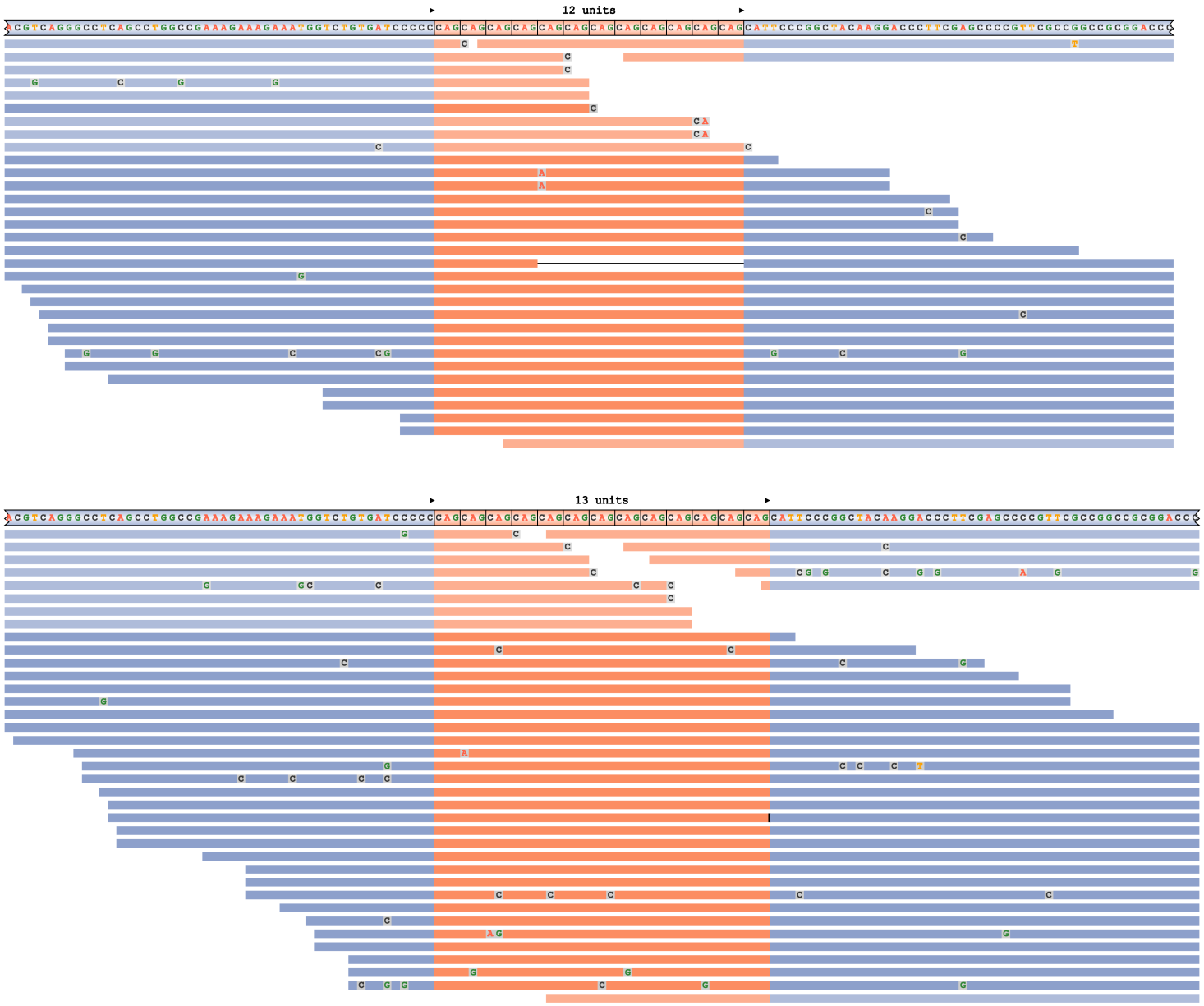

Fig. S20: Representative REViewer image of read alignments from ExpansionHunter for *DMPK*.

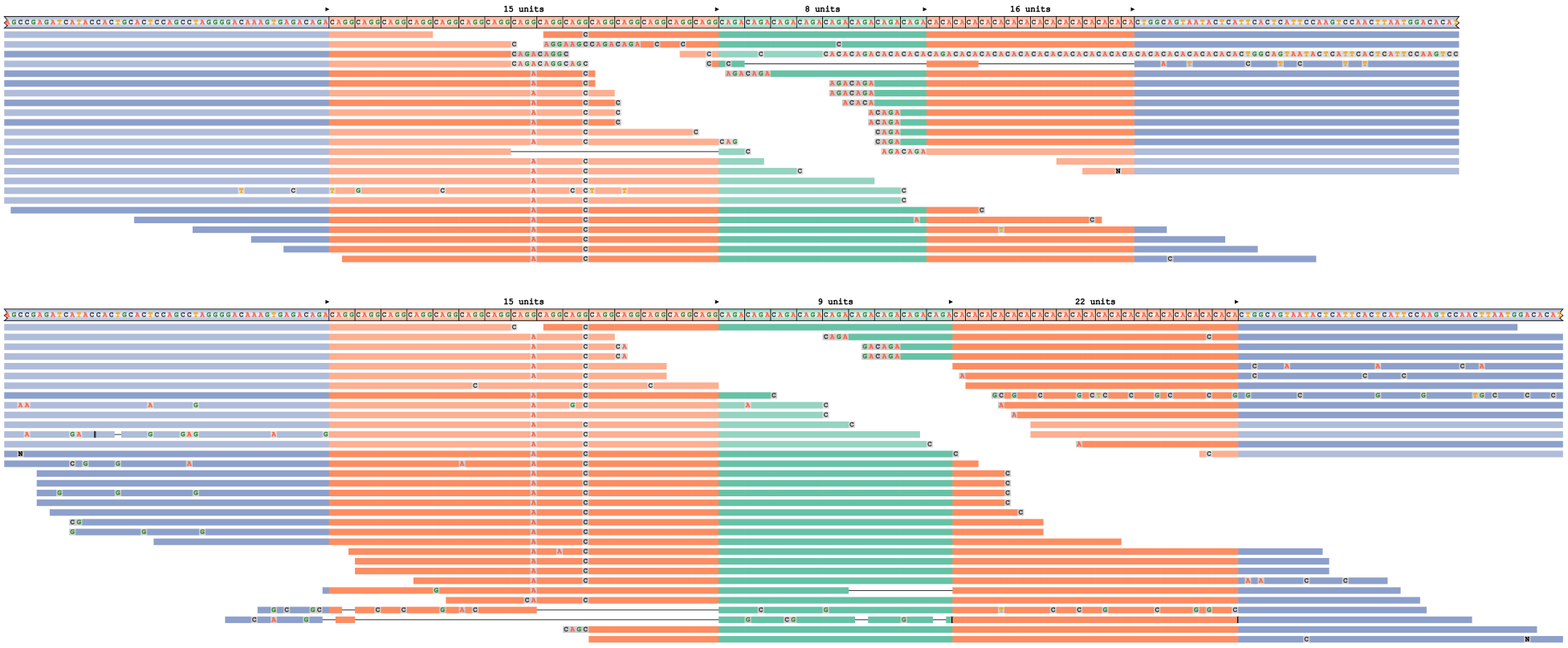

Fig. S21: Representative REViewer image of read alignments from ExpansionHunter for *CNBP*.

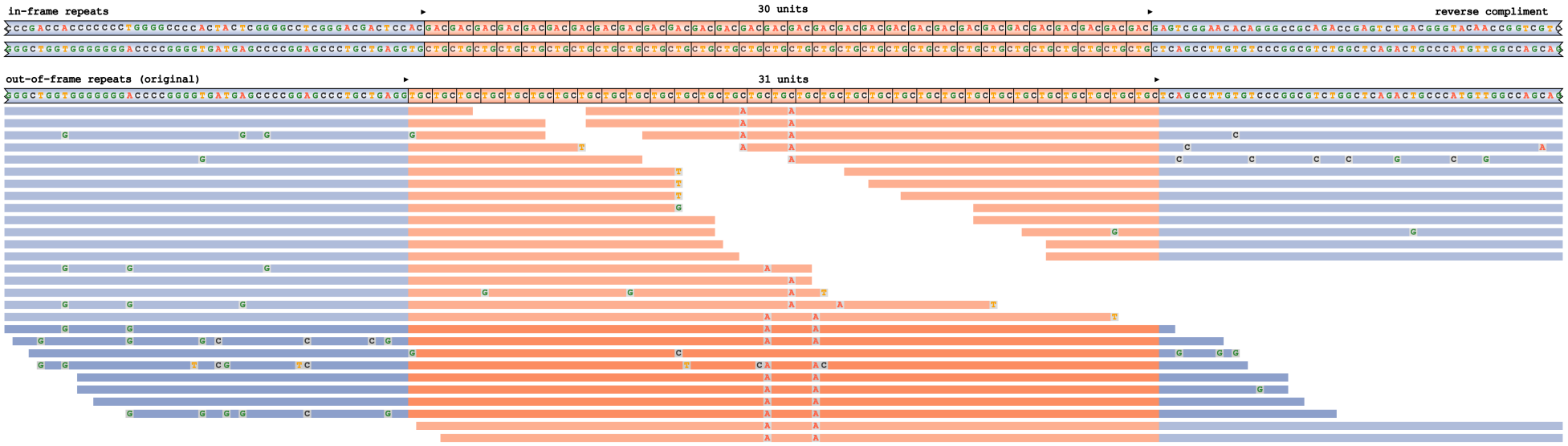

Fig. S22: Read alignments over the *ATXN1* STR locus in one sample using REViewer. ExpansionHunter called 31 repeat units over this locus, however the repeat boundaries are out-of-frame leading to the false inclusion of an additional codon in the length estimate. The in-frame repeat boundaries are displayed in the top reference sequence (forward and reverse complement provided). The corrected repeat length for this example is 30 repeat units; one repeat unit shorter than the length estimated by ExpansionHunter. This correction applies to all patients and control participants.

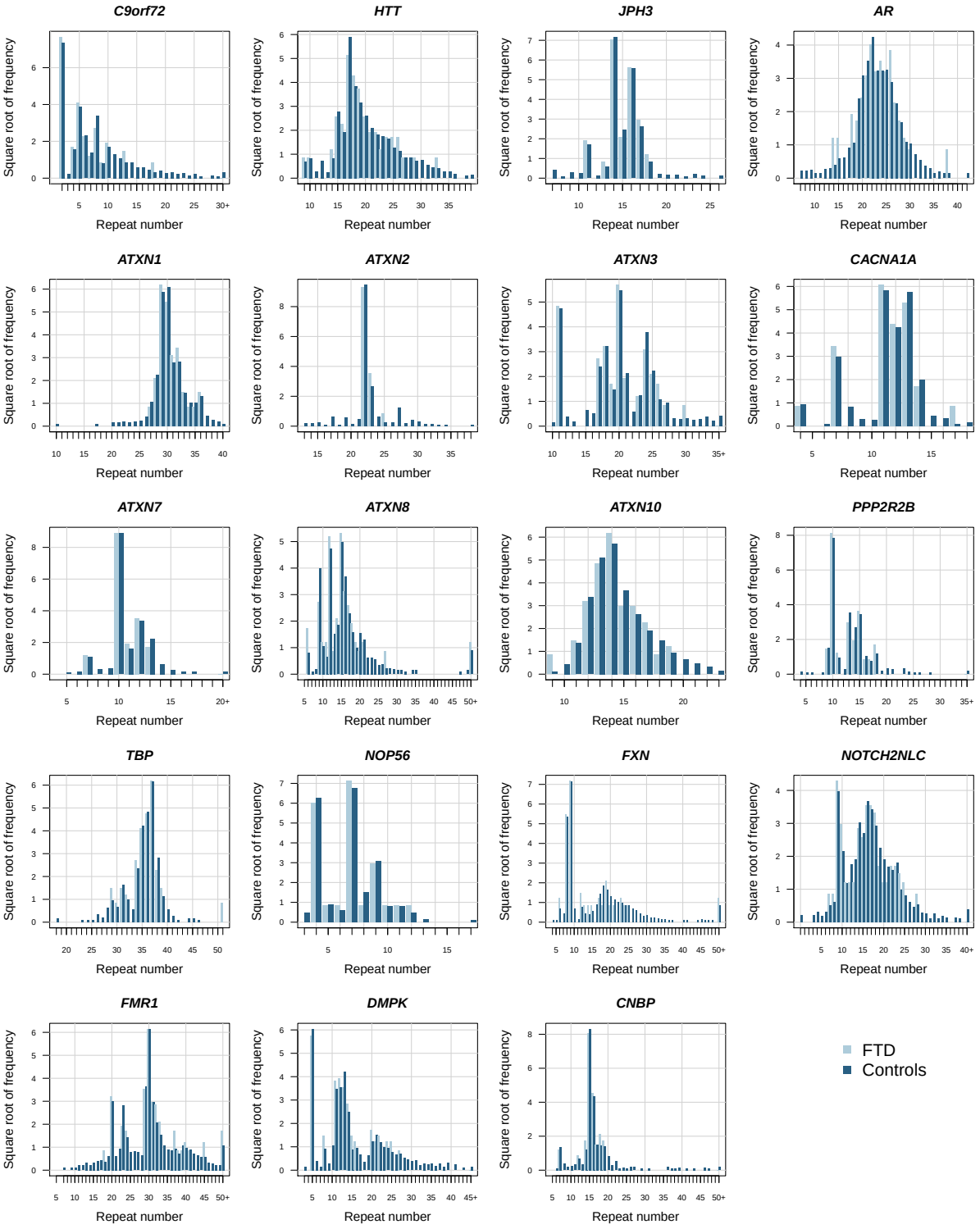

Fig. S23: ExpansionHunter STR length frequency distributions in 68 sFTD patients and 4,703 control participants for 19 neurodegenerative disease loci. The y-axis is the square root of the total number of alleles for each repeat length to allow better depiction of frequency variations.

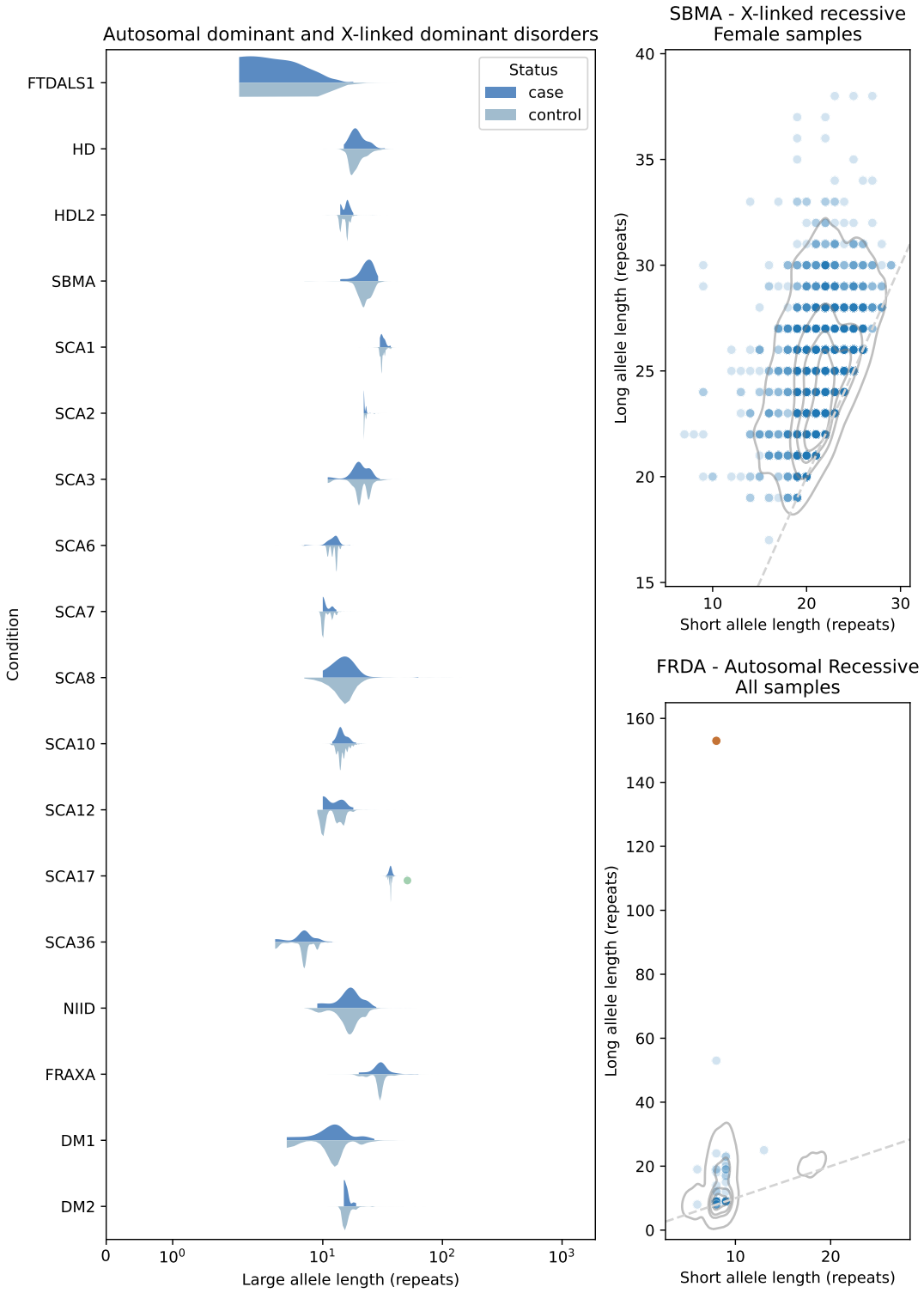

Fig. S24: Outlier alleles in 68 sFTD patients using 99.9th percentile data-derived thresholds. Distributions of repeat lengths in sFTD patients (dark blue) and controls (light blue) are shown for diseases inherited in a dominant pattern (either autosomal dominant, X-linked dominant, or male carriers of X-linked recessive STRs). Two recessive disorders (spinal-bulbar muscular atrophy (SBMA), an X-linked STR; and Friedreich's ataxia (FRDA), an autosomal recessive STR) are shown in scatter plots of patient allele lengths with control distributions rendered as contours at the quartiles of the distribution. Allele lengths detected as outliers in sFTD patients are indicated by green points. For recessive disorders, patients with only one allele detected as an outlier are indicated by orange points (i.e. carriers).

Supplementary Tables

Disease	Disease ID	Inheritance	Gene	Location (GRCh38)	Gene region	Motif	Intermediate lower bound	Pathogenic lower bound	Reference
Amyotrophic lateral sclerosis/ Frontotemporal dementia	FTDALS1	AD	*C9orf72*	chr9:27573485-27573546	intron	GGCCCC	NA	30	(14)
Huntington disease	HD	AD	*HTT*	chr4:3074877-3074940	coding	CAG	36	40	(64)
Huntington disease-like 2	HDL2	AD	*JPH3*	chr16:87604283-87604329	3'UTR	CTG	29	42	(65, 66)
Kennedy disease	SBMA	XLR	*AR*	chrX:67545317-67545419	coding	CAG	37	38	(67)
Spinocerebellar ataxia 1	SCA1	AD	*ATXN1*	chr6:16327634-16327724	coding	CAG	33	39	(38)
Spinocerebellar ataxia 2	SCA2	AD	*ATXN2*	chr12:111598950-111599019	coding	CAG	29	34	(68)
Spinocerebellar ataxia 3\ Machado-Joseph disease	SCA3/MJD	AD	*ATXN3*	chr14:92071011-92071052	coding	CAG	45	61	(69)
Spinocerebellar ataxia 6	SCA6	AD	*CACNA1A*	chr19:13207859-13207898	coding	CAG	19	20	(35)
Spinocerebellar ataxia 7	SCA7	AD	*ATXN7*	chr3:63912685-63912716	coding	CAG	36	37	(70)
Spinocerebellar ataxia 8	SCA8	AD	*ATXN8*	chr13:70139384-70139429	coding	CAG	51	80	(71)
Spinocerebellar ataxia 10	SCA10	AD	*ATXN10*	chr22:45795355-45795424	intron	ATTCT	30	400	(66)
Spinocerebellar ataxia 12	SCA12	AD	*PPP2R2B*	chr5:146878728-146878759	5'UTR	CAG	33	51	(65, 66)
Spinocerebellar ataxia 17	SCA17	AD	*TBP*	chr6:170561907-170562017	coding	CAG	43	47	(72)
Spinocerebellar ataxia 31	SCA31	AD	*BEAN*	chr16:66490396-66490399	intron	TGGAA	NA	110	(73)
Spinocerebellar ataxia 36	SCA36	AD	*NOP56*	chr20:2652733-2652775	intron	GGCCTG	15	650	(66)
Spinocerebellar ataxia 37	SCA37	AD	*DAB1*	chr1:57367043-57367046	intron	TGAAA	NA	31	(74)
Friedreich ataxia	FRDA	AR	*FXN*	chr9:69037285-69037304	intron	GAA	41	70	(75)
Neuronal intranuclear inclusion disease	NIID	AD	*NOTCH2NLC*	chr1:149390804-149390831	5'UTR	CGG	44	60	(76)
Fragile-X site A/ Fragile X-associated tremor ataxia syndrome	FRAXA/FXTAS	XLD	*FMR1*	chrX:147912037-147912111	5'UTR	CGG	55	200	(77)
Myotonic dystrophy 1	DM1	AD	*DMPK*	chr19:45770205-45770266	3'UTR	CTG	38	50	(46)
Myotonic dystrophy 2	DM2	AD	*CNBP*	chr3:129172577-129172659	intron	CAGG	27	75	(78)

Table S1: Description of 21 STR expansions screened using ExpansionHunter v4. AD = autosomal dominant, AR = autosomal recessive, XLD = X-linked dominant, XLR = X-linked recessive.

Genes included for comparison	ExpansionHunter v4 frequencies				PCR validation frequencies	
	Control		sALS and sFTD		sALS and sFTD	
	n	%*	n	%*	n	%*
All genes	766	16.29	157	23.22	150	22.19
C9orf72 excluded	758	16.12	125	18.49	119	17.6

Table S2: Total number of sALS, sFTD and control participants with intermediate and pathogenic STR expansions.
* Percentages are calculated assuming 4,703 control participants and 676 ALS/FTD patients.

Gene	PCR type	Primer	Sequence 5' >3'	PCR reaction	Thermocycler protocol
ATXN1	Standard	Forward	[HEX]CAACATGGGCAGTCTGAG	1X MyTaq HS Mix (Bioline), 0.4 µM F primer, 0.4 µM R primer, 20 ng gDNA	95° C for 2 min (1 cycle) 95° C for 30 sec, 60° C for 30 sec, 72° C for 30 sec (35 cycles) 72° C for 5 min (1 cycle)
		Reverse	AGAACTGGAAATGTGGACGTAC		
ATNX2	Standard	Forward	[6-FAM]GGGCCCCTCACCATGTCG	1X MyFi Mix (Bioline), 0.4 µM F primer, 0.4 µM R primer, 20 ng gDNA	95° C for 2 min (1 cycle) 95° C for 30 sec, 60° C for 30 sec, 72° C for 30 sec (35 cycles) 72° C for 5 min (1 cycle)
		Reverse	CGGGCTTGCGGACATTGG		
TBP	Standard	Forward	[HEX]CCTTATGGCACTGGACTGAC	1X MyTaq HS Mix (Bioline), 0.4 µM F primer, 0.4 µM R primer, 20 ng gDNA	95° C for 2 min (1 cycle) 95° C for 30 sec, 60° C for 30 sec, 72° C for 30 sec (35 cycles) 72° C for 5 min (1 cycle)
		Reverse	GTTCCCTGTGTTGCCTGCTG		
DMPK	Standard	Forward	[HEX]GAAGGGTCCTTGTAGCCGGGA	1X MyTaq HS Mix (Bioline), 0.4 µM F primer, 0.4 µM R primer, 20 ng gDNA	95° C for 2 min (1 cycle) 95° C for 30 sec, 60° C for 30 sec, 72° C for 30 sec (35 cycles) 72° C for 5 min (1 cycle)
		Reverse	GGAGGATGGAACACGGACGG		
CNBP	RP-PCR	Forward	[6-FAM]GCCTAGGGGACAAAGTGAGA	1X Phusion Flash High-Fidelity PCR Master Mix (Thermo Fisher Scientific), 1M Betaine (Sigma Aldrich), 0.2 µM F primer, 0.3 µM A primer, 0.1 µM R primer, 50 ng DNA	98° C for 3 min (1 cycle) 98° C for 10 sec, 60° C for 10 sec, 72° C for 20 sec (35 cycles) 72° C for 5 min (1 cycle)
		Anchor	AGCGGATAACAATTTCACACAGGA		
		Reverse	AGCGGATAACAATTTCACACAGGAC CTGCCTGCCTGCCTGCCTG		
C9orf72	RP-PCR	Forward	[6-FAM]AGTCGCTAGAGGCGAAAGC	1X MyTaq HS Mix (Bioline), 0.2 mM 7-deaza dGTP (NEB), 1 M Betaine (Sigma Aldrich), 7% (v/v) DMSO (Sigma Aldrich), 1.4 µM F primer, 1.4 µM A primer, 0.7 µM R primer, 50 ng gDNA	95° C for 10 min (1 cycle) 95° C for 30 sec, 70° C* for 45 sec, 72° C for 3 min (8 cycles) 95° C for 30 sec, 56° C for 45 sec, 72° C for 3 min (32 cycles)
		Anchor	TACGCATCCCAGTTTGAGACG		
		Reverse	TACGCATCCCAGTTTGAGACGGGGG CCGGGGCCGGGGCCGGGG		
NOTCH2NLC	RP-PCR	Forward	[6-FAM]GGCATTTGCGCCTGTGC	1.12 U Faststart Taq (Roche), 1X FST Buffer (Roche), 2 mM $MgCl_2$, 0.9 mM $MgCl_2$, 0.18 mM 7-deaza-dGTP, 0.2 mM dNTPs, 1 M Betaine, 7% DMSO, 1.4 µM F primer, 1.4 µM A primer, 0.7 µM R primer, 1000 ng gDNA	95° C for 10 min (1 cycle) 95° C for 30 sec, 70° C* for 45 sec, 72° C for 3 min (8 cycles) 95° C for 30 sec, 56° C for 45 sec, 72° C for 3 min (32 cycles) 72° C for 10 min (1 cycle)
		Anchor	CAGGAAACAGCTATGACC		
		Reverse	CAGGAAACAGCTATGACCTCCTCC GCCGCCGCCGCC		
	Standard	Forward	[6-FAM]ATTTGCGCCTGTGCTTC	4 U Faststart Taq (Roche), 1X FST Buffer (Roche), 2 mM $MgCl_2$, 0.16 mM dATP, 0.56 mM dCTP, 1.25 µM F primer, 1.25 µM R primer, 100 ng gDNA	95° C for 10 minutes (1 cycle) 95° C for 45 sec, 98° C for 10 sec, 58° C for 30 sec, 78° C* for 6 minutes (35 cycles) 72° C for 10 minutes (1 cycle)
		Reverse	TCAGCCCGATACTCACCATGC		
ATXN8	Available from authors on request				

Table S3: PCR primers and conditions used to validate ExpansionHunter determined short tandem repeat sizes.
* Touchdown cycle from 70 - 56°C in 2°C increments. RP-PCR, repeat-primed PCR.

Supplementary Text: Clinical Data

Historical clinical and available post-mortem neurology records for 17 sALS patients and 2 sFTD patients with intermediate or pathogenic expansions in *ATXN8* (SCA8, n=8), *TBP* (SCA17, n=1), *HTT* (HD, n=2), *DMPK* (DM1, n=1), *CNBP* (DM2, n=3) and *FMR1* (FRAXA/FXTAS, n=4).

SALS1 (SCA8 pathogenic + *C9orf72* pathogenic)

Diagnosis of ALS was at age 54 in this patient after first noticing weakness in his right arm at age 51. No family history of ALS or dementia was reported, however his mother died of kidney failure in her 40s, his father died of an acute myocardial infarction at 58 and there was no knowledge of the grandparents. This patient was a heavy smoker and had been diagnosed with diabetes at age 45. At presentation at the clinic, aged 54, he reported a gradual progression of weakness to both arms over a three-year period and was aware of the current fasciculations in his arms and shoulders. He had no lower limb symptoms. Upon examination, his mental state and speech were normal. There was no definitive fasciculations in the tongue, nor evidence of weakness of the face or cervical musculature. He had widespread fasciculations affecting the shoulder girdle and quadriceps. Ankle clonus was sustained in both ankles. He displayed moderate to severe weakness in the upper limbs and fine finger movements were poor. All tendon jerks in the limbs were brisk and his gait was stiff. EMG showed widespread fasciculation and evidence of acute and chronic denervation and motor axon loss in the upper and lower limbs. MRI showed cervical disk degeneration. This patient died at age 55.

SCA8 PCR genotype: $105|25$

SALS2 (SCA8 pathogenic)

This patient was diagnosed with MND at age 46, seven months after first symptom onset. Upon presentation at the clinic, he reported a 6-week history of slurred speech and mild numbness of the right side of the face around the mouth. No fasciculations or bulbar signs were evident. His parents died in their late 80s and early 90s respectively and no family history of motor neuron disease or ataxia was reported. A CT scan and MRI scan of the brain were normal. He deteriorated rapidly in 6 months, with progressive slurred speech, trouble swallowing, weakness in his right arm and hand and generalised muscle twitching. Upon assessment, he displayed widespread fasciculation in the upper limbs and tongue. His deep tendon reflexes in the upper limb were very brisk and an EMG examination revealed denervation in upper right limb.

SCA8 PCR genotype: $> 100|25$

SALS3 (SCA8 pathogenic)

This patient was diagnosed with MND at age 60 following an 8-month progressive weakness of upper limbs and a 5-month progressive weakness of the lower limbs. Five months after first symptom onset, an EMG showed denervation in left upper limb with fasciculations in biceps. MRI scan showed a normal spinal cord and small protrusions of three cervical intervertebral discs. A second EMG two weeks later detected lower limb involvement. Upon examination post-diagnosis, he had widespread fasciculation in upper limbs, trunk, and lower limbs. Tendon reflexes in limbs were brisk. He displayed prominent wasting in the dorsal interossei and was severely weak in the upper limbs. This patient died at age 62.5. There was no family history of neurological disease.

SCA8 PCR genotype: $80|24$

SALS4 (SCA8 pathogenic)

This patient was diagnosed with MND at age 47. There was no family history of MND, however his father was reported to have progressive supranuclear palsy (PSP). This patient reported first symptoms as weakness in his left upper limb at age 45. He initially presented at the clinic with left arm pain and paraesthesia into the thumb, index, and middle finger. Fasciculations were evident in his left arm with weakness of the triceps, finger extensors and bicep reflex. 18 months after initial clinic visit, he had a progressive weakness and wasting in the left arm and hand with fasciculations in the right deltoid and trapezius muscles. Reflexes were brisk normal and cervical MRI scan was normal. Widespread denervation in the left upper limb was confirmed by EMG.

SCA8 PCR genotype: $97|25$

SALS5 (SCA8 pathogenic)

In 2012 at the age of 43, this right-handed Australian woman was diagnosed with lower limb onset of amyotrophic lateral sclerosis with a four-month history of recurrent falls. There was not family history of neurological disease, her father dying from mesothelioma at 74 years, and her mother alive and well. The patient had two sisters and a twin brother who were all well. She had a past history of migraine. She had reduced exercise tolerance, and a history of increased cramps in her upper and lower limbs. Physical examination was concordant with lower limb onset of ALS with a combination of upper and lower motor neurone abnormalities. MRI scans of her brain and spinal cord were normal. Neurophysiology revealed widespread denervation and reinnervation confirming the clinical diagnosis of ALS. There were no cerebellar features. In particular, eye movements were normal with no evidence of nystagmus. There was no dysarthria on presentation and no cerebellar features. She was commenced on Riluzole, and participated in an experimental trial for ALS with the antiretroviral therapy (Triumeq) that was withdrawn within a month due to intolerance.

The patient progressed with evolution of pyramidal weakness in upper and lower limbs, with normal bulbar function. Over the next four years her weakness and disability progressed requiring increased supportive care and assistive and adaptive devices. Following the development of nocturnal hypoventilation due to sleep disordered breathing, non-invasive ventilation was commenced in December 2016. Intercurrent problems developed including contact dermatitis and recurrent low-grade temperatures unexplained by infections. Colchicine was introduced with effect to control elevated temperatures. In June 2018 with deterioration of respiratory function, the patient transitioned from non-invasive ventilation to tracheostomy and mandatory ventilation without which she would have succumbed. She remains alive at time of clinical summary with extensive support and mandatory ventilation. She has flickers of voluntary movement in all four limbs. Her eye movements remain normal. She communicates via Neuronode TrilogyTM with normal language, syntax and grammar.

SCA8 PCR genotype: $> 100|25$

SALS6 (SCA8 pathogenic)

This 70-year-old right-handed Sicilian builder was diagnosed with upper limb onset of amyotrophic lateral sclerosis in May 2015. There was no family history of neurological disease, specifically motor neuron disease. Intercurrently he was on therapy for gastroesophageal reflux and elevated cholesterol. He has a remote history of follicular non-Hodgkin's lymphoma treated with oral chemotherapy in 2001. In December of 2014 the patient developed weakness and wasting in his right upper limb and was found to have fasciculation together with upper and lower motor neuron features in his right upper limb. Neurophysiology demonstrated widespread

evidence of denervation and reinnervation and MRI scans of the cervical spine and brain were normal. At diagnosis he had evidence of involvement of both upper limbs with widespread fasciculation in the lower limbs as well. At diagnosis there was dyspnoea on exertion with no disturbance of speech or swallowing. There was no cognitive involvement. At time of diagnosis there was a moderate asymmetrical pyramidal weakness on the right compared to the left. The cranial nerves were normal. Eye movements were normal without nystagmus. Speech was normal. Hyperreflexia and extensor plantar responses were elicited.

The patient was commenced on Riluzole 50mg and with identification of nocturnal hypoventilation was commenced on non-invasive ventilation with symptomatic improvement. There was progressive clinical deterioration despite all supportive measures. Progressive respiratory failure and limb weakness lead to death of the patient in March 2017, 22 months following diagnosis and 28 months after symptom onset. During the progression of the disease, cognition was intact and there were no extrapyramidal or cerebellar features.

SCA8 PCR genotype: $> 100|24$

SALS7 (SCA8 intermediate)

This patient was diagnosed with MND at age 56. She presented at the clinic with persistent left hand and leg weakness over a three-month period, which had progressed to a significant slowing of her walking. She had no symptoms on her right side, nor speech or swallowing symptoms. She had no relevant family history except for an aunt with Parkinson's Disease. On examination, she had mild weakness and wasting in her left hand, but no fasciculations. Tone was increased in both legs, but there was no clonus, and she walked with a foot drop gait. Her reflexes were on the brisker side of normal. Nerve conduction studies showed motor responses were all at the lower limit of normal or reduced. A subsequent EMG showed evidence of acute and chronic denervation in the left upper and lower limb. Four months after her first clinic visit, she had progressively worsened. Her left-side weakness had increased and there was now a subtle weakness on her right side. She had noticed difficulty eating. Her tongue was not wasted but there were mild fasciculations and slow tongue movements. She now walked with a mildly spastic gait. At end-stage of disease, she had dysarthric speech, difficulty swallowing liquids and solids and was required to have a PEG inserted. She died at age 57.5, seventeen months after first symptom onset.

SCA8 PCR genotype: $78|24$

FTD1 (SCA17 intermediate)

This patient was diagnosed with semantic dementia at the Frontier FTD clinic at age 59. She reported difficulties with short term memory starting four to five years previously, followed by a deterioration in language skills, and behaviour/personality changes. She had a history of alcohol dependence, in remission for several months, gambling problems, which had recently relapsed, and was being treated for depression. No family history of dementia or ataxia was reported. MRIs revealed severe temporal atrophy bilaterally, with worse atrophy on the right side, moderate bilateral subcortical and periventricular white matter changes, and minor small vessel changes. At her last follow up at age 60, a further decline in memory, fluency and language was observed, although MRI revealed no significant further increase in brain atrophy.

SCA17 PCR genotype: $44|36$

FTD2 (SCA8 intermediate)

This patient was initially diagnosed with behavioural variant FTD at the Frontier FTD clinic at age 62. He had started wearing hearing aids, and had been assessed for short term memory

dysfunction, six years previously. Both of his parents had died in their sixties from cancer, and no family history of dementia or ataxia was reported. At age 62 he was reported to have ongoing problems with memory and to be confused, unable to learn new procedures, to have difficulty following simple instructions, and altered judgement. A cerebral perfusion scan performed earlier in the year showed mild to moderate reduction in the temporal cortices and equivocal reduction in the left frontal cortex. On assessment, he showed abnormal affect and very marked apathy with problems of initiation. He made repetitive sighing sounds but very little conversation and a tendency towards echolalia. His appetite was increased towards sweet food. No formal language deficits were observed, although there was a marked reduction in verbal fluency. He showed some facial akinesia, eye movements full range but with slow saccades, abnormal gait, some rigidity and bradykinesia and mild postural instability. MRI revealed a mild degree of frontal atrophy affecting interhemispheric and dorsal lateral regions, with ventricular enlargement, but no cerebellar abnormalities. He was initially diagnosed with behavioural variant FTD, but upon a subsequent clinic visit at age 63 this was changed to a diagnosis of progressive supranuclear palsy (PSP). His speech now showed loss of prosody, was strained and had an explosive quality. He exhibited orobuccal and mild limb apraxia. Gait had become more prominently disturbed and unsteady, and vertical eye movements were markedly reduced. At age 64 his balance had become more problematic and he required a walker for mobility. At age 65 he had become wheelchair bound, with prominent hypomimia and sialorrhoea, increased echolalia and perseveration. Eye movements were significantly limited and his vision was blurred. His speech was increasingly hypotonic and slurred and he choked on swallowing liquids. MRI revealed symmetric cortical and subcortical atrophy, with some suggestion of brainstem/midbrain atrophy, but no significant abnormality seen in the cerebellum. He died at age 67, and received a neuropathological diagnosis of FTLD-tau PSP, with aging-related tau astrogliopathy in the amygdala and incidental capillary telangiectasia in the right entorhinal cortex.

SCA8 PCR genotype: $73|24$

SALS8 (HD intermediate)

This patient was diagnosed with MND at age 77. There was no reported family history of MND, however, the patient had no knowledge of paternal family history except for her father. Her father died at age 94 and mother died at age 65. She presented at the clinic with progressive speech and swallowing difficulties for about 7 months. Upon examination, her speech was dysarthric and dysphonic. Her gag jerk was exaggerated and jaw jerk intact. Mild weakness of right hip flexors and dorsiflexors of the right ankle, but power in other limbs was normal. Limb reflexes were brisk. The MRI of her brain was normal. Nerve conduction studies/EMG showed evidence of denervation confined to right tibialis anterior, with fasciculations present in right gastrocnemius, left tibialis anterior and right biceps. Two months later she had evidence of a bulbar and pseudobulbar palsy, and mild to moderate weakness in her right leg. This patient had a rapid disease progression, requiring a PEG to be inserted six months after diagnosis. She died at age 78, 22 months after first symptom onset.

HD PCR genotype: $38|19$

SALS9 (HD intermediate)

This patient was diagnosed with MND at age 62. His medical history included depression, ischaemic heart disease, right carpal tunnel release, Barrett's oesophagus, and 15 years of significant arthritic changes in the cervical region of his spine. There was no relevant family history reported. Mother had dementia and died at 57 from CVA, father died at 62. At age 61, He presented with a 6-month history of gradual progressive limp in his right leg and problems with

balance. In the upper limbs, he had occasional numbness of his right middle finger. Upon examination he had increased tone of the legs, but no clonus, nor muscle wasting. He had minor weakness of the right leg, all reflexes were brisk, and he had a spastic gait. One month later, he had further deteriorated. Fasciculations were evident in both thighs with occasional fasciculations in the right arm. No fasciculations were evident in the tongue. Nerve conduction studies were normal. EMG showed evidence of acute denervation in right upper and lower limb, confirming the diagnosis of MND.

HD PCR genotype: $36|15$

SALS10 (DM1 pathogenic)

This patient was diagnosed with progressive bulbar palsy (PBP) at age 54, after 12 months of a progressive dysarthria and more recent dysphagia. Patient was a heavy smoker for 15 years but had not smoked for 2 decades prior to symptom onset. He reported development of early cataracts which were removed 2 decades prior to symptom onset. The patient reported that his mother had frontal lobe dementia and Alzheimer's disease. There was no evidence of any wasting or fasciculations of the limbs, or reduction in limb strength. Two years following diagnosis of PBP, the patient had deteriorated significantly and was observed as weak and increasingly frail with breathing problems. He had cramps in muscles and painful spasms in right forearm flexors. His weight had been maintained through use of PEG feeding. Upon examination, there was bilateral facial weakness, bulbar palsy, and weakness in neck flexors and extensors. The patient had progressive right arm distal weakness with marked weakness of intrinsic hand muscles, yet reflexes were brisk. There was mild fasciculations in right brachioradialis but absence of widespread fasciculations.

DM1 PCR genotype: $81|5$

SALS11 (DM2 pathogenic + SCA2 intermediate + SCA1 intermediate)

This patient was diagnosed with MND at age 39. She was a heavy smoker for 26 years (20 cigarettes/day) with a medical history of severe anxiety and depression. She had developed bilateral carpal tunnel syndrome at age 31. At age 37, the patient reported increasing numbness and weakness in both hands. She had carpal tunnel surgery at age 37 and the surgery alleviated numbness but not the weakness. EMG confirmed a diagnosis of MND. Upon examination post-diagnosis, the patient had severe wasting of small muscles of hand but no obvious fasciculations. Tongue was weak with noticeable dysarthria and no significant jaw weakness. Her gait was slow and stiff. In lower limbs, there was weakness of hip flexors and knee flexors, left ankle dorsiflexion, and increased tone in both legs with pathological clonus.

DM2 repeat-primed PCR genotype (expanded allele): > 103

SALS12 (DM2 pathogenic)

This 69-year-old retired Austrian engineer was first seen in July 2011 referred for further care of his presentation with frontotemporal dementia and motor neuron disease. There was no contributory past medical or family history. There was not history of neuromuscular disease, his father dying from prostatic carcinoma at 71 and his mother dying in her 97 from age related causes. He had a sister and a brother in their 70s with no neuromuscular disease, together with two adult daughters, neither with neurological problems.

In 2007, he developed slurred speech and difficulty with controlling his mouth. Initial concerns regarding a stroke were excluded on neurological review and a normal MRI scan. In early 2008, he developed problems with his language. He had difficulty with executive thinking and higher order function, unable to discriminate left from right and following initially complex and

then simple instructions. Behavioural changes occurred, with aggression and paranoia. These issues continued throughout 2008 and into 2009. Diagnosed with behavioural variant of frontotemporal dementia he was found to have denervation and reinnervation on electromyography. His dysarthria progressed and then he developed problems with dysphagia, often gagging and coughing on relatively innocuous fluid and food losing 10 kilograms over the last year. He did not sleep well at night, going to bed and then getting up at midnight and watching the same video.

On examination he was well presented. He responded to questions appropriately. There was perseveration in his language. He had a strangled soft upper motor neurone dysarthria. His visual acuity was N6 corrected with normal fields and fundi. He had increased latency to saccade and multi-step saccade in horizontal and vertical planes. There was limited restriction of his vertical eye movements, corrected by fixation. He had a normal jaw jerk. His masseters and facial muscles were normal. There were no frontal release reflexes. He had problems with orobucco-facial dyspraxia. He had impaired rapid alternating movements of his tongue, with fasciculations evident. His palate moved in the midline. He had normal cervical flexion and extension. Tone was normal in his limbs. He had evidence of wasting in his right first dorsal interosseous and thenar eminence. Fasciculation was present in his deltoids and left triceps. His deep tendon reflexes were normal, without propagation. He had a mild degree of weakness in the intrinsic muscles in his right hand, but no weakness proximally. His respiratory muscles were normal. He had normal muscle bulk and power in his legs. His deep tendon reflexes were normal in the legs, with flexor plantar responses. There was no sensory abnormality. His stance, gait and balance are normal.

Over the next three and a half years the patient deteriorated with increased behavioural disturbance accompanied by increased bulbar dysfunction with dysarthria and dysphagia. At the time of death in January 2015, behavioural issues required antipsychotic therapy and institutional care to manage his impulse control. With increasing dysphagia leading to dehydration and weight loss, the patient was palliated in January 2015 at the age of 73 years and two months.

DM2 repeat-primed PCR genotype (expanded allele): > 80

SALS13 (DM2 intermediate + *C9orf72* pathogenic)

This patient was diagnosed with MND at age 57, presenting with a 6-month history of right wrist pain and decrease in muscle strength of right hand with worsening weaking in the left hand. Upon examination at time of diagnosis, gait and balance were normal. Right upper limb had wasting of intrinsic muscles, with less wasting in the left. Fasciculations were present in right deltoid, biceps, and triceps. Deep tendon reflexes were brisk. Her lower limb had no fasciculation or wasting, there was no tongue fasciculation or dysarthria. EMG showed both active and chronic denervation.

DM2 repeat-primed PCR genotype (expanded allele): > 47

SALS14 (FTXAS intermediate + FRAXA pathogenic + *C9orf72* pathogenic)

Pathology report for PCR validation of FMR1 expansion states that two signals for FMR1 were found; one expansion in the intermediate range (repeat number $= 71$) and one full-range expansion (repeat number >200). The possibility that this individual is mosaic for an undetected full mutation should be considered.

This patient was diagnosed with ALS at age 57, with no family history of anterior horn cell disease. First symptom onset was identified after a fall where injuries were sustained to the patient's right shoulder and right knee. An allied health professional was treating the patient's shoulder injury and observed fasciculations in his shoulder girdle. The patient's local doctor was treating his right leg problems and observed foot drop. Subsequent neurologist examination

identified wasting around the shoulder girdle and prominent fasciculations in deltoid, biceps, and triceps. Mild weakness was observed in his right hand and progressive weakness in right tibialis anterior. He had increased tone in right arm and right leg with non-sustained clonus at the right ankle. The patient had normal cognition, speech and language, and no disturbance of mood. Nerve conduction study/EMG showed evidence of widespread fasciculation and fibrillation. This patient had a rapid disease duration of 18 months and died at age 58. Post-mortem neuropathology reported a severe loss of both upper motor neurons in frontal motor cortex and spinal anterior horn motor neurons, loss of hypoglossal motor neurons, anterior spinal root atrophy and severe pyramidal tract atrophy, confirming the initial diagnosis of ALS. At time of death, C9orf72 had not yet been linked to ALS and as such, post-mortem assessment of dipeptide repeat pathology was not performed for this patient.

FRAXA PCR genotype: $> 200|71$

SALS15 (FRAXA intermediate + *SOD1* p.I114T)

This patient was diagnosed with MND at age 55. Although the patient was retrospectively found to carry a SOD1 p.I114T mutation, at time of presentation at the clinic there was no reported relevant family history of MND. Her father died at age 66, her mother was still alive at age 85 and her paternal grandfather was reported to have had Parkinson's Disease in late life. This patient presented with an 18-month history of leg cramps and her left foot had been weak, intermittently tingly, and numb for 12 months. Recent symptoms had included soreness and sharp pain in her hands and mild decline in memory and concentration. Upon examination, there were fasciculations in the thighs and anterior trunk. She had weakness in the left hand and left foot. Tendon reflexes are generally brisk. MRI of brain was essentially normal with tiny T2/FLAIR hyperintensities in the right frontal lobe. MRI of the spinal cord was normal with cervical degeneration and mild lumbar degeneration, but no spinal cord pathology. Nerve conduction studies were normal, but EMG showed evidence of denervation and fibrillations of both lower limbs and the left arm.

FRAXA PCR genotype: $63|30$

SALS16 (FRAXA intermediate)

This patient presented at age 72 with a 12- to 18-month history of progressive generalised weakness, left foot drop and physical signs consistent with MND. The combination of upper and lower motor neuron signs in the same limb, combined with EMG showing active and chronic denervation in all limbs confirmed a MND diagnosis. Examination showed reduced power in the lower limbs. He had significant hip girdle weakness and fasciculations in the quadriceps and shoulder girdle. His left ankle jerk was absent but reflexes normal.

FRAXA PCR genotype (hemizygous): 64

SALS17 (FRAXA intermediate)

This patient was diagnosed with MND at age 64, with a six-month history of walking difficulties. She presented at hospital with bilateral leg pain and weakness. MRI of the brain and spinal cord was mostly normal, with altered signal intensity in the left cerebellar hemisphere. EMG showed widespread chronic partial denervation in her weakest muscles. Three months post-diagnosis, she had deteriorated and had difficulty walking. She now had weakness of the left arm, and progressively worse bilateral lower limb weakness. All reflexes were exaggerated. Within 6 months of diagnosis, she was unable to walk and had lost function of her hands.

FRAXA PCR genotype: $73|35$

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