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Early-onset Alzheimer's disease versus frontotemporal dementia: resolution with genetic diagnoses?

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Abstract

We report a diagnostically challenging case of a 64-year-old man with a history of remote head trauma who developed mild behavioral changes and dyscalculia. He was diagnosed with clinical Alzheimer's disease, with additional features consistent with behavioral variant frontotemporal dementia. Structural MRI revealed atrophy in bilateral frontal and parietal cortices and hippocampi on visual inspection and left frontal pole and bilateral anterior temporal encephalomalacia, suspected to be due to head trauma. Consistent with a diagnosis of Alzheimer's pathology, positron emission tomography (PET) with Pittsburgh compound B suggested the presence of beta-amyloid. Fluorodeoxyglucose PET demonstrated hypometabolism in bilateral frontal and temporoparietal cortices. Voxel-based morphometry showed atrophy predominant in ventral frontal regions (bilateral orbitofrontal cortex, pregenual anterior cingulate/medial superior frontal gyrus), bilateral mid cingulate, bilateral lateral temporal cortex, and posterior insula. Bilateral caudate, thalamus, hippocampi and cerebellum were prominently atrophied. Unexpectedly, a pathologic hexanucleotide repeat expansion in *C9ORF72* was identified in this patient. This report underscores the clinical variability in *C9ORF72* expansion carriers and the need to consider mixed pathologies, particularly when imaging studies are inconsistent with a single syndrome or pathology.

Keywords

frontotemporal dementia; Alzheimer's disease

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Introduction

Since the discovery that the hexanucleotide expansion in *C9ORF72* is the most common cause of familial and sporadic frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) (Dejesus-Hernandez et al., 2011; Renton et al., 2011), clinical series have reported heterogeneous phenotypes associated with this mutation. Most often, *C9ORF72* presents as behavioral variant FTD (bvFTD) with or without comorbid motor neuron disease (MND) or ALS (Boeve et al., 2012; Murray et al., 2011; Sha et al., 2012; Simon-Sanchez et al., 2012; Snowden et al., 2012). Less commonly, *C9ORF72* carriers with semantic variant and non-fluent variant primary progressive aphasia (PPA) and Alzheimer's disease (AD) have been described (Majounie et al., 2012; Murray et al., 2011; Snowden et al., 2012).

Although *C9ORF72* mutations most often manifest as bvFTD and/or ALS, reports with limited clinical data have also identified the *C9ORF72* expansion in patients with clinically-defined AD. Harms and colleagues identified five *C9ORF72* expansion carriers in 872 patients with clinical AD (Harms et al., 2013). Three *C9ORF72* carriers harbored 1200 to 1300 repeats: two patients diagnosed with AD in their early seventies demonstrated a predominantly amnestic presentation, while the third patient diagnosed with AD at age 60 was reported to have memory and behavioral changes. One *C9ORF72* carrier in the series also had an autopsy study, which showed pathological evidence of AD, but histopathological studies were not performed for frontotemporal lobar degeneration (FTLD). Another study identified three *C9ORF72* carriers in 114 patients with early-onset AD whose CSF biomarker profiles were consistent with AD (Wallon et al., 2012). Although these three *C9ORF72* carriers were diagnosed with clinical AD, all had behavioral changes at follow up evaluations. A clinicopathological study showed four *C9ORF72* carriers with final clinical diagnoses of AD, all diagnosed with FTLD due to TDP (FTLD-TDP) at autopsy (Murray et al., 2011), suggesting that FTLD-TDP due to *C9ORF72* could present as clinical AD.

Several possibilities arise when considering patients with clinical AD harboring the *C9ORF72* expansion: 1) *C9ORF72*-related neurodegeneration manifests as clinical AD, 2) bvFTD is misdiagnosed as clinical AD, 3) both AD and FTLD pathology co-occur, and 4) AD pathology manifests as clinical AD and *C9ORF72*-related neurodegeneration has not yet emerged clinically. Because previous reports have provided limited clinical detail on *C9ORF72* carriers with clinical AD, we describe a patient with clinical AD and features of bvFTD, who presented as a diagnostic dilemma. We provide a comprehensive profile of this patient, including neuropsychological and social-emotional testing and neuroimaging analysis, to detail his unique confluence of AD and bvFTD features. The patient's clinical details were altered to obscure his identity.

Case report

A 64-year-old man developed progressive cognitive and behavioral changes starting 8 years prior to his first evaluation. His first symptom occurred when he was unable to identify a friend who called him on the telephone. Six years prior to evaluation, he began making calculation errors when dealing with financial matters.

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Five years before evaluation, he developed personality changes. He grew particularly agitated if others cut him in line or pushed past him on the sidewalk. About two years prior to evaluation, he grew emotionally labile, easily irritated and excitable, with bouts of uncontrollable laughter. Criticism readily triggered his anger. Collecting baseball cards was a lifetime hobby, and he became increasingly focused on this pursuit. He also began collecting trash. He became slightly more disinhibited, speaking more with strangers, but he was able to modulate this behavior with reminders. He developed a mild preference for sweet foods, but he did not gain weight.

Two years before evaluation, his sense of direction worsened. Around this time, he also had word-finding difficulties and asked the meaning of “umbrella” on one occasion. Comprehending multi-step instructions grew difficult. He developed memory problems six months before evaluation, often misplacing objects. He seemed more sensitive to pain. By the time of presentation, he was regularly repeating himself and had significant difficulty understanding complex instructions.

Significant past medical history included two head injuries with loss of consciousness, one resulting in a skull fracture occurring during his early twenties. Family history revealed that his mother developed language difficulties during her late sixties and died of dementia during her late seventies. A sibling had a history of depression and a suicide attempt.

On neurological examination, he repeated phrases several times. He was cooperative and appropriate; for example, he politely motioned for the examiner to enter through an open door first. He was distractible and stimulus-bound during testing with uncontrolled laughing spells. He was tangential and emotionally labile. Mood was euthymic, but he grew frustrated when he felt criticized. Orobuccal and limb apraxia were absent. He had a high frequency postural tremor in his upper extremities bilaterally, but the remainder of the neurological examination appeared normal.

Neuropsychological battery

Cognitive Testing

Mini-Mental State Examination was 15/30. Verbal and visual memory were significantly impaired, with both encoding and recognition affected. Visuospatial construction was impaired; he was unable to copy intersecting pentagons and the Benson figure accurately. Written calculations were significantly impaired. Abbreviated Boston naming test demonstrated difficulties in naming, 6 standard deviations (SD) below the mean for age, but semantic knowledge was intact. Executive functions were impaired, including attention (digit span forward was 2.4 SD below mean for age), interference (Stroop interference was 5.4 SD below mean for age) and set shifting (could not complete a modified Trail-making test). Working memory was impaired (digit span backward was 1.8 SD below mean for age). Verbal and design fluency were severely impaired.

In sum, he demonstrated deficits across multiple cognitive domains including verbal learning and memory, visuospatial function, calculations, naming, and executive function.

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Social-Emotional Testing

Social and emotional testing (Narvid et al., 2009) revealed severe impairments in complex social cognition, aspects of emotion and person perception, and severe self-conscious anxiety. Social semantic knowledge, empathic concern, and behavioral drive remained relatively preserved. During testing, self-conscious, mentally rigid, and perseverative behavior emerged, and he tended to lose task set (Social Behavior Observer Checklist).

Emotion Reading/Person-Perception Tasks: (Comprehensive Affective Testing System [CATS]; The Awareness of Social Interference Test [TASIT]; Dynamic Affect Recognition Test [DART]; Famous Faces [FF]). Emotion naming for both static pictures of faces (CATS Affect Matching: 10/16) and dynamic videos depicting emotions (TASIT Emotion Evaluation task: 4/14; DART: 7/12) were impaired. His ability to recognize sarcasm from a speaker's paralinguistic vocal and facial cues was impaired (TASIT Simple Sarcasm: 4/20). He performed poorly in naming famous individuals (FF: 4/16) despite his intact ability to discriminate facial features.

Complex Social Cognition Tasks: (TASIT; UCSF Cognitive Theory of Mind Task [UCSF ToM]; Interpersonal Reactivity Inventory [IRI]; Social Norms Questionnaire [SNQ]). He demonstrated mild reductions in social semantic knowledge, performing in the low average/normal range when asked to identify behaviors that would violate social norms (SNQ: 18/22). When social reasoning tasks included a cognitive dimension, however, his performance was severely impaired, as reflected in answering questions about others' knowledge in a video-based perspective taking task without an emotional element (UCSF Cognitive ToM: 14/24) and other videos depicting actors conveying complex insincere (sarcastic, deceptive) speech (TASIT Social Interference-Enriched [TASIT SI-E: 35/60). His wife described that he was generally unable to take others' perspectives in his real-life behavior (IRI Perspective Taking: 7/35).

Emotional Reactivity/Responsiveness: [Behavioral Inhibition/Behavioral Activation Scales; IRI] His scores revealed highly emotionally-reactive, self-critical, and self-conscious behavior, with normal drive and some preserved ability to respond empathically to others' emotions. According to his wife's report, he scored above the 99th percentile in both his tendency to behave in an anxious, self-conscious manner (BIS: 27/28) and reactive distress towards others' emotions (IRI-Personal Distress: 33/35). However, scores reflected that his drive towards reinforcing stimuli was in the high average normal range (BAS: 40/52), and his responsiveness to help others in a prosocial manner was in the low-average normal range (IRI-Empathic Concern: 25/35).

Neuroimaging

Structural MRI revealed atrophy in bilateral frontal and parietal cortices and hippocampi on visual inspection. Left frontal pole and bilateral anterior temporal encephalomalacia was seen on FLAIR (Figure 1).

A voxel-based morphometry (VBM) analysis compared the patient's T1 structural MRI scan at initial evaluation to a group of 30 healthy controls matched for age (mean 64.3, SD 2.9

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years), sex, handedness, and scanner type (See supplementary materials). VBM demonstrated atrophy in bilateral orbitofrontal cortex, pregenual anterior cingulate, medial superior frontal gyrus, bilateral mid cingulate, and bilateral posterior insula. Also, bilateral lateral temporal cortex, precuneus, caudate, medial pulvinar nucleus of the thalamus, hippocampi, and cerebellum were atrophied (Figure 2).

Positron Emission Tomography (PET) imaging with [^{18}F] fluorodeoxyglucose (FDG-PET) and beta-amyloid ligand [^{11}C]PiB (PIB-PET) was performed. FDG-PET showed hypometabolism in bilateral frontal and temporoparietal cortices and PIB-PET was diffusely positive for presence of amyloid (Figure 3) (See supplementary materials for methods).

Genetic testing

APOE genotype was E3/E4. *C9ORF72* testing performed with repeat-primed PCR revealed that he carried a pathologic hexanucleotide repeat expansion (Figure 4) (Dejesus-Hernandez et al., 2011). Repeat length was not available via this method. He tested negative for mutations in other known FTLD genes, including *GRN* (Baker et al., 2006), *MAPT* (Hutton et al., 1998), and AD genes such as *PS1*, *PS2*, and *APP*.

Discussion

We report a diagnostically challenging case of a man with clinical features of both AD and bvFTD. An additional consideration was chronic traumatic encephalopathy associated with mild right temporal behavioral features, including rigidity and compulsions. Positive PIB-PET confirmed the presence of amyloid pathology. He carried one APOE E4 allele, and no autosomal dominant mutations for AD. Surprisingly, he also tested positive for the *C9ORF72* expansion.

Research criteria were helpful but not definitive for making the clinical diagnosis

Although the patient's symptoms were consistent with three elements required for possible bvFTD (compulsions, dietary changes, and disinhibition), he did not meet research criteria for bvFTD (Rascovsky et al., 2011) because none of these symptoms developed within the first three years of onset. One possibility is that amyloid pathology accounted for his initial memory and calculation difficulties, and bvFTD symptoms due to *C9ORF72* emerged later in the disease course. Another consideration is that the risk of amyloid positivity was increased by his possession of an APOE E4 allele and *C9ORF72*-related neurodegeneration drove his clinical syndrome. While atypical for bvFTD, episodic memory impairment has been previously reported in *C9ORF72* bvFTD series (Boeve et al., 2012; Simon-Sanchez et al., 2012; Snowden et al., 2012). A third possibility is that his clinical syndrome was driven by amyloid pathology and *C9ORF72*-related neurodegeneration had not yet ensued, which is less likely given that he had diffuse atrophy consistent with a bvFTD pattern.

Consistent with clinical AD, his first symptom, dyscalculia, was a cognitive, rather than a behavioral symptom, and suggestive of parietal dysfunction. Memory and visuospatial deficits ensued subsequently, both consistent with mesial temporal and further parietal dysfunction as seen in clinical AD. On the other hand, prominent behavioral changes

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prevented AD from being an all-encompassing diagnosis. Formal social-emotional testing demonstrated clear deficits in detecting emotions and understanding complex social interactions requiring executive function, but his extremely high level of self-conscious emotional reactivity is atypical for bvFTD, and is more commonly observed in patients with AD (Sturm et al., 2013).

Mapping neuroanatomical degeneration alluded to several etiologies

Visual inspection of his structural MRI brain which showed frontal, parietal, and hippocampal atrophy, did not clarify his diagnosis. Because FTD typically affects medial frontal, orbitofrontal and insular cortices (Boccardi et al., 2005; Broe et al., 2003; Perry et al., 2006; Rosen et al., 2002; Seeley et al., 2008), while AD typically affects mesial and lateral temporal and parietal cortex (Coleman, 2007; Jobst et al., 1992), both AD and bvFTD remained diagnostic considerations. We suspected that the bilateral anterior temporal encephalomalacia may have been associated with rigidity and compulsions, reminiscent of right temporal neurodegeneration (Seeley et al., 2005) and disinhibition, reported in head trauma (Cato, Delis, Abildskov, & Bigler, 2004; Lippert-Grüner, Kuchta, Hellmich, & Klug, 2006). Although his slowly progressive symptomatic decline did not support the notion that his remote head trauma was the primary etiology, we considered that head trauma may have initiated chronic traumatic encephalopathy (Gavett, Stern, & McKee, 2011) and that it also poses a risk for amyloid pathology (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Mielke et al., 2014). Both acute and remote head trauma have been associated with increased amyloid accumulation on PIB-PET (Hong et al., 2014; Mielke et al., 2014), although it remains unknown whether increased amyloid persists after brain injury and directly causes Alzheimer's disease.

VBM showed a ventral frontal pattern, with orbitofrontal and pregenual anterior cingulate cortices prominently atrophied, most suggestive of bvFTD-related neurodegeneration. Group-level neuroimaging studies demonstrate that *C9ORF72*+ bvFTD atrophy predominantly emerges in the anterior insula, anterior cingulate and frontotemporal cortex, as in sporadic bvFTD (Irwin et al., 2013; Mahoney et al., 2012; Sha et al., 2012; Whitwell et al., 2012b). *C9ORF72*+ bvFTD also show atrophy in parietal and occipital cortex, cerebellum (Irwin et al., 2013; Mahoney et al., 2012; Whitwell et al., 2012a), and bilateral medial pulvinar nucleus of the thalamus (Lee et al., 2014). VBM also showed bilateral atrophy in hippocampi, precuneus, and posterior lateral temporal cortex. Although temporoparietal degeneration suggests AD (Jobst et al., 1992), *C9ORF72* bvFTD also show parietal atrophy (Irwin et al., 2013; Sha et al., 2012; Whitwell et al., 2012b).

Further suggestion of his underlying parietal dysfunction emerged on FDG-PET, with hypometabolism seen in frontotemporal and parietal cortices. Hypometabolism in the parietal lobes and posterior cingulate are characteristic of patients with AD (Minoshima et al., 1997). Positive PIB-PET scan provided the strongest evidence of underlying AD pathology. Although amyloid imaging can be positive in 15–30% of healthy individuals older than 65 (Laforce Jr & Rabinovici, 2011), and does not exclude the possibility of other co-pathologies, this patient was less likely to have a false positive PIB-PET scan, given his young age of onset. Additionally, the presence of an APOE4 allele increases the likelihood

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of amyloid pathology and decreases the age of onset of disease by approximately 10 years (Corder et al., 1993), lending further support to underlying AD pathology in this patient. Overall, imaging results suggested strong evidence for amyloid pathology and an atrophy pattern consistent with *C9ORF72* bvFTD.

Patients with Alzheimer's disease and C9ORF72 present a diagnostic challenge

Few reports have described the identification of *C9ORF72* carriers within clinically-defined Alzheimer's disease cohorts. Although previous reports have alluded to behavioral changes occurring in a subset of *C9ORF72* carriers with clinical AD (Harms et al., 2013; Wallon et al., 2012), we report an in-depth cognitive and behavioral evaluation with quantitative structural imaging analysis and amyloid imaging to elucidate the clinical complexity of diagnosing such patients. Because our patient's symptoms occurred at such an early age of onset at age 54, co-morbid AD and FTLD pathology were not highly suspected. Although his mother had dementia with symptom onset in her late sixties and a sibling had psychiatric disease, limited family history was elicited for an autosomal dominant inheritance pattern. It is unlikely that genetic testing for the *C9ORF72* expansion would have been ordered for our patient if he had not enrolled in our research cohort.

Overall, it is likely that multiple pathologies including AD, FTD-ALS/DPR, FTLD-TDP and possibly chronic traumatic encephalopathy influenced the mixed clinical presentation in our patient. Unfortunately, autopsy data was unavailable for this patient. Although obtaining the genetic diagnosis of *C9ORF72* in this case affirmed our suspicions of FTLD pathology, the timing of FTLD due to *C9ORF72* during his disease course remains unclear. Such diagnostically challenging cases will greatly benefit from genetic testing and molecular imaging. In patients who are likely to suffer from mixed pathologies, biomarkers for underlying pathology remain crucial for disease detection to determine time points for future treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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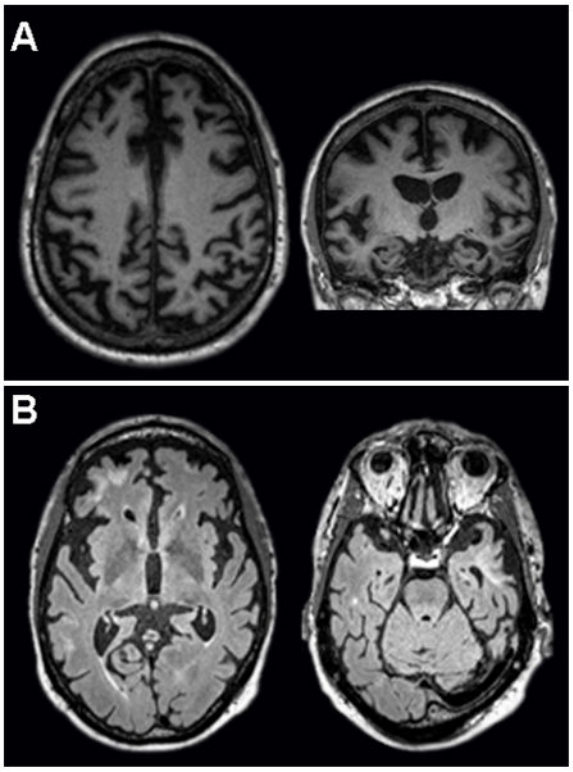

Figure 1. Structural MRI

3T structural brain MRI. A: Axial T1 showing bilateral frontal and parietal atrophy (left); Coronal T1 showing bilateral hippocampal atrophy (right). B: Axial FLAIR displaying encephalomalacia in the left frontal and right temporal pole. The left side of the axial image corresponds to the left side of the brain.

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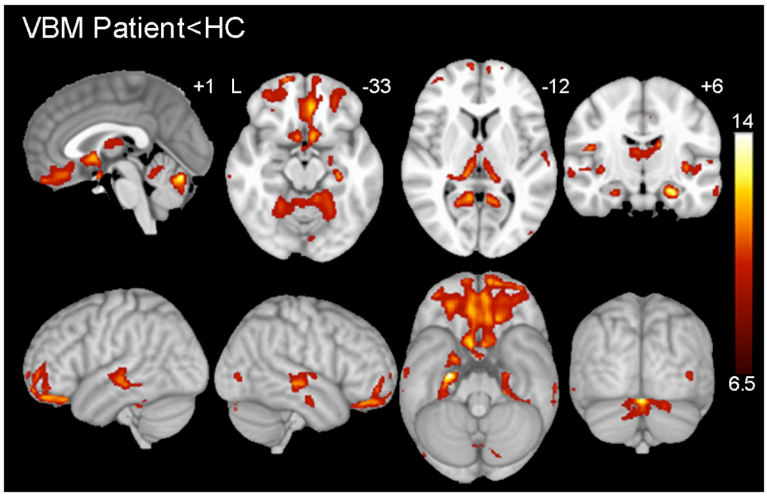

Figure 2. VBM analysis of patient compared to 30 healthy controls

Group difference maps comparing the patient with 30 healthy controls (HC) showed atrophy in bilateral orbitofrontal cortex, pregenual anterior cingulate, bilateral posterior insula, bilateral lateral temporal cortex, caudate, medial thalamus, hippocampi, and cerebellum. Significant clusters were defined at a t-threshold of pFWE ≤0.05 with a minimum cluster size of 50 voxels. The color bar represents the t-score and statistical maps are superimposed on the Montreal Neurological Institute template. The left side of the axial and coronal images corresponds to the left side of the brain.

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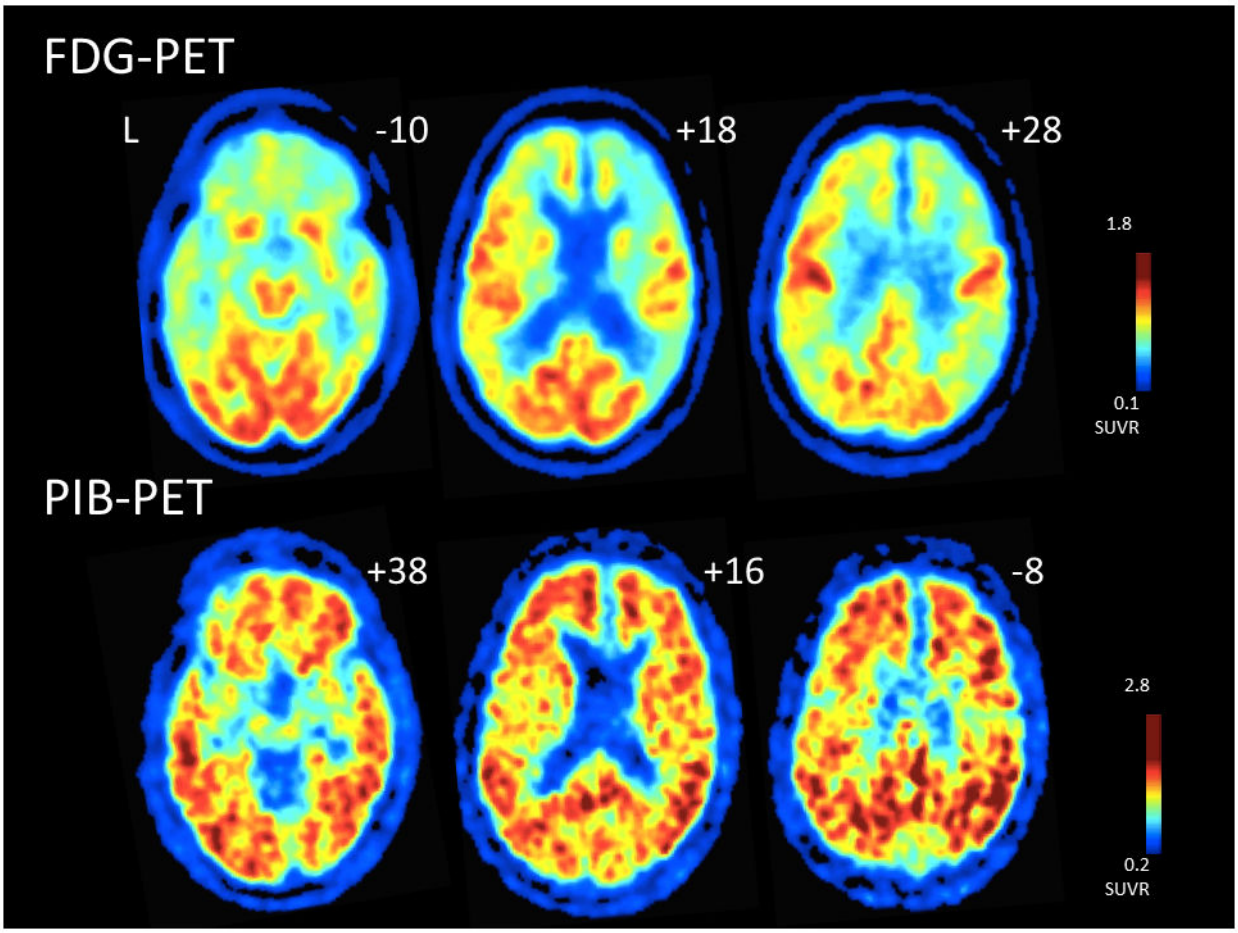

Figure 3. Fluorodeoxyglucose (FDG) and Pittsburgh compound B (PIB) PET

Top panel: FDG-PET demonstrated hypometabolism in the frontal and temporoparietal lobes. Bottom panel: PIB-PET showed diffuse cortical and striatal binding. The left side of the axial images corresponds to the left side of the brain with the NIH color scale.

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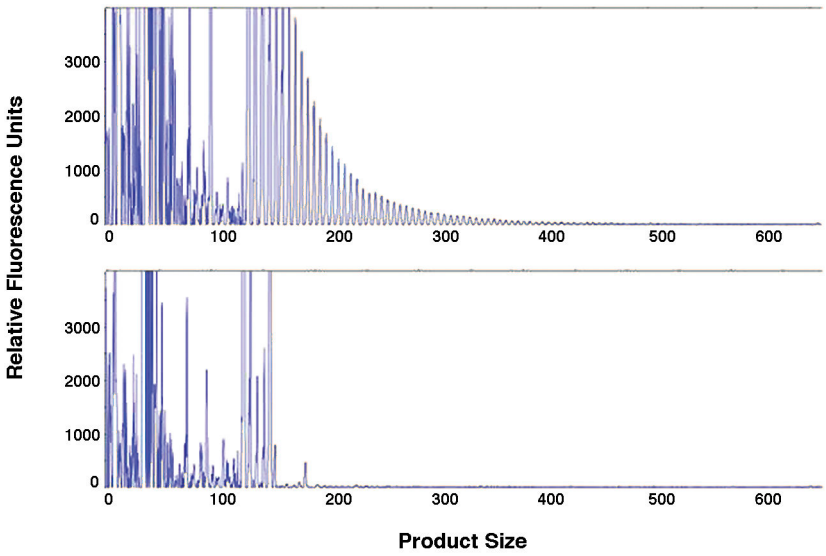

Figure 4. Electropherogram revealing the patient's hexanucleotide expansion in *C9ORF72*

Electropherograms of the repeat-primed PCR assay show the arbitrary relative fluorescence units versus the product size (base pairs). The patient (top panel) exhibits the "saw-tooth" stutter pattern, characteristic among *C9ORF72* repeat expansion carriers and absent in non-carriers (bottom panel).